Perfluorinated resin-sulfonic acid (Nafion-H): an efficient, environment friendly and recyclable heterogeneous catalyst for the one-pot multicomponent synthesis of β-acetamido ketones

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Abstract
Multi component condensation of an aryl aldehyde, acetyl chloride, acetonitrile and enolisable ketone in presence of Nafion-H, as an efficient, environment friendly heterogenous and recyclable catalyst for the one-pot synthesis of β-acetamido ketones in high yields is described.

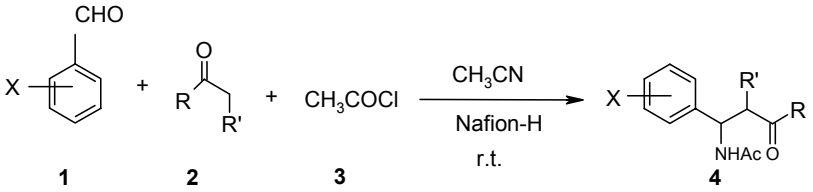
Keywords: Acetonitrile, acetophenones, acetyl chloride, aromatic aldehydes, Nafion-H, β-acetamido ketones

Introduction

β-Acetamido ketones are considered as versatile intermediates as their basic skeleton exist in a number of biologically or pharmacologically important compounds.[1,2] These compounds are also useful in the synthesis of other important organic molecules like 1,3-amino alcohols [3, 4] units common in natural nucleoside peptide antibiotics, e.g., nikkomycines or neopolyoxins.[5,6] Synthetic strategies based on one-pot multicomponent reactions overriding the conventional linear type synthesis and considered as powerful tools in the modern drug discovery process.[7] Earlier reports on the synthesis of β-acetamido ketones through multi component reactions is mainly using catalysts like $CoCl_2$,[8] montmorillonite K10 clay, [9] $BiCl_3$,[10] silica sulphuric acid,[11,12] and solid acid Hβ-zeolite.[13]

The interest is continuously growing in recent years on the use of eco-friendly and recyclable catalysts due to environmental legislations. Perfluorinated resin sulfonic acid (Nafion-H)[14] an acid catalyst extensively used for alkylation's,[15] acylation,[16] nitration,[17] acetal synthesis[18] and in Diels-Alder reaction.[19] The Nafion-H catalyst, an insoluble resin is inert to corrosive environments, stable up to 201 ^{0}C, easy to recover and to reuse. Nafion-H is used as a catalyst for multi component condensation reaction for the first time and found to be an efficient catalyst to obtain β-acetamido ketones under mild conditions.

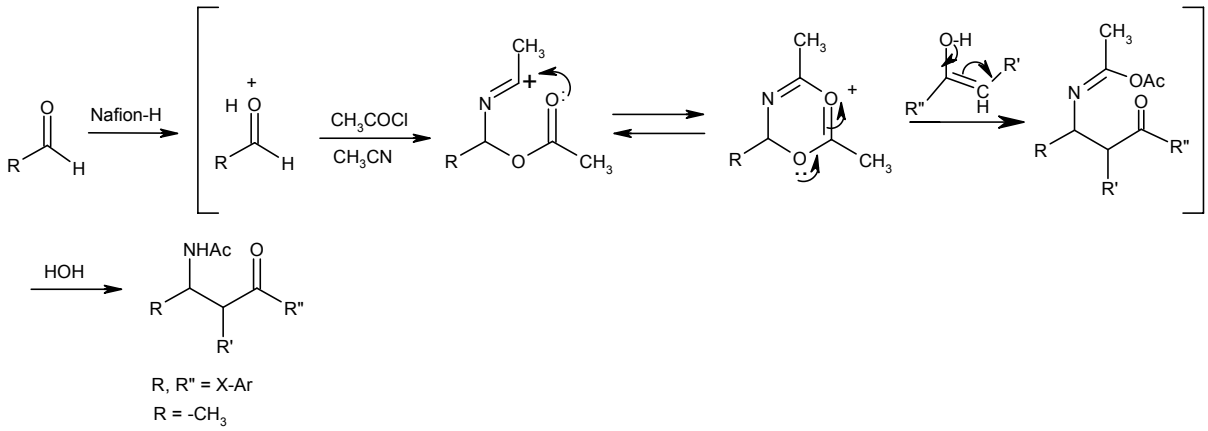
IICT Communication No. 050814



Scheme 1. Nafion-H catalysed synthesis of β-acetamido ketones.

Results and Discussion

In a typical reaction, the enolisable ketone (acetophenone) was reacted with various aldehydes in presence of acetyl chloride in acetonitrile medium using Nafion-H as catalyst. The catalyst is the source of protons which protonates aldehyde and acetonitrile to form a six membered intermediate. Subsequently, the enolisable ketone attacks methine carbon and give β-acetamido ketones. The probable mechanism for sequence of reactions [8,10, 12] is represented in Scheme 2.



Scheme 2

The role of substituents in phenyl ring of aldehyde and in CH_3 of ketone on rate of reaction and yield of products is studied in detail. It is found that the reaction is smooth in almost all the cases irrespective of substituent used. Similarly reactions with aliphatic aldehydes, aliphatic ketones and also nitriles than acetonitriles were independently tried and found to be no reaction.

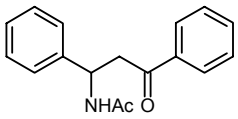
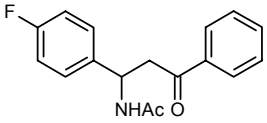
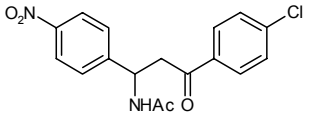
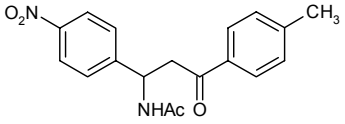
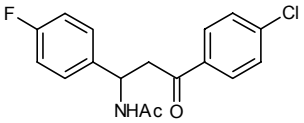
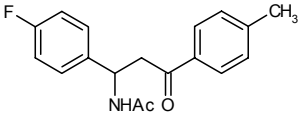
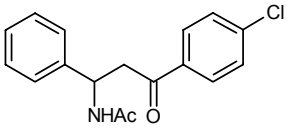
The catalyst is recovered and recycled with different proportions five times for entry 1 (Table 2) and found to have no loss of activity. In case of entry 1, the reaction is up scaled to 5 m moles with 94% yield. The results are tabulated in Table 1

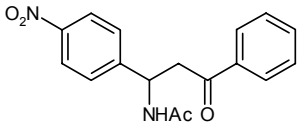
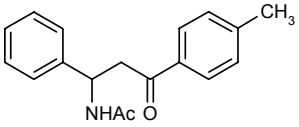
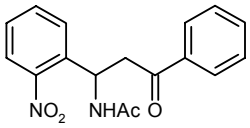
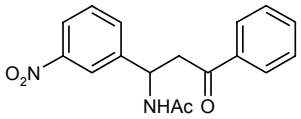
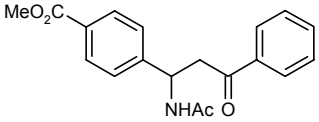
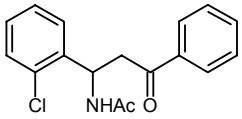
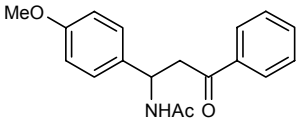
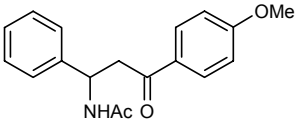
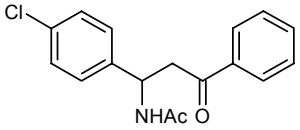
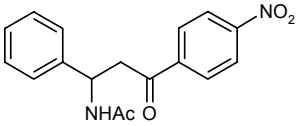
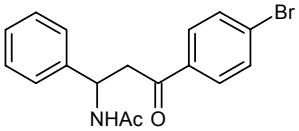
Table 1. Recycling of Nafion-H for entry – 1 (Table 2)

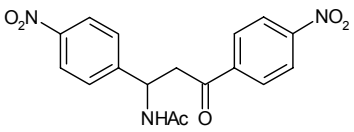
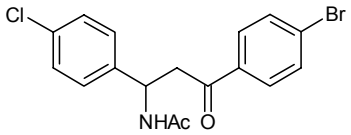
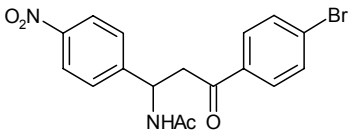
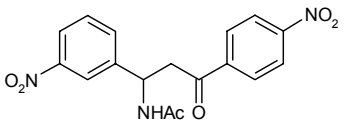
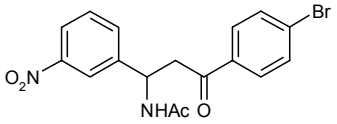
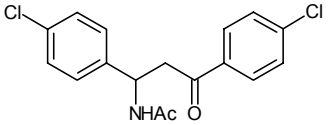
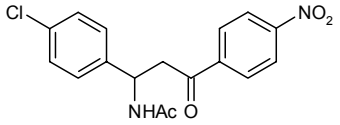
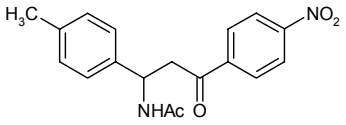
No. of cycle	Aldehyde (m.mol.)	Wt. of catalyst (mg)	Yield (%)
1st	1.00	500	90
2nd	1.00	488	88
3rd	1.00	483	87
4th	1.00	472	85
5th	1.00	465	85

The number of compounds prepared have been tabulated in Table 2.

Table 2. Reaction of substituted acetophenones with various aryl aldehydes

Entry	β-acetamido ketone	Yield (%)[a]	Time (h)	mp, °C (Lit)[R]
1		96	4	102-104 (104-106)[10]
2		95	6	110-112 (109-111)[12]
3		91	8	123-125 (125-127)[12]
4		85	6	-
5		93	5	109-111 (108-110)[12]
6		89	4	102-104 (104-106)[12]
7		92	3.5	115-117 (114-115)[12]

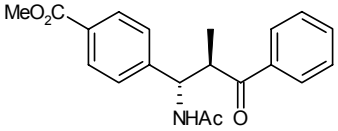
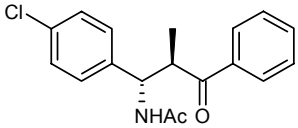
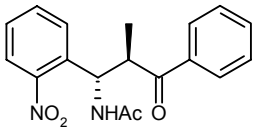
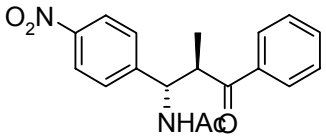
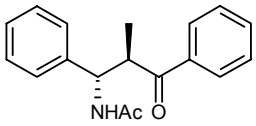
8		89	4.5	150-151 (148-149)[9]
9		90	4	119-121 (121-123 [12]
10		92	8	188-190 (190-191)[11]
11		79	5.5	114-116 (112-115)[10]
12		78	7	(236-237)[8a]
13		91	4.5	132-134 (135-136)[9]
14		90	3	106-108 (109-111)[13]
15		92	2.5	130-131 (128-130)[10]
16		95	2.5	147-148 (146-148)[11]
17		86	5.5	118-120[11]
18		96	3.5	143-145 [11]

19		84	6	221-223[11]
20		93	4	125-127[11]
21		95	5	182-183[11]
22		85	7	198-200[11]
23		91	5.5	153-155[11]
24		95	4	139-142 (141-143)[11]
25		89	5	139-142[11]
26		83	4.5	115-117[11]

[a] Isolated yields.

Similarly propiophenone (α-substituted enolisable ketone) is reacted with various aromatic aldehydes under given conditions resulted two diasteriomeric products in definite proportions. In all the cases anti isomer is formed in major quantity. The ^{1}H NMR pattern is interesting in that in a specific example of entry 3 (table 3) shows a doublet of doublet for CHCO proton with coupling constant values (J) 7.7 Hz for syn isomer and 13.7 Hz for trans isomer.The products are tabulated in table **3.**

Table 3. Reaction of propiophenone with various substituted aryl aldehydes

Entry	β-acetamido ketone	Syn:anti [a]	Yield (%)[b]	Time (h)	mp, ^{0}C (Lit) [R]
1		32:68	82	6	236-238[8a]
2		35:65	89	6.5	151-153[8a]
3		40:60	81	7	120-122 (122-124)[9]
4		30:70	84	6.5	133-135[8b]
5		40:60	96	3	140-142 (140)[9]

[a] Ratio of syn and anti isomers is estimated with ^{1}H NMR for methine proton (CHCO) based on coupling constants. [b] Isolated yields.

In conclusion, we have developed an efficient method for the preparation of β-acetamido ketones using an environment friendly heterogeneous catalyst. The recycle of catalyst and versatility of reaction is established.

Experimental Section

Typical procedure for the preparation β-acetamido ketones

To a stirred mixture of Nafion-H (500mg), aldehyde (1mmol), enolisable ketone (1mmol) in acetonitrile (4mL) acetyl chloride (3mL) was added. The reaction mixture was stirred at room temperature for 2.5-8h. After completion of reaction (as monitored by TLC using precoated silica gel 60 F_{254} (Merck); spots were visualized with UV light.), the reaction mixture was filtered, diluted with ethyl acetate and washed with brine solution. The separated organic layer was dried over Na_2SO_4 , concentrated and the residue was purified by column chromatography

on Silica gel It was purified by the column chromatography using 100–200 mesh silica gel(Merck) as stationery phase and ethylacetate–n-hexane (35 : 65) as eluents. Representative examples are given below.

***N*1- [1-(4-Fluorophenyl)-3-(4-methylphenyl)-3-oxopropyl] acetamide (**entry 6, Table 2**).** Mp 104-106 ^{0}C, ^{1}H NMR ($CDCl_3$ +DMSO(d_6), 200 MHz): δ 1.90 (s, 3H, CH_3), 2.40(s, 3H, CH_3), 3.30 (dd, J = 7.8 & 19.0Hz, 1H, CH_2), 3.58 (dd, J = 4.8 & 18.2Hz, 1H, CH_2), 5.40 (q, 1H, methyne H), 6.90-7.05 (m, 2H, aromatic H), 7.20-7.40 (m, 4H, aromatic H), 7.80 (d, J = 12.1Hz, 2H, aromaticH), 8.05 (d, 1H, NH). IR (KBr): 3290, 3065, 2958, 2362, 1688, 1646, 1546, 1367, 1202, 758, 685 cm.,$^{-1}$ MS m/z: 299 (M^+), 257, 191, 119, 43.

***N*1- [(1*S, 2R*)-2-Methyl-1- (2-nitrophenyl) 3-oxo-3-diphenylpropyl] acetamide** (entry 3**,** Table 3). Mp 122-124 ^{0}C. ^{1}H NMR ($CDCl_3$ + DMSO (d_6), 300 MHz): δ 0.87 (d, J = 7.0 Hz, 3H, CH_3), 1.56 (s, 3H, CH_3), 3.98- 4.13 (m, 1H, -CH-N), 5.67 (dd, J = 7.7 and 13.7 Hz, 1H, -CH-CO), 7.30- 7.80 (m, 7H, aromatic H), 7.97-8.14 (d, J = 6.8Hz, 1H, aromatic H), 8.44 (d, J = 7Hz, 1H, aromatic H). IR (KBr): 3264, 3058, 1979, 1646, 1527, 1454, 1354, 1295, 970, 711 cm.$^{-1}$MS m/z: 327 (M + 1), 280, 266, 237, 211, 193, 177, 133, 120, 105.

Acknowledgements

The authors are thankful to Dr. J. S. Yadav, Director, IICT, and Shri S. Narayan Reddy, Head, Fluoroorganic Division, IICT, Hyderabad for their constant encouragement and financial support from the industry-sponsored project.

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