Amberlyst-15 in organic synthesis

Rammohan Pal,* Taradas Sarkar and Shampa Khasnobis

Department of Chemistry, Acharya Jagadish Chandra Bose College,
1/1B, A. J. C. Bose Road, Kolkata 700 020, India
E-mail: pal_rammohan@yahoo.com

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Abstract

Commercially available Amberlyst-15 has played an important role in organic synthesis. This review summarizes the versatile synthetic applications of Amberlyst-15 in different chemical transformations. Reactions include esterification, transesterification, Michael addition, aza-Michael addition, Prins cyclization, Friedel-Crafts alkylation, acylation, metal free hydro-arylation, hydroalkylation, halogenation, protection of carbonyls, amines, deprotection of acetals, acetates, Boc-protected amines, cleavage of epoxides, crossed-aldol condensation, synthesis of quinolines, pyrazolines, indolinones, acridines, calix[4]pyrroles, xanthenes, coumarins, benzopyrans theaspirane, furans, and substituted phosphonates. Applications of this catalyst allow mild and highly selective transformations and synthesis in a facile and environmentally friendly manner. The catalysts can be regenerated and recycled.

Keywords: Amberlyst-15, heterogeneous, recyclable, acid catalysis, organic synthesis

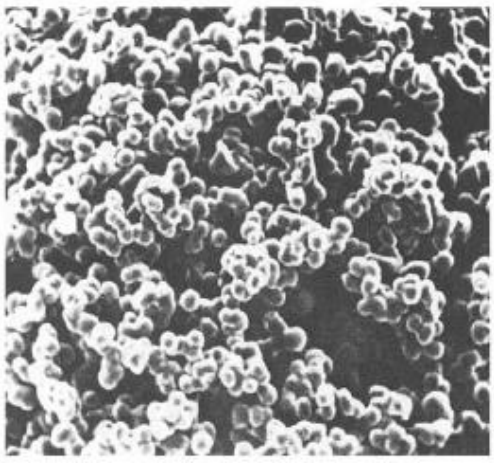
Contents

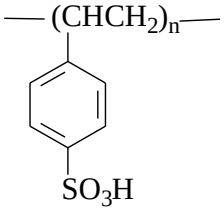
1. Introduction

In the past decade, the chemistry of Amberlyst-15 has experienced a rapid development. This growing interest in Amberlyst-15 is mainly due to its mild and highly selective properties, combined with its environmentally benign character and commercial availability. Amberlyst-15 is now routinely used in organic synthesis as other heterogeneous reusable acid catalysts[1a-d] for various selective transformations of simple and complex molecules. The purpose of the present review is to summarize the utility of Amberlyst-15[1e-i] with emphasis on recent synthetic applications; literature coverage is through the end of 2011.

2. General Information and Structural Features of Amberlyst-15

Amberlyst-15 is brown-grey solid having the following physical properties[2a]
Ionic form as shipped : hydrogen
Concentration of active sites: ≥ 1.7 eq/L; ≥ 4.7 eq/kg
Moisture holding capacity : 52 to 57% (H^+ form)
Shipping weight : 770 g/L
Particle size : 0.600 to 0.850 mm
Average pore diameter : 300Å
Total pore volume : 0.40 mL/g
Maximum operating temperature: 120 ºC (250 ºF)
Figure 1 (left) shows an SEM of Amberlyst-15 resin.[2b] It is a macro reticular polystyrene based ion exchange resin with strongly acidic sulfonic group (Figure 1, right). Thus, it serves as an excellent source of strong acid. It has been used in various acid catalyzed reactions. It is easy to measure, safe to use, and readily removed at the end of the reaction. An additional advantage is that the catalyst can be regenerated and can be used several times.



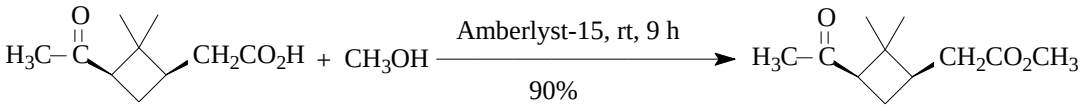


Amberlyst-15

Figure 1

3. Esterification and Transesterification Reaction

Amberlyst-15 is a powerful and selective acid catalyst for esterification reactions. Petrini *et al*. have reported a mild and selective methyl esterification of aliphatic carboxylic acids using Amberlyst-15 in methanol at room temperature in excellent yield (Scheme 1).[3a] No racemisation, epimerization and ketalization products have been observed with this method. Excellent results are obtained in the esterification of bile acids. However, aromatic carboxylic acid such as 5-methylfuroic acid and conjugated carboxylic acid such as *trans*-aconitic acid do not react with methanol at room temperature. They can be transformed into esters only by refluxing the mixture for a long time.



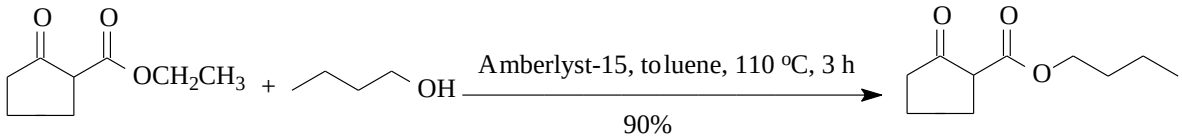
1 **2**

Scheme 1

Amberlyst-15 has also been used for production of biodiesel (BD). Talukder and coauthors reported that palm fatty acid distillate (PFAD), a byproduct from the palm oil refinery process, has been utilized as an alternative feedstock for biodiesel production via Amberlyst-15 catalyzed esterification.[3b] The BD yield obtained using Amberlyst-15 is 97%.

Transesterification of esters with alcohols has been accomplished using Amberlyst-15. Chavan and co-workers reported that Amberlyst-15 acts as a Bronsted acid catalyst for transesterification of various β-ketoesters with different alcohols including allylic alcohols and sterically hindered secondary and primary alcohols in refluxing conditions. In a specific example, the transesterified β-ketoester **4** can be prepared from β-ketoesters **3** using Amberlyst-15 under refluxing in toluene. (Scheme 2).[3c]

Pappu *et al*.[3d] reported that methyl stearate, a model biodiesel compound undergoes transesterification with higher alcohol n-butanol using Amberlyst-15 as acid catalyst.

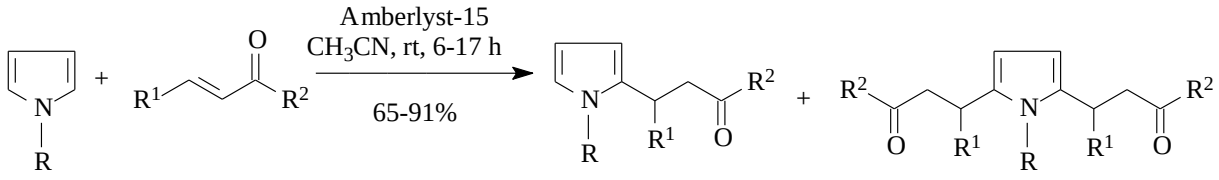


3 **4**

Scheme 2

4. Michael Addition Reaction

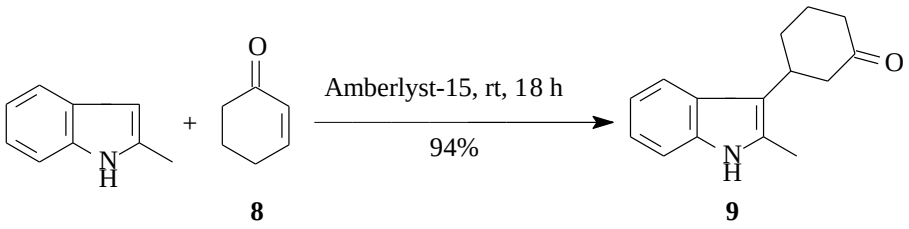
Michael addition of pyrroles to α,β-unsaturated ketones has been accomplished in presence of Amberlyst-15 in acetonitrile at room temperature to obtain the corresponding 2-alkyl and 2,5-dialkyl pyrroles in good to excellent yields (65-91%) without polymerization. The method can thus be used to produce C-alkylated pyrroles **6** and **7** from pyrroles and **5** (Scheme 3).[4a] Acetonitrile was found to be the best solvent in this reaction.



R =H, Me, COPh
R^1 = H, Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4
R^2 = Me, Et, Ph

Scheme 3

Bandini *et al*. reported Amberlyst-15 catalyzed Michael-type addition of indoles to α,β-unsaturated carbonyl and nitro compounds. Thus, when 2-methylindole was treated with **8** in presence of Amberlyst-15 Michael addition adduct **9** was formed in 94% yield (Scheme 4).[4b]

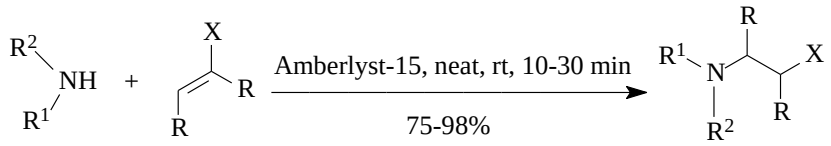


Scheme 4

5. Aza-Michael Addition Reaction

Aza-Michael reaction of a series of amines with α,β-unsaturated carbonyls and nitriles to produce β-amino carbonyls and nitrile compounds **12** in good to excellent yields, using Amberlyst-15 under solvent-free conditions was reported by Das and Chowdhury (Scheme 5).[5a]

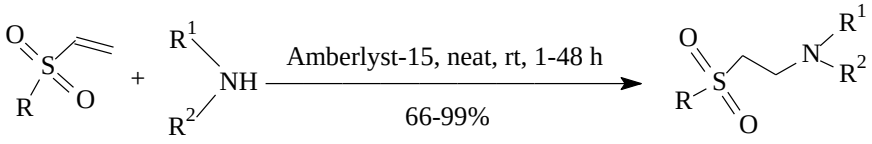
Esteves *et al*., however, used primary and secondary aliphatic amines as substrates with methyl vinyl sulfone **13a** and vinyl *p*-aminophenylsulfone **13b** in presence of Amberlyst-15 (30%, w/w) at room temperature to produce the corresponding aza-Michael addition product **14** in moderate to high yield (Scheme 6).[5b]



10 **11** **12**

X =COMe, COOMe, CN

Scheme 5



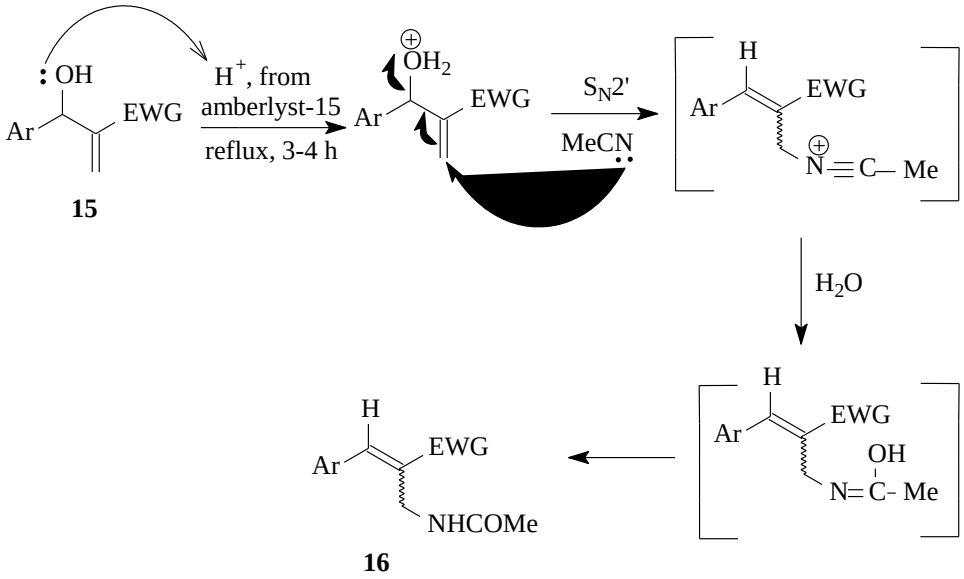
13 **14**

a: R= Me; **b**: R= *p*-$H_2NC_6H_4$

Scheme 6

6. S_N2' Reaction

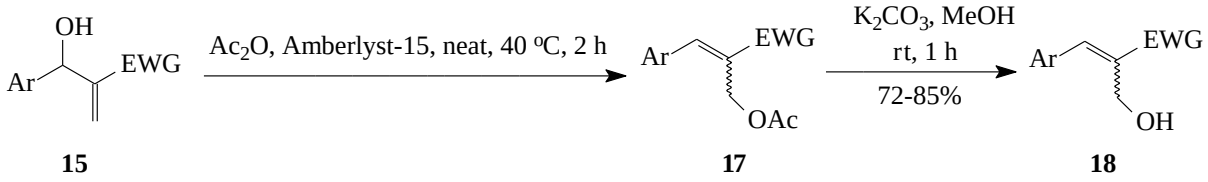
Nucleophilic substitution reaction in allylic alcohols was also studied using Amberlyst-15 as catalyst. The Baylis-Hillman adduct **15** which contains allylic alcohol functionality are highly useful in various chemical transformation and in synthesis of several bioactive compounds.[6a-d]



Scheme 7

Das and co-workers utilized these adducts for the stereoselective synthesis of a series of (*E*) and (*Z*) allyl amides **16** through S_N2' reaction of **15** and MeCN, using Amberlyst-15 as acid catalyst (Scheme 7).[7a]

(*E*)-cinnamyl alcohols **18**[7b] were also synthesized from the isomerization of Baylis-Hillman adduct **15** using Amberlyst-15 as a heterogeneous reusable catalyst (Scheme 8). The plausible mechanism for the formation of allyl primary acetates **17,** from **15** is similar to that in Scheme 7. Compound **17** on hydrolysis with K_2CO_3 in MeOH afforded the corresponding cinnamyl alcohols **18**.

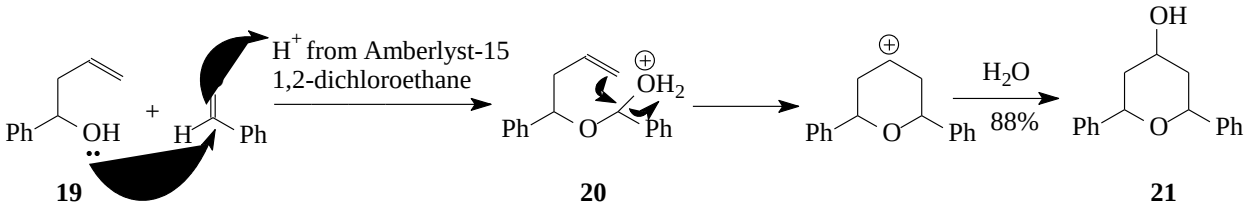


Scheme 8

7. Prins Reaction

The acid catalyzed condensation of olefins with carbonyl compounds known as Prins reaction is an important carbon-carbon bond forming reaction.[8a,b] The tetrahydropyran ring is a part of the backbone of various important carbohydrates and natural products.[9a,b]

Yadav *et al*. reported that Amberlyst-15 catalyses the synthesis of tetrahydropyranols through the Prins-type cyclization. Thus, when 1-phenyl-3-buten-1-ol **19** and benzaldehyde was stirred in refluxing 1,2-dichloroethane in presence of Amberlyst-15 for 2 hrs. 2,6-Diphenyl-4-hydroxytetrahydropyran **21** was produced in 88% yield with high diastereoselectivity. The formation of **21** may be explained by Prins-type cyclization of the intermediate hemi-acetal **20** (Scheme 9).[10]



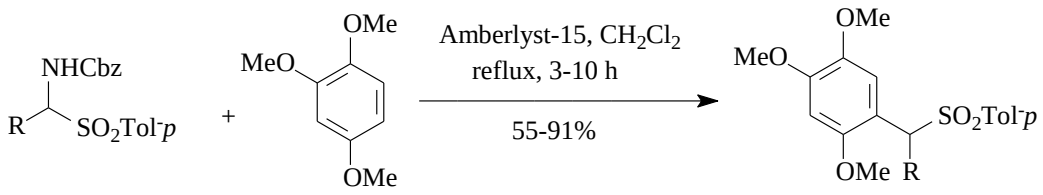
Scheme 9

8. Friedel-Crafts Reaction

Friedel-Crafts reaction of aromatic and heteroaromatic compounds is one of the fundamental reactions for forming carbon-carbon bond. Friedel-Crafts alkylation and acylation reactions have been studied by using Amberlyst-15 as acid catalyst.

8.1 Alkylation

Kadam *et al*. demonstrated that Amberlyst-15 can act as a powerful catalyst for the alkylation of activated arenes or heteroarenes and α-amido sulfones. Friedel-Crafts alkylation by various α-amido sulfones **22** was achieved on treatment with 1,2,4-trimethoxybenzene using Amberlyst-15 in refluxing CH_2Cl_2 to give the products **23** in very good yield (Scheme 10).[11a] The reaction of *N*-benzyloxycarbonylaminophenyl-*p*-tolylsulfones with indoles (heteroarenes) afforded C-3 alkylation of indoles in moderate yield.



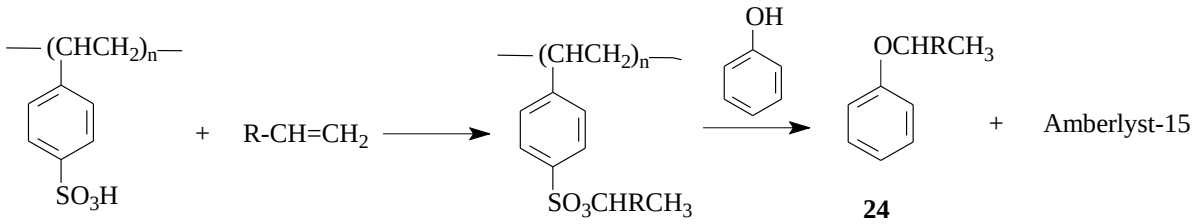
22

R= alkyl, aryl

23

Scheme 10

Alkylated phenols are widely used as additives in gasolines, lubricants, and a host of consumer products.[11b] Various alkylated phenols **24** was synthesized by Ma and co-workers from phenol and olefins using eco-friendly heterogeneous catalyst Amberlyst-15 (Scheme 11).[11c] The mechanism involves an exothermic reaction between olefin and benzene sulphonic acid (from Amberlyst-15) to form an ester followed by three reaction pathways leading to direct O-alkylation, o-C-alkylation and *p*-C-alkylation.



Amberlyst-15

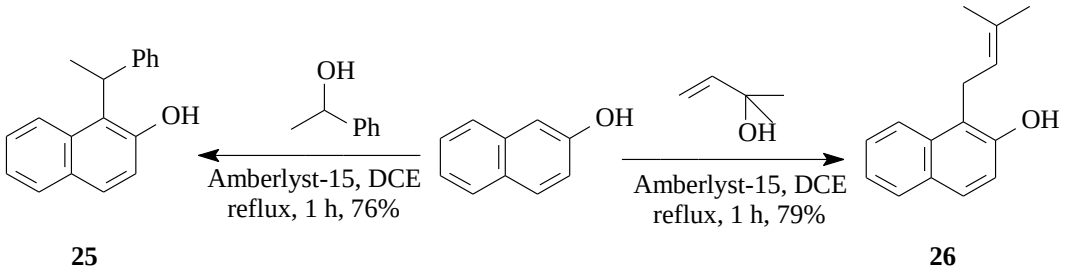
Ester

24

O-alkylation

Scheme 11

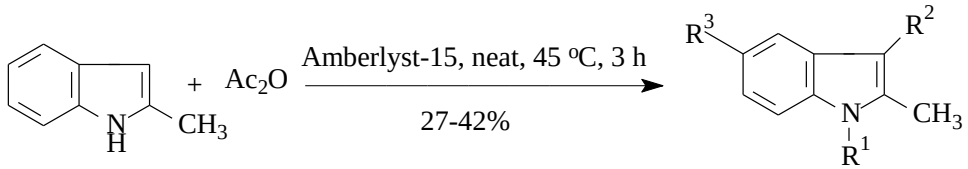
Regioselective alkylation at the C-1 position of 2-naphthol using Amberlyst-15 was reported by Das *et al*. When a mixture of β-naphthol, benzylic/allylic alcohol and Amberlyst-15 was refluxed in 1,2-dichloroethane (DCE), the corresponding alkylation products **25** and **26** was produced respectively (Scheme 12).[11d] Compounds **25** and **26** shows interesting biological properties, including antitubercular activity[12a,b] and inhibitory effect on cyclooxygenease I and II.[12c] Also several naphthol compounds that are formed are also useful intermediates in organic synthesis.[12d,e]



Scheme 12

8.2 Acylation

Heteroaromatics like, indole, 2-methylindole and pyrrole undergoes Friedel-Crafts acylation reactions in presence of Amberlyst-15. Thus indole, 2-methylindole and pyrrole were treated with Ac_2O under solvent-free conditions at room temperature for 3 hrs in presence of Amberlyst-15 afforded the acetylation products of the compounds (Scheme 13).[13a] Indole produced 3-acetylindole and *N*-acetylindole. On the other hand, 2-methylindole produced the *N*-acetyl-2-methylindole **27a**, *N*,3-diacetyl-2-methylindole **27b** and 5-acetyl-2-methylindole **27c** on treatment with Ac_2O in presence of Amberlyst-15. Pyrrole yielded 3-acetylpyrrole and 2,4-diacetylpyrrole under the same conditions.

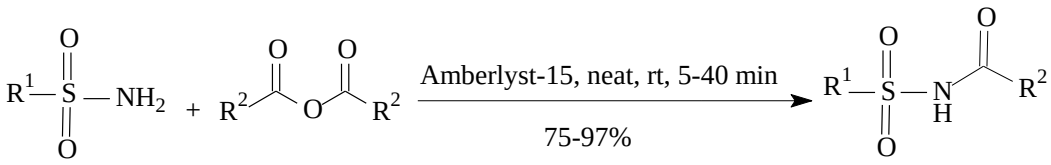


27

a: R^1= Ac; R^2= R^3= H
b: R^1= R^2= Ac; R^3= H
c: R^1= R^2= H; R^3= Ac

Scheme 13

A series of *N*-sulfonamides **29** were synthesized from sulfonamides **28** and acid anhydrides by Friedel-Crafts acylation reaction using Amberlyst-15 under solvent-free conditions at room temperature (Scheme 14).[13b] Wu *et al*. reported that Amberlyst-15 is the best catalyst amongst the previously reported catalyst for the same reaction.



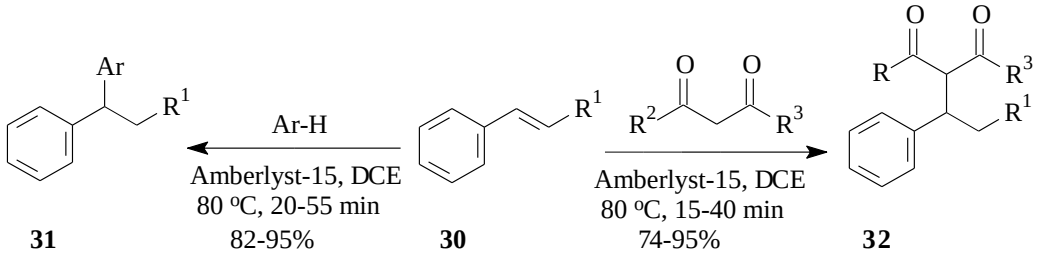
28 **29**

R^1= Aryl and alkyl; R^2= Ph, Me and i-pr

Scheme 14

9. Hydroarylation and Hydroalkylation Reaction

Hydroarylation and hydroalkylation of styrenes was achieved by Das *et al*. using Amberlyst-15 (Scheme 15).[14] Various styrenes **30** when treated with different aromatic compounds or 1,3-dicarbonyl compounds underwent hydroarylation or hydroalkylation reactions to produce the diarylalkanes **31** and alkylation products **32** respectively. Both the reactions were conducted in 1,2-dichloroethane (DCE) at 80 ºC.

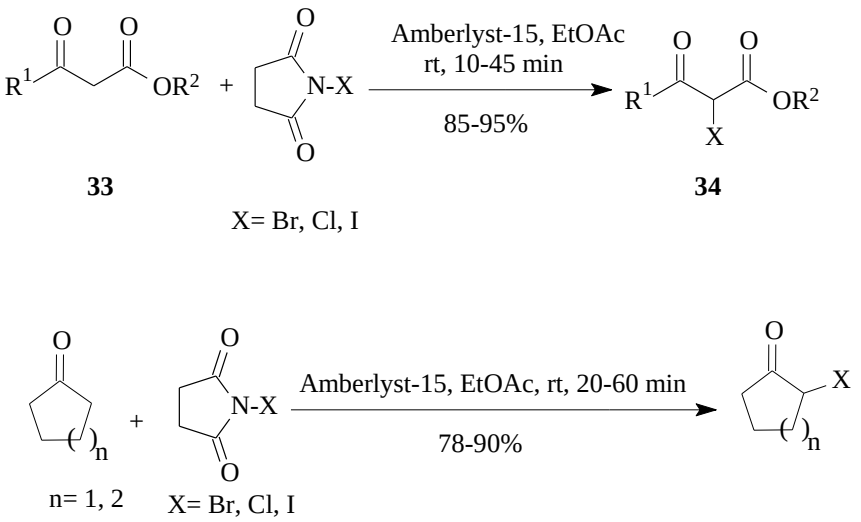


31 **30** **32**

Scheme 15

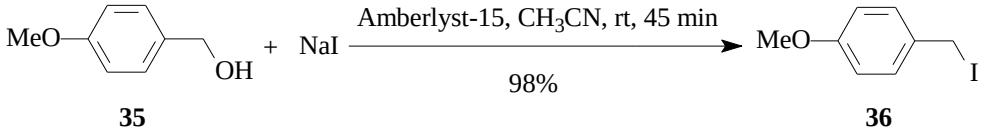
10. Halogenation Reaction

N-Halosuccinimides are powerful and selective halogenating reagents for organic substrates. Various 1,3-keto-esters can be selectively halogenated at the 2-position with *N*-halosuccinimides using Amberlyst-15 as a heterogeneous solid catalyst. The 2-halogenated products **34** can be prepared from β-ketoesters **33** in good yields under mild conditions (Scheme 16).[15a] Cyclic ketones can also be directly halogenated at the α-position by NXS under the same reaction conditions.



Scheme 16

Amberlyst-15 can also be used for the iodination of primary, secondary allylic and benzylic alcohols using NaI. *p*-Methoxybenzylalcohol **35** is selectively iodinated with NaI/Ambeylyst-15 in acetonitrile at room temperature to give **36** in good yield (Scheme 17).[15b] Electron donating groups attached to the benzene ring accelerate the iodination reaction and electron-withdrawing group retard the transformation.



Scheme 17

11. Protection and Deprotection Reactions

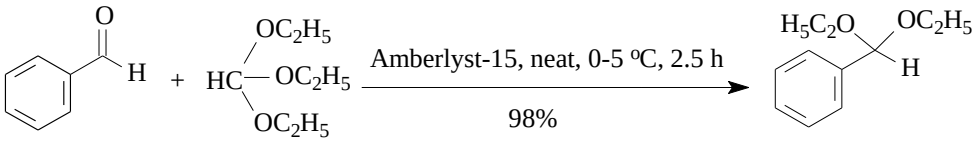
Protection and deprotection reactions are very important and widely used strategy for organic synthesis. Reactions involving selective protection of functional groups such as carbonyl, hydroxyl carboxylic acids and amines in presence of other functional groups, and their deprotection, are of common importance in the multi-step synthesis of complex natural products[16a,b].

11.1 Protection of carbonyls and amines

Protection of carbonyl group as acetals (acetalization reaction), thioacetals (thioacetalization reaction) and diacetates (acylation reaction) are widely used owing to their stability towards a wide range of reagents.[17a,b] A number of methods have been reported for acetalization,[18a,b] thioacetalization,[19a,b] and acylation[20a-c] reactions. Protection of amines as *N*-*tert*-butoxycarbonyl (*N*-Boc) group has become very popular in peptide synthesis.[21a,b] A survey of the literature revealed that Amberlyst-15 has been efficiently used for the protection of carbonyl and amine functional groups.

11.1.1 Acetalization reaction

Patwardhan and Dev reported that carbonyl group can be protected by acetalization process using catalytic amount of Amberlyst-15. Thus, when benzaldehyde was treated with triethyl orthoformate in presence of Amberlyst-15, the corresponding acetal **37** was obtained in excellent yield (Scheme 18).[22a] In case of ketones the reaction produced the corresponding ketals and in some cases the enol ethers was directly formed in good yield under similar conditions.

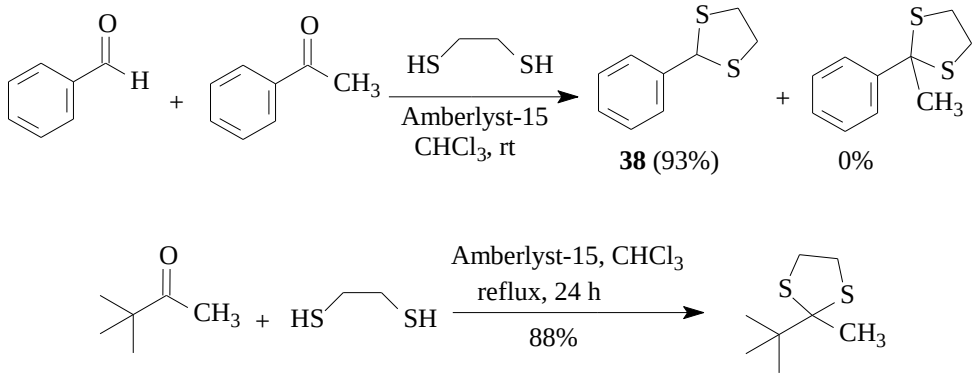


37

Scheme 18

11.1.2 Thioacetalization reaction

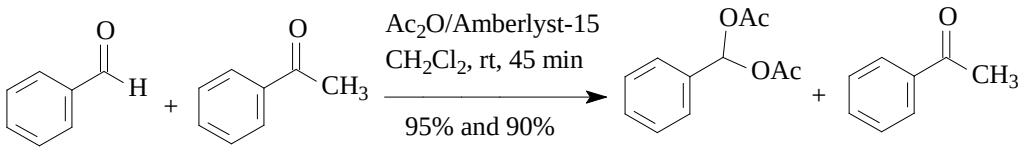
Chemoselective thioacetalization of carbonyl group with Amberlyst-15 was reported by Perni *et al*. when benzaldehyde and acetophenone was allowed to react with one equivalent of ethanedithiol and Amberlyst-15 in chloroform overnight at room temperature, a high yield of **38** was obtained and the ketone recovered in unchanged condition (Scheme 19).[22b] However, ketones can be protected by this method by refluxing the reaction mixture.



Scheme 19

11.1.3 Acyloxy-acylation reaction

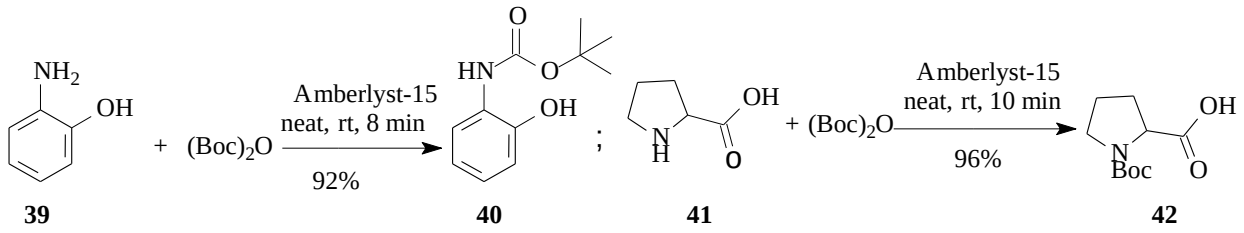
Reddy *et al*. demonstrated that Amberlyst-15 works as an efficient catalyst for chemoselective acyloxy-acylation of aldehydes. Thus, when a mixture of benzaldehyde and acetophenone in (1:1) ratio was reacted with acetic anhydride in presence of Amberlyst-15 catalyst in dichloromethane at room temperature, the 1,1-diacetate of benzaldehyde was exclusively formed (Scheme 20).[22c]



Scheme 20

11.1.4 *N-tert*-butoxycarbonylation reaction

Chemoselective *N-tert*-butoxycarbonylation of amines in presence of Amberlyst-15 was reported by Kumar et al. A variety of primary, secondary and aryl amines were reacted with di-*tert*-butyl dicarbonate $(Boc)_2O$ in presence of Amberlyst-15 in CH_2Cl_2 at room temperature to produce the corresponding *N-tert*-butylcarbamates in good to excellent yields. However, 2-aminophenol **39** and proline **41** reacted slowly with $(Boc)_2O$ in comparison with the other amines, to yield **40** and **42** respectively (Scheme 21).[22d] This method was found to be selective for the protection of amines as the hydroxyl and carboxylic acid groups were not affected during the reaction.



39 **40** **41** **42**

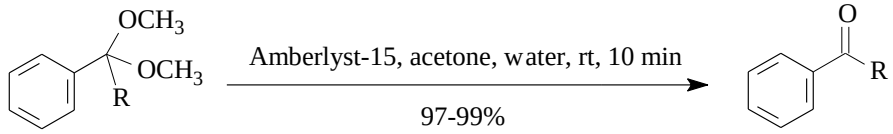
Scheme 21

11.2 Deprotection of acetals, thioacetals, acetates and Boc-protected amines

The importance of the deprotection of acetals,[23a-c] thioacetals,[24a-c] acetates[25a-c] and Boc-protected amines[26a,b] to their corresponding functional groups in multi-step organic synthesis can not be overstated. Amberlyst-15 has been shown to catalyze such reactions efficiently to give good yields of the deprotected products.

11.2.1 Deacetalization reaction

Coppola demonstrated that Amberlyst-15 can be used as an excellent catalyst for the hydrolysis of acetals or ketone acetals to the corresponding carbonyl derivatives (Scheme 22).[27a] Thus, when a solution of acetal **43** in acetone, containing water is added to Amberlyst-15 and the mixture is stirred at room temperature for 10 min the corresponding carbonyl compounds **44** was produced in high yield.



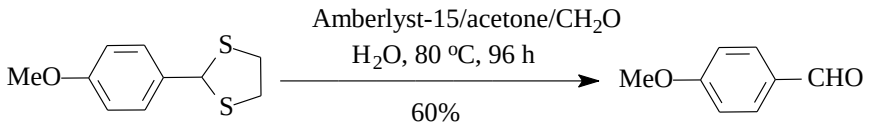
43 **44**

R= H, CH_3

Scheme 22

11.2.2 Dethioacetalization reaction

Ballini and Petrini reported a new procedure for dethioacetalization via equilibrium exchange with aqueous acetone, paraformaldehyde and Amberlyst-15 as acidic catalyst at 80 ºC (Scheme 23).[27b] *p*-Methoxybenzaldehyde **46** was regenerated from corresponding ethanediyl *S,S*-acetals **45** under the experimental conditions in good yields. The presence of ester, ether and hydroxyl groups in thioacetal or thioketal compounds do not interfere with the deprotection process. The author previously also demonstrated that Amberlyst-15 is an excellent and far superior catalyst for regeneration of carbonyl compounds from nitrogeneous derivatives,[27c] like tosylhydrazones, oximes, 2,4-dinitrophenylhydrazones and semicarbazones when wet acetone is used as exchange reagent.

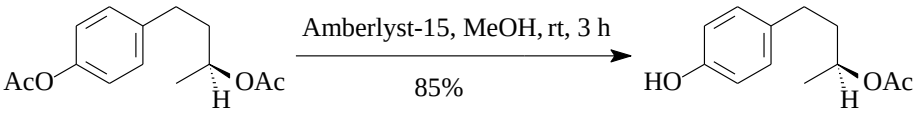


45 **46**

Scheme 23

11.2.3 Hydrolysis of aromatic acetates

Aromatic acetates of the type **47** were selectively deprotected to the corresponding phenols **48** using Amberlyst-15 as catalyst in methanol at room temperature (scheme 24).[27d] Alkyl acetates were unaffected by the catalyst. Ethers, esters and lactones functionality present in acetate compounds also remained unchanged under this reaction condition.



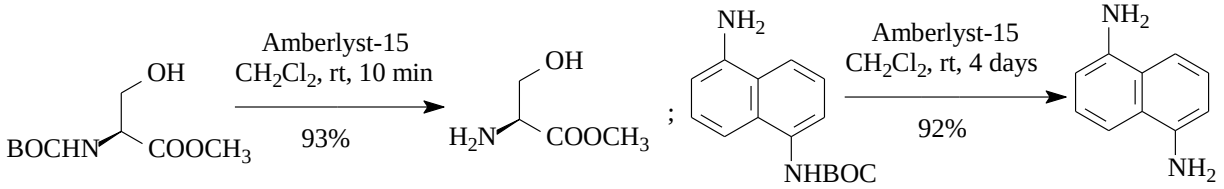
47 **48**

Scheme 24

11.2.4 Deprotection of Boc-protected amines

Lu and his groups demonstrated that the strongly acidic ion-exchange resin Amberlyst-15, effectively deprotects, purifies, and isolates BOC-protected amine compounds. Both primary and

secondary BOC-protected aliphatic amines can be deprotected effectively with reaction times that ranged from 4 to 29 hours at ambient temperature. The presence of other functional groups such as alcohols esters and carboxylic acids do not interfere with the deprotection process. However, BOC-protected aromatic amines react slowly than the aliphatic ones (Scheme 25).[27e]

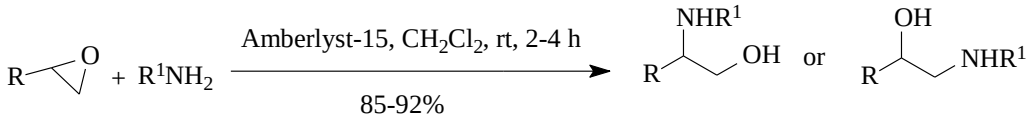


Scheme 25

12. Epoxide Ring Opening Reaction

Epoxides are versatile and important intermediates in organic synthesis. They undergo ring-opening reactions to give β-substituted alcohols with a variety of nucleophilic species.[28a-d]

Vijender *et. al*. reported that epoxides undergo rapid ring-opening reaction with various amines catalyzed by Amberlyst-15 under mild conditions to afford the corresponding β-amino alcohols in excellent yields (Scheme 26).[29a] The epoxide ring-opening occurs in a high regio-selective manner with the attacking of nucleophile either at the more hindered carbon or the terminal carbon of the epoxide.

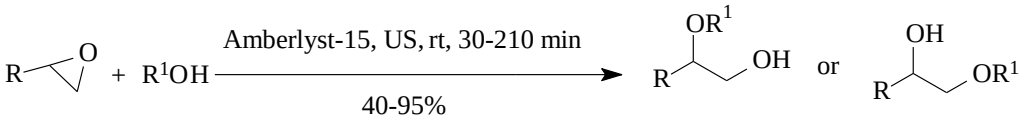


R= aryl, aryloxy, alkyl, cycloalkyl
R^1= aryl, alkyl, heterocycle

Scheme 26

Various β-alkoxy alcohols were synthesized in good to excellent yields using Amberlyst-15 catalyzed regioselective ring opening reaction of epoxide by primary, secondary and tertiary alcohols under ultrasound irradiation (Scheme 27).[29b] The likely role of Amberlyst-15 is to act as a Bronsted acid in this case for the activation of epoxide and render the epoxide more susceptible to nucleophilic attack by alcohols. Methanol gave the best yield among the alcohols used for this

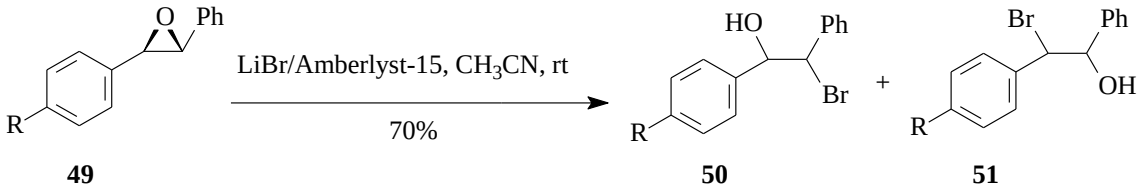
reaction. As the alkyl group of alcohol becomes bulkier, the yield of the ring-opening reaction gradually decreases.



R= $CH_2OC_6H_5$; CH_2Cl; cycloalkyl
R^1= CH_3; C_2H_5; $CH(CH_3)_2$; $C(CH_3)_3$

Scheme 27

Solladie-Cavallo and his group demonstrated that Amberlyst-15 can act as an effective acid catalyst for regio- and stereoselective ring opening of 2,3-diaryl oxiranes by LiBr (Scheme 28).[29c] In the case of symmetrical *trans*-stilbene oxide, the *syn*- versus *anti*-bromohydrins ratio ranged between 88/12 and 30/70, by varying the reaction temperature from 20 to -30 ºC. In the case of nonsymmetrical *para*-substituted *trans*-2,3-diaryloxiranes **49**, the regioselectivity is



49 **50** **51**

R= NO_2, CF_3
R= OCH_3

Scheme 28

determined by electronic effects. If one phenyl bears a strong electron withdrawing group (NO_2 or CF_3), the nucleophilic attack takes place totally on the β-carbon with respect to the substituted phenyl ring to produce **50**. The regioselectivity was reversed if one phenyl contains strong electron realeasing group (OCH_3) to give **51**.

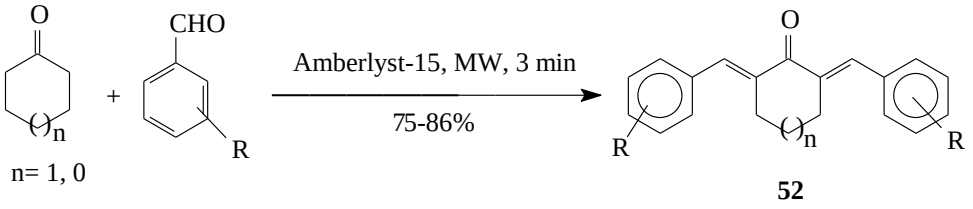
13. Condensation Reaction

Cross-aldol condensation of aldehydes with ketones is an important synthetic reactions for the synthesis of α,β-unsaturated carbonyl compounds, which are known to show diverse biological activities.[30a-c] These types of compounds are used as intermediates for synthesis of various pharmaceuticals, agrochemicals and perfumes.[31a,b] On the other hand condensation of carbonyls and indoles give bis(3-indolyl)methanes that show a wide variety of biological activities.[32] It was found that Amberlyst-15 effectively catalyses both types reactions.

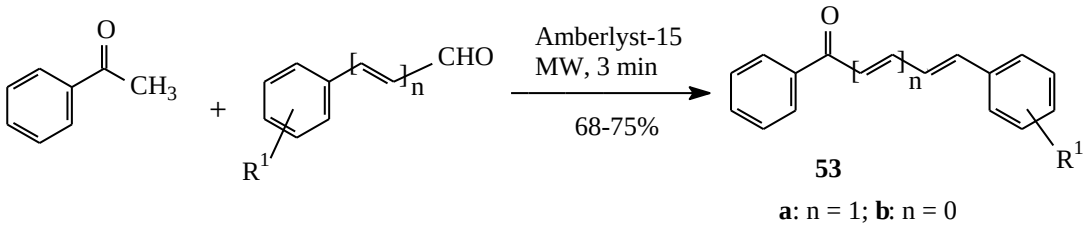
13.1 Crossed-aldol condensation reaction

Pal and his co-workers showed that Amberlyst-15 can act as an efficient heterogeneous acid catalyst for the cross-aldol condensation reaction under solvent free conditions. Thus, when various aldehydes and ketones were mixed thoroughly with Amberlyst-15 and neutral alumina, and the mixture were subjected to microwave irradiation, the condensation products **52** and **53** were produced smoothly in very good yields (Scheme 29 and 30).[33a] α,α′-Bis(arylmethylene)-cycloalkanones **52**, α-cinnamylideneacetophenones **53a** and chalcones **53b** were produced in this process.

Mandal *et al*. reported that *E*-3-Arylidenechroman-4-ones **54a**, *E*-3-arylidene-thiochroman-4-ones **54b**, *E*-3-cinnamylidenechroman-4-ones **55a**, and *E*-3-cinnamylidenethiochroman-4-ones **55b** could be synthesized by the reaction between different aromatic aldehydes including cinnamaldehyde and chroman-4-ones or 1-thiochroman-4-ones in presence of Amberlyst-15 under microwave irradiation in solvent-free condition in good yield (Scheme 31 and 32).[33b]



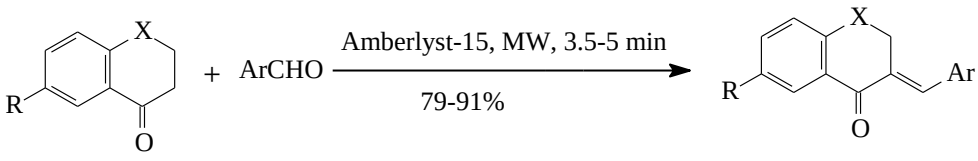
Scheme 29



53

a: n = 1; **b**: n = 0

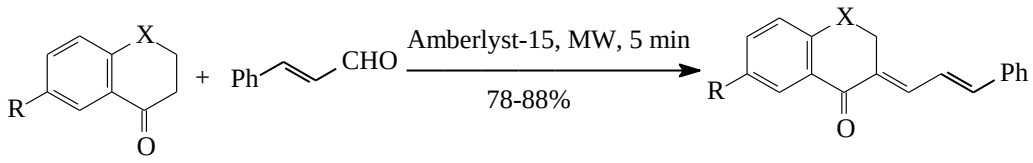
Scheme 30



a: X= O
b: X= S

54

Scheme 31



a: X= O
b: X= S

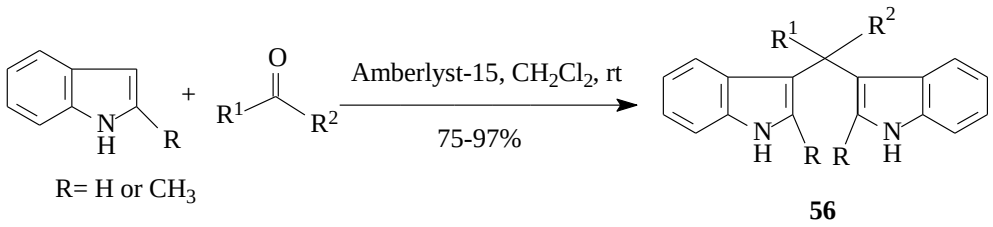
55

Scheme 32

13.2 Condensation of carbonyl compounds and indoles

Ramesh and coworkers observed that of Amberlyst-15 can be utilized for the condensation of indoles with carbonyl compounds for the synthesis of bis- and tris(1*H*-indol-3-yl)methanes **56**. Thus, when Amberlyst-15 was added to a stirring solution of indole and carbonyl compounds in CH_2Cl_2 at room temperature, **56** was formed in high yield within 2-3 hrs. (Scheme 33).[34a]

The same condensation reaction was reported by Ke *et al*.[34b] using acetonitrile as solvent.



Scheme 33

Tri(heteroaryl)methanes were synthesized by Farhanullah and his group by the condensation of indoles with 4-formyl pyrazoles **57** and bis-(4-formylphenoxy)alkanes **59** separately, in $CHCl_3$ at room temperature using Amberlyst-15 to give indole-pyrazole **58** and indole-oxyaryl **60** respectively (Figure 2).[34c] The method is concise and economic at the same time.

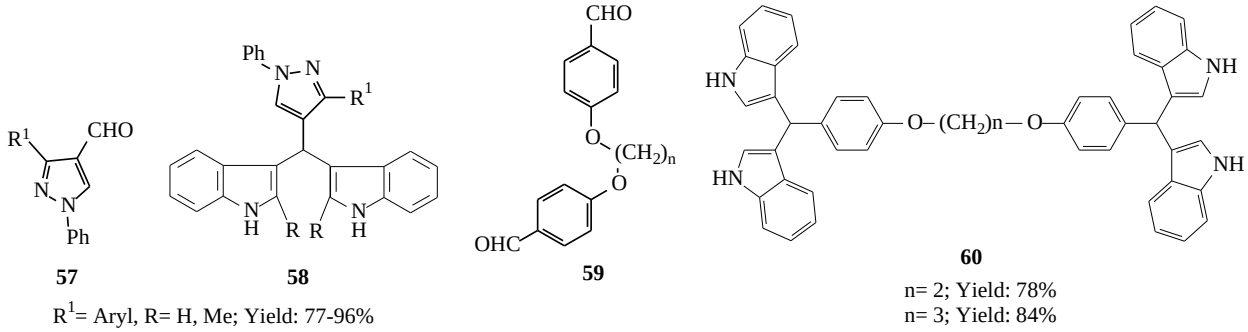
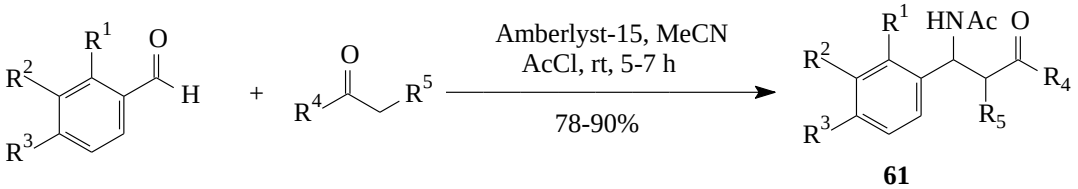


Figure 2

14. Multicomponent Reaction

Multicomponent reactions have recently gained much practical importance due to their speed, diversity and efficiency.[35a-c] Das and Reddy reported an efficient one-pot multicomponent synthesis of β-acetamido ketones **61** from aromatic aldehydes, enolizable ketones or keto esters and both acetyl chloride (AcCl) and acetonitrile (MeCN) at room temperature using Amberlyst-15 as catalyst (Scheme 34).[36a] Aromatic aldehydes containing either electron-donating or -withdrawing groups underwent the conversion smoothly. Several functional groups such as halogen (Cl, Br), NO_2, ester and ether moieties were found to be stable under the reaction condition. Compared with the other methods for multicomponent synthesis of β-acetamido ketones, this new method using Amberlyst-15 offers better yields, shorter reaction times and economic viability.

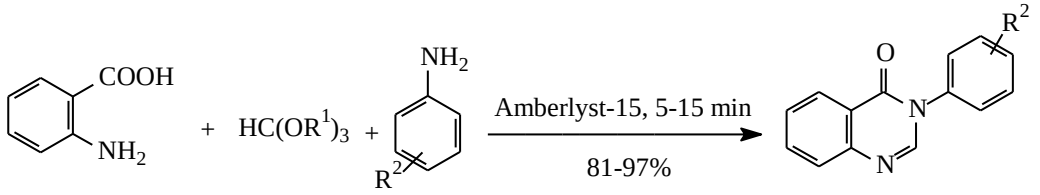


61

R^1= R^2= H, NO_2; R^3= H, Me, OMe, NO_2, Cl
R^4= Me, Ph, aryl; R^5= H, Me, COOMe

Scheme 34

A similar single-step multicomponent reaction has been reported for the coupling of anthranilic acid, orthoesters and amines to their corresponding 4(3*H*)-quinazolines **62**, using a catalytic amount of Amberlyst-15 under solvent-free conditions (Scheme 35).[36b]



62

R^1= Me, Et; R^2= H, Me, OMe, NO_2, F, Cl, Br

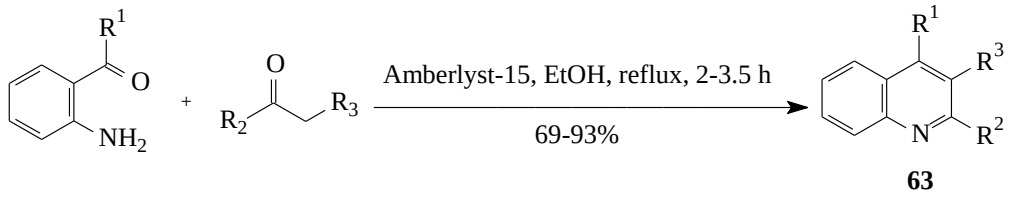
Scheme 35

15. Formation of Nitrogen Heterocycles

Nitrogen heterocycles form the backbone for a host of biologically active molecules. Quinoline[37a,b] and pyrazoline[38a-c] systems are known to be important constituents of many pharmaceutical and agrochemical products. Indoline-3-ones have been used for chromogenic detection of esterase activity.[39a,b] Acridine derivatives are interesting chemotherapeutic having antibacterial and antiparasite properties.[40] Calix[4]pyrroles are conformationally flexible macrocycles[41a] of significant importance due to their binding property with anions,[41b] neutral substrates[41c] and metal ions[41d] under different reaction conditions.These important nitrogeneous heterocycles have efficiently been synthesized using heterogeneous solid acid catalyst, Amberlyst-15.

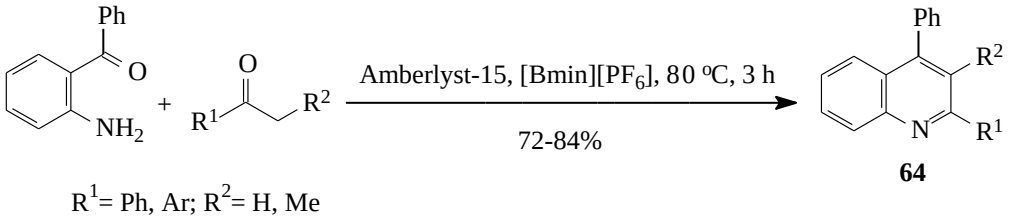
15.1 Synthesis of quinolines

A series of substituted quinolines **63** were synthesized by Das *et al*. from the reaction between 2-aminoaryl ketones and α-methylene carbonyl compounds using Amberlyst-15, a heterogeneous solid acid catalyst (Scheme 36).[42a] The catalyst was found to be most effective for the synthesis of quinolines in terms of reaction times, yields and reusability, over the other heterogeneous solid acid catalysts like $NaHSO_4$-SiO_2, H_2SO_4-SiO_2 and $HClO_4$-SiO_2.



Scheme 36

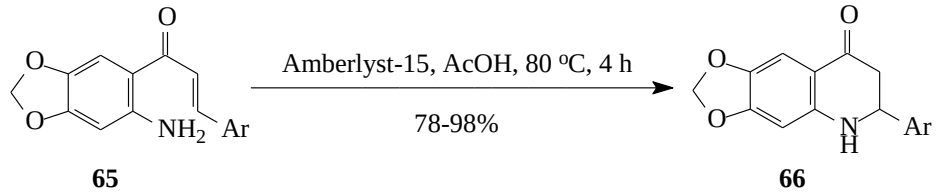
Hou and coauthors reported a simple and reliable method for the direct synthesize of quinolines **64** from 2-aminobenzophenone and arylketones in ionic liquid [Bimn][PF_6] using Amberlyst-15 as catalyst (Scheme 37).[42b]



R^1= Ph, Ar; R^2= H, Me

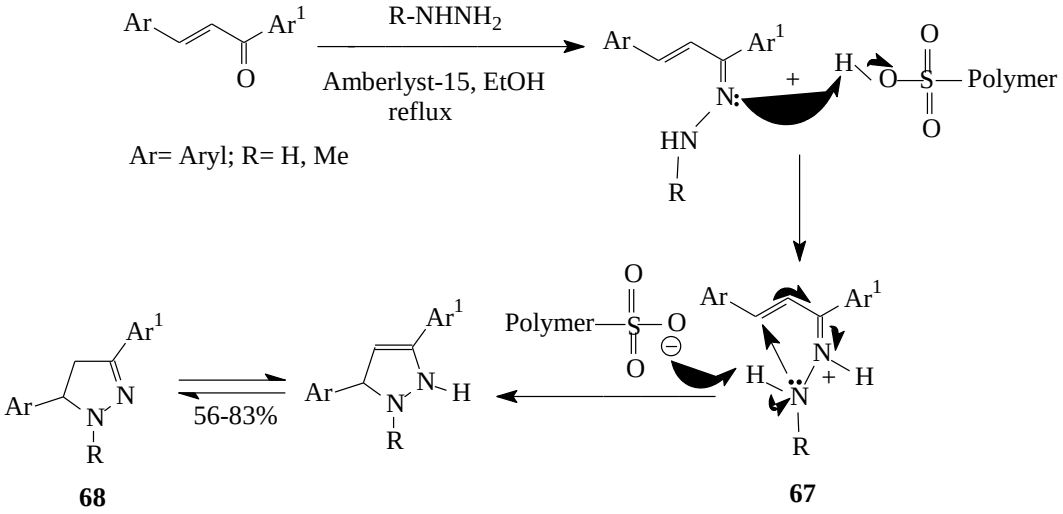
Scheme 37

Dioxoloquinolonone derivatives **66** were synthesized by Abonia and his groups using Amberlyst-15 as catalyst. When various 2'-amino[1,3]dioxolochalcones **65** were dissolved in acetic acid and stirred at 80 ºC in the presence of Amberlyst-15, the corresponding dihydroquinolin-8-ones were isolated in good to excellent yields (Scheme 38).[42c]



Scheme 38

15.2 Synthesis of pyrazolines

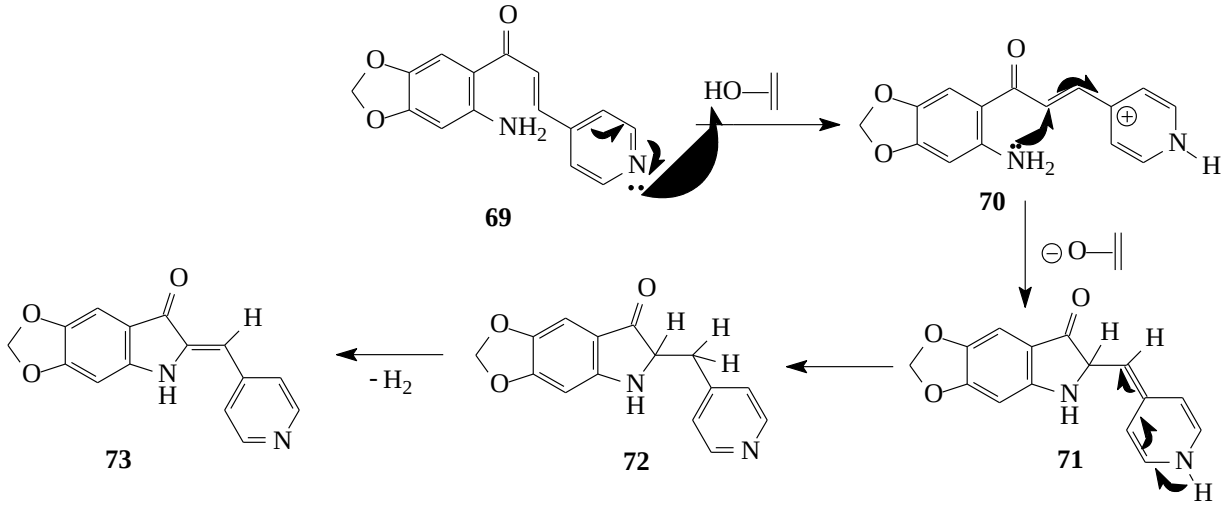


Scheme 39

Pyrazolines, a biologically active and an important constituent of many pharmaceutical and agrochemical products were synthesized by Hola and his groups using Amberlyst-15. Thus, when chalcones were treated with hydrazine or substituted hydrazines in presence of Amberlyst-15 in refluxing toluene the substituted pyrazolines **68** were produced in good yields (Scheme 39).[43] The proposed reaction mechanism involves a 5-*endo-trig* cyclization of the intermediate **67**.

15.3 Synthesis of indolin-3-ones

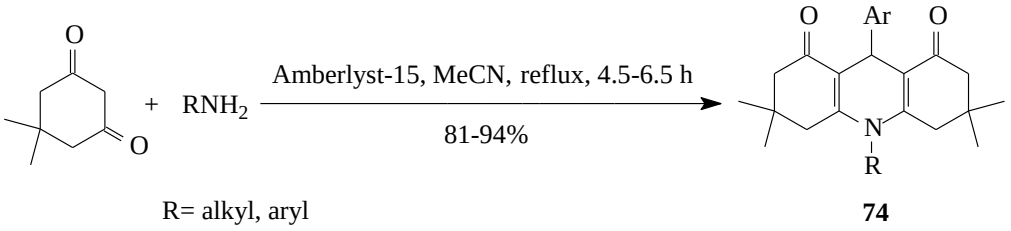
2'-Aminochalcone **69** derived from 4-pyridinecarboxaldehyde undergoes intramolecular cyclization in presence of Amberlyst-15/AcOH media. Unexpectedly, the reaction proceeded through a 5-*exo* process thus providing an alternative approach for the synthesis of 2-(pyridinylmethylene)indolin-3-one **73** (Scheme 40).[44] The key step is the formation of resonant species **70**, where the *ipso* carbon atom of the pyridine ring, rapidly acquire a positive charge after the protonation of the basic pyridine nitrogen atom. This species **70** is also stabilized via an exocyclic allylic type cation, which favors the 5-*exo* attack of the amino group towards the α-position of **70** producing the species **71** which rapidly tautomerizes to structure **72**. A subsequent dehydration of the intermediate **72** generated **73**.



Scheme 40

15.4 Synthesis of 1,8-dioxodecahydroacridines

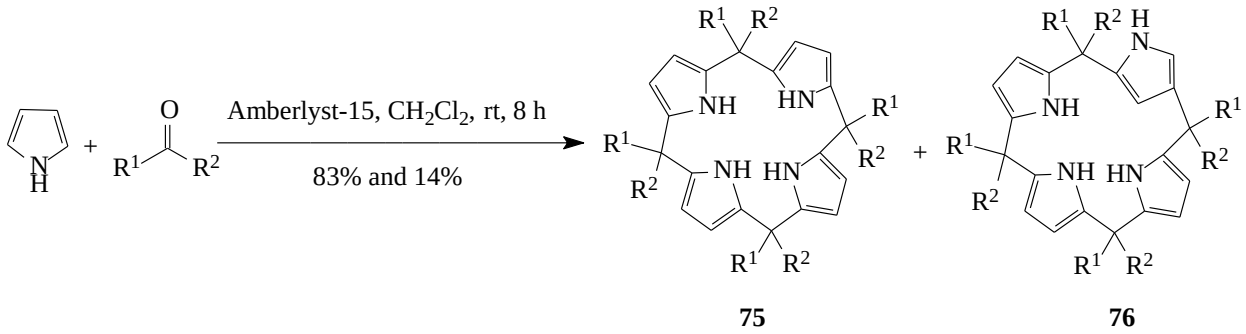
Das and co-workers have reported that Amberlyst-15 acts as an excellent catalyst for the synthesis of 1,8-dioxodecahydroacridines **74**, a class of tricyclic nitrogeneous heterocyclic compounds. When amines and 5,5-dimethyl-1,3-cyclohexedione were refluxed in CH_3CN in presence of Amberlyst-15 for a specified time, **74** was furnished in excellent yields (Scheme 41).[45] Aromatic and aliphatic amines underwent the conversion with same efficiency.



Scheme 41

15.5 Synthesis of calix[*4*]pyrroles

A facile and efficient protocol was reported by Chauhan *et al*. for the synthesis of calix[*4*]pyrroles **75,** and *N*-confused calix[*4*]pyrroles **76** in moderate to excellent yields by reaction of dialkyl or cycloalkyl ketones, catalyzed by Amberlyst-15 under eco-friendly conditions (Scheme 42).[46]



Scheme 42

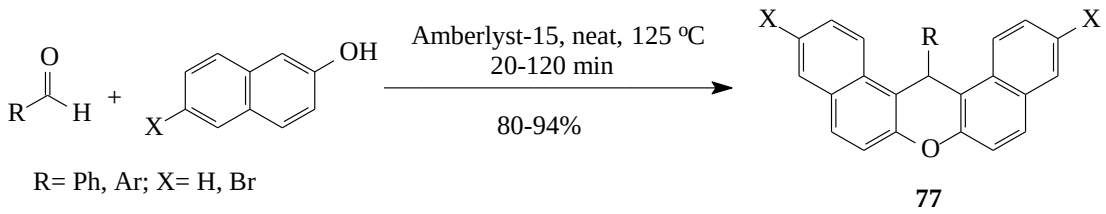
16. Formation of Oxygen Heterocycles

Oxygen heterocycles also represent a very important class of biologically active compounds. Xanthenes show antiviral, antibacterial activities,[47a,b] coumarins find applications as fragrances and pharmaceuticals.[48a,b] On the other hand benzopyrans form the backbone of many natural products and is also present in the recently discovered HIV inhibitory class of benzotripyrans.[49a,b] Moreover, theaspiranes form the aroma components in tea and functionalized furan derivatives are the structural moieties in many bioactive natural products and important

pharmaceuticals.[50a,b] These oxygen heterocycles may be synthesized by using Amberlyst-15 as catalyst.

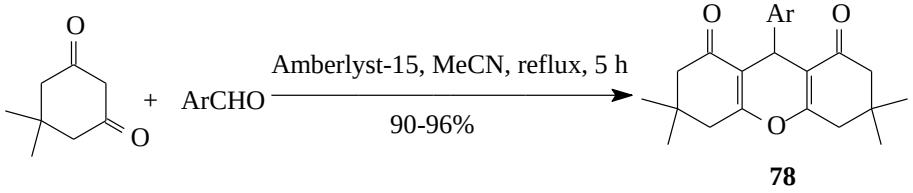
16.1 Synthesis of xanthenes

Ko and Yao developed a simple and reliable method for the direct construction of biologically active 14-substituted-14*H*-dibenzo[*a*,*j*]xanthenes **77** in high yield from a one-pot condensation of β-naphthol with aldehydes in presence of Amberlyst-15 under solvent-free conditions (Scheme 43).[51] The mechanism of this reaction includes the initial generation of the carbocation, followed by the formation of aryl- or alkyl-methanebisnaphthols, which then undergo dehydration to give the final product.



Scheme 43

Das *et al*. have demonstrated that Amberlyst-15 acts as an excellent catalyst for the synthesis of 1,8-dioxo-octahydroxanthenes **78**, a tricyclic oxygen heterocycle. When an aldehyde and 5,5-dimethyl-1,3-cyclohexedione were refluxed in CH_3CN in presence of Amberlyst-15 for specified time, **78** was furnished in excellent yield (Scheme 44).[45]

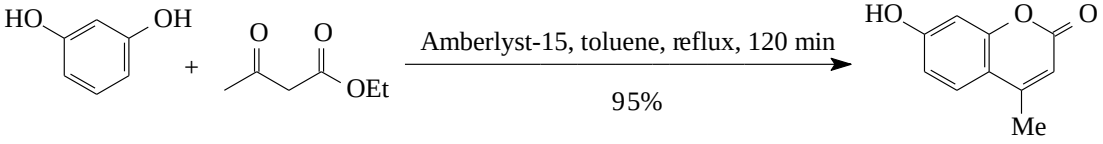


Scheme 44

16.2 Synthesis of coumarins

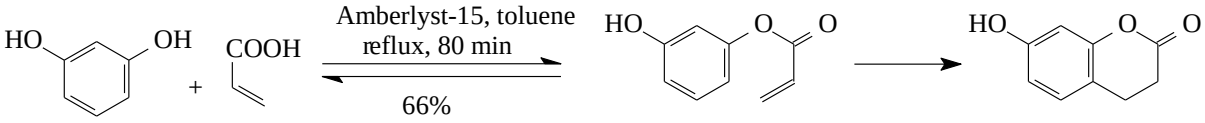
Sabou *et al*. worked on the synthesis of 7-hydroxy-4-methylcoumarin **79** *via* the Pechman reaction of resorcinol and ethyl acetate over various Amberlyst-type catalysts, such as Amberlyst-Cl, Amberlyst-15, Amberlyst-35, Amberlyst-36 and Amberlyst-S. Amongst these Amberlyst-15 afforded **79** with 95% conversion and 92% selectivity in refluxing toluene after 2 hrs. of reaction time at 120 ºC (Scheme 45).[52] However, the new catalysts, such as Amberlyst-Cl and Amberlyst-S materials showed better activity and were more stable than Amberlyst-15.

Amberlyst-15 catalyzed synthesis of 7-hydroxy-3,4-dihydrocoumarin from resorcinol and propenoic acid in toluene was reported by Gunnawegh *et al*. (Scheme 46).[53] The probable mechanism involves esterification followed by alkylation (ring closure) activated by Amberlyst-15.



79

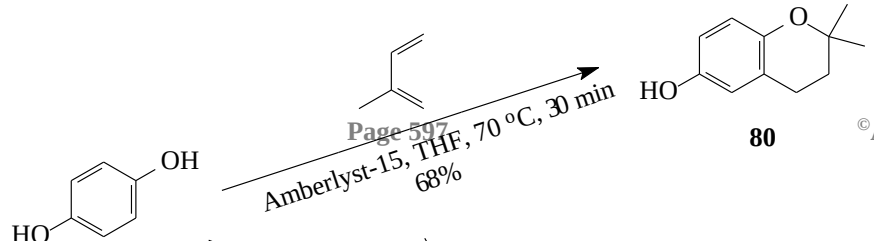
Scheme 45



Scheme 46

16.3 Synthesis of benzopyrans

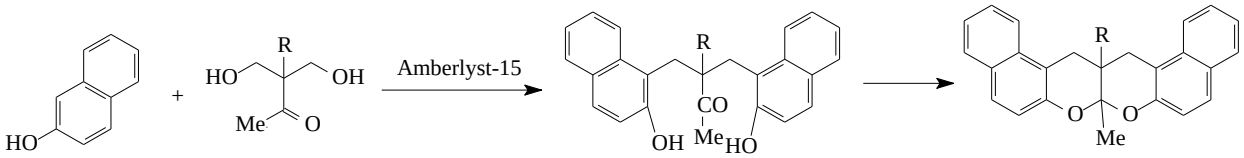
Kalena and his groups demonstrated that Amberlyst-15 has been utilized as solid acid catalyst for the synthesis of benzopyrans *via* prenylation of phenolics. 2,2-Dimethyl-6-hydroxychroman **80** and 2,2-dimethyl-6-hydroxychromene **81** were synthesized from the reaction of hydroquinone with 2-methyl-1,3-butadiene and 3-hydroxy-3-methylbut-1-yne respectively (Scheme 47)[54] using Amberlyst-15.



80

Scheme 47

Pyranopyran derivatives were synthesized by Talinli *et al*. using Amberlyst-15 in the reaction between 2-naphthol and dimethylol ketones **82** (Scheme 48).[55] The first step involves the production of ketodinaphthol **83** by condensation of 2-naphthol and **82**, which undergoes intramolecular acetalization reaction to afford the pyranopyran **84** in the second step.

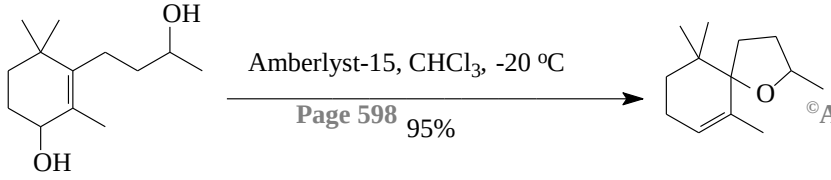


82 **83** **84**

Scheme 48

16.4 Synthesis of theaspirane

Young *et al*. demonstrated that the route for Amberlyst-15 catalyzed intramolecular oxaspiro-cyclization of secondary allylic alcohol **85,** can be applied to the synthesis of theaspirane **86**, an allylic oxaspirocycles, to give high yields of the product (Scheme 49).[56]

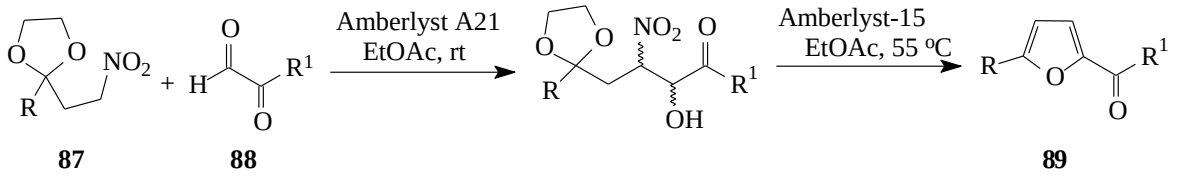


85 **86**

Scheme 49

16.5 Synthsis of furan derivatives

Amberlyst-15 has also been used for the synthesis of furan derivatives. Palmieri and his group have synthesized a series of disubstituted furan derivatives **89** from functionalized nitroalkane **87** with the aldehydes **88** in ethyl acetate using successive Amberlyst-A21 and Amberlyst-15 catalyzed processes (Scheme 50).[57]

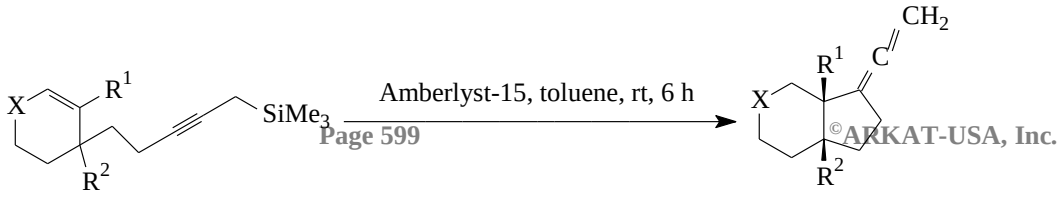


87 **88** **89**

Scheme 50

17. Synthesis of Homocyclic Compounds

Fused homocyclic compounds **91**, were also synthesized by using Amberlyst-15. Schinzer *et al*. reported that additions of propargylicsilanes **90** to enones or ene-ketones can be achived in a simple fashion using Amberlyst-15 (Scheme 51)[58]. A non-aqueous work-up and room temperature conditions makes this novel cyclization technique very attractive for sensitive cyclization substrates.



90 **91**

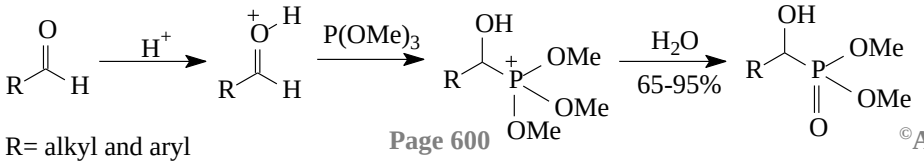
Scheme 51

18. Synthesis of Substituted Phosphonates

Phosphorus-carbon [P-C] bond formation reactions[59a-d] have drawn much interest in recent times. Substituted phosphonates such as α-hydroxy phosphonates,[60a,b] sulphonamido-phosphonates,[61a-c] and alkyl/aryl/heteroaryl phosphonates[62] are the pentavalent phosphorus compounds of considerable synthetic interest due to their utility as reagents in several reactions, and also for their applications in bioorganic and pharmacological fields.

18.1 Synthesis of α-hydroxy phosphonates

Tajbakhsh and coauthors have developed an efficient procedure for synthesis of α-hydroxy phosphonates **92** from aldehydes and trimethyl phosphite using Amberlyst-15 in water (Scheme 52).[63] Probably, the solid acid catalyst, Amberlyst-15 generates a hydronium ion in water that activates the carbonyl group, which consequently undergoes nucleophilic attack by trialkyl phosphite. Water was found to be the most appropriate solvent over the other organic solvents such as diethyl ether, CH_2Cl_2, $CHCl_3$, MeCN, THF and MeOH, in respect of yields.

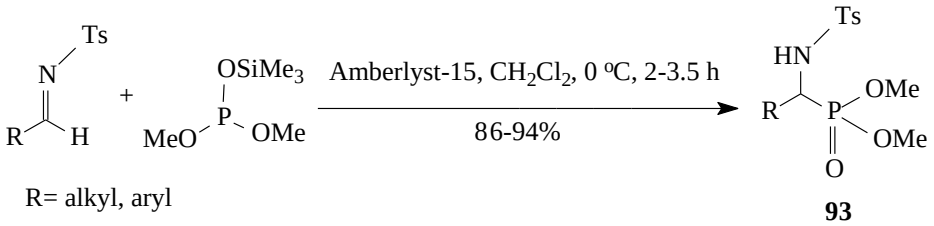


R= alkyl and aryl

Scheme 52

18.2 Synthesis of sulphonamido-phosphonates

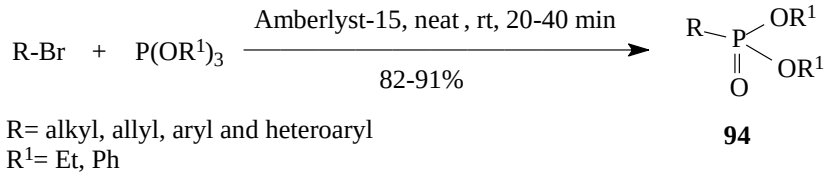
Very recently, Sudhakar and his group have reported the preparation of sulphonamido-phosphonates **93** from *N*-tosyl aldimines and dimethyl trimethylsilyl phosphate at 0 ºC in presence of Amberlyst-15 as a heterogeneous catalyst (Scheme 53).[64]



Scheme 53

18.3 Synthesis of alkyl/aryl/allyl/heteroaryl phosphonates

A new and convenient procedure for the synthesis of alkyl/aryl/allyl/heteroaryl phosphonates **94** using Amberlyst-15 under solvent-free conditions was developed by Kundu *et al.* (Scheme 54).[65] This solvent-free protocol is highly efficient and affords the product in excellent yields with high purity.



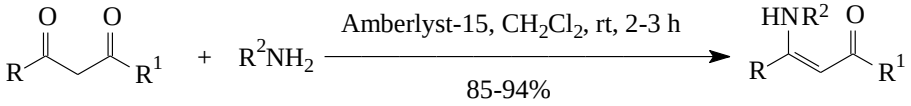
R= alkyl, allyl, aryl and heteroaryl
R^1= Et, Ph

94

Scheme 54

19. Synthesis of *β*-Enaminones and *β*-Enaminoesters

The β-enaminone derivatives are very useful synthons for the synthesis of various active heterocyclic compounds which exihibits a wide range of biological activities.[66a-d] Narsaiah *et al*. reported that Amberlyst-15 can be used for the synthesis of β-enaminones and β-enamino esters. Thus, when various β-keto carbonyls and β-keto esters were treated with different amines in presence of Amberlyst-15 at room temperature β-enaminones and β-enamino esters respectively were produced in excellent yields (Scheme 55).[67]



R= Me; R^1=Me, OEt, OBn

Scheme 55

20. Conclusions

This review demonstrates an active current interest in synthetic applications of Amberlyst-15 catalyst. This growing interest of Amberlyst-15 is mainly due to their very useful acidic properties, combined with benign environmental character, reusability and commercial availability. There has been a major surge of catalytic activity in several areas of the Amberlyst-15 chemistry. These areas include the application of Amberlyst-15 acid catalysts in various organic transformations such as formation of C-C, C-N, C-P and C-S bonds in different synthetically important compounds. We anticipate that these areas of Amberlyst-15 chemistry will continue to attract significant research activity in the future.

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Authors' biographical data

Rammohan Pal was born in 1978 in Kolkata, India. He obtained his B.Sc. in 1999 and M.Sc. in 2001 in Chemistry from University of Calcutta, India. He worked as a DBT-project fellow at the Biological Department of Chemistry, Indian Association for the Cultivation of Sciences (IACS), Kolkata and as a UGC-JRF at the Natural Product Laboratory, Indian Institute of Chemical Technology (IICT), Hyderebad, India. He carried out his predoctoral research work at the Department of Chemistry, Jadavpur University under the supervision of Prof. Asok Kumar Mallik. He received his Ph.D. degree in 2011 from Jadavpur University on synthesis and reactions of some nitrogen heterocycles. He has published over 13 scientific papers. His current research interests cover the development of synthetic methodology, green chemistry and synthesis of heterocyclic compounds. Presently, he is an Assistant Professor of Organic Chemistry at the Acharya Jagadish Chandra Bose College, Kolkata, India.

Taradas Sarkar received his B.Sc. and M.Sc. in Chemistry from the Burdwan University, India. He carried out his predoctoral research work at Bose Institute, Kolkata on the biophysical study of structure-function relationships of tubulin, a microtubular protein and received his Ph.D. in 2004 from Jadavpur University, Kolkata. His postdoctoral work at NCI-Frederick, NIH, Maryland (2006-2008) was primarily on biophysical and cell biological studies for preliminary screening of antimitotic drugs. He has published over 15 scientific papers in leading international journals. Presently, he is an Assistant Professor of Physical Chemistry at the Acharya Jagadish Chandra Bose College, Kolkata, India.

Shampa Khasnobis completed her B.Sc. in 1991 and M.Sc. in 1993 from University of Calcutta, India. Her predoctoral research work at the Department of Chemistry, Bose Institute, Kolkata was primarily based on synthesis and reactions of nitrogen and oxygen heterocycles. She received her Ph.D. degree from Jadavpur University in 2001. Her postdoctoral work at the Department of Microbiology, Colorado State University, Fort Collins, USA was mainly on synthesis and biological assay of bacterial polysachharides as a part of antituberculosis drug research. She has published over 12 scientific papers in journals of international repute. Presently, she is working as an Assistant Professor of Organic Chemistry at the Acharya Jagadish Chandra Bose College, Kolkata, India.

