Regio- and stereoselective syntheses and cycloadditions of substituted 2*H*-pyran-2-ones and their fused derivatives

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Abstract

Microwave-assisted conditions have been shown to be very efficient for the synthesis of a variety of compounds containing 2*H*-pyran-2-one skeleton that plays important roles in nature and in synthetic chemistry. Furthermore, such compounds (especially those incorporating a 3-acylamino group) were shown to be efficient partners for the Diels–Alder reactions with a variety of dienophiles including acetylene derivatives, maleic anhydride, substituted maleimides, vinyl-moiety-containing dienophiles, as well as (*Z*)-1-methoxybut-1-en-3-yne. Reactions were carried out under conventional thermal conditions, microwave irradiation and under high pressure (13–15 kbar) and resulted in a plethora of different product types: anilines, bi- and terphenyls, indoles, isoindoles, 2-oxabicyclo[2.2.2]oct-5-enes and bicyclo[2.2.2]octenes. Many of the transformations showed remarkable regio- and stereoselectivity, depending primarily on the substitution patterns of the reactants and reaction conditions applied.

Keywords: Diels–Alder reactions, microwave-assisted synthesis, bicyclo[2.2.2]octenes, cyclohexadienes, indoles, anilines

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6. References
1. Introduction

2*H*-Pyran-2-ones and their fused derivatives are well-represented structural units of a variety of natural products,[1] their synthetic analogs and many other compounds not having natural counterparts, but nevertheless in many cases exhibiting important biological activity. Furthermore, due to their multifunctional character they display a plethora of potential applications in organic synthesis.[2] For example, a recent report by Lee *et al*.[3] shows a promising *in vitro* anticancer activity for 6-substituted-4-amino-2*H*-pyran-2-ones (APO) representing a simplified version of the tanshinlactones, which were shown to be even more potent against the ER+ human breast cancer cell lines than the tamoxifen citrate. In 2009 Cardellina II and co-workers isolated[4] (*R*)-rugulactone from the plant *Cryptocarya rugulosa*, possessing 5,6-dihydropyran-2-one skeleton and inhibiting nuclear factor κB activation pathway that is active in many types of cancers. (*R*)-Rugulactone and both epimers of its 4-hydroxy analog have been recently prepared *via* a stereoselective synthesis by employing proline-catalyzed α-aminooxylation, Sharpless epoxidation and Mitsunobu reaction as chirality introducing steps.[5] 3,4,6-Triaryl-2*H*-pyran-2-ones and their analogs exhibited high *in vitro* ability to inhibit the cyclooxygenase isozymes COX-1 and COX-2.[6] This inhibition is important when treating inflammatory diseases such as rheumatoid arthritis and osteoarthritis. Development of selective COX-2 inhibitors has furthermore brought significant advances in the treatment of colon, breast and prostate cancers.
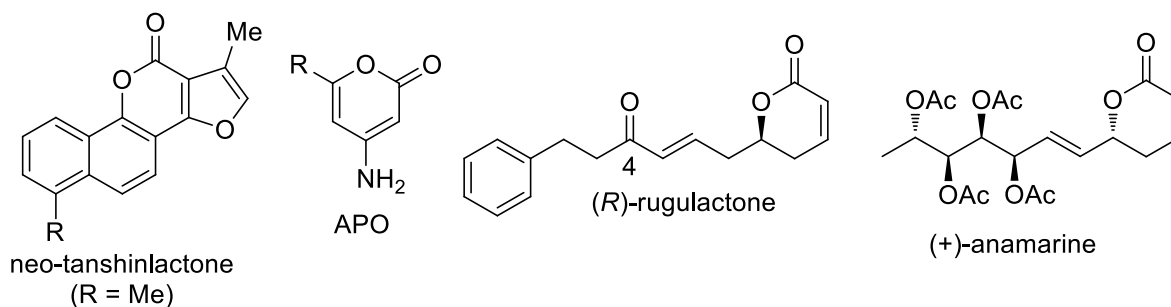

Anamarine, a polyoxygenated natural product isolated from the flowers and leaves of a plant from the genus *Hyptis*, was often a target of various synthetic approaches. Recently both enantiomers were prepared: (–)-anamarin was synthesized from D-tartaric acid *via* β-keto phosphonate intermediate derived from the tartaric acid amide,[7] whereas (+)-anamarin was obtained by a cross-metathesis strategy starting from but-3-en-1-ol and glycidol additionally involving Sharpless asymmetric epoxidation, dihydroxylation and deoxygenation-isomerization through allene rearrangement.[8] In the latter synthesis, published by Kumar and Reddy,[8] the formation of the 2*H*-pyran-2-one ring was achieved by a lactonization of a 5-hydroxyester **1** (PMBO = *p*-methoxybenzylether) with the use of an acid as the catalyst (*p*-toluenesulfonic acid) yielding the cyclic intermediate that in three further steps provided the crucial vinyl lactone

building block **2** (Scheme 1). The former synthesis of (–)-anamarin developed by Prasad and Penchalaiah[7] relied upon a ring-closing metathesis effected by the first-generation Grubbs catalyst, as described in the case of the preparation of (–)-spicigerolide and (+)-dodoneine (see chapter 2 and Scheme 8).
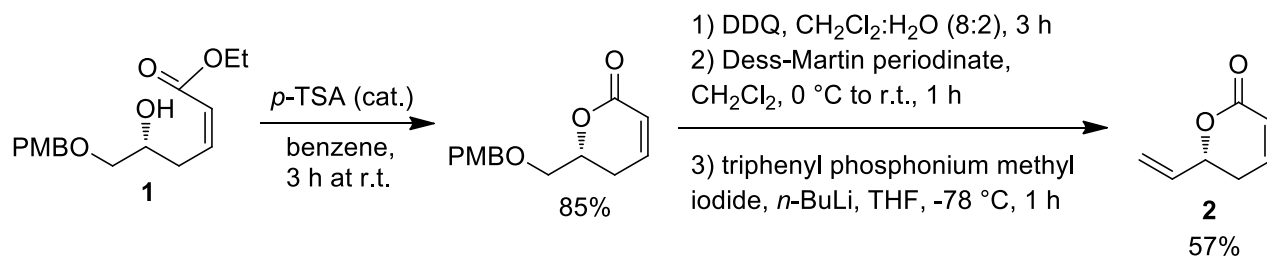
Scheme 1

Lam, Hua and Wu with co-workers[9] have recently reported promising cytotoxicity against human non-small-cell lung carcinoma cell lines of various polyene derivatives (the best two cases having IC$_{50}$ values of 0.6 and 0.01 μM). All of the compounds synthesized and investigated were of the gymnoconjugatin, auxarconjugatin and isorumbrin classes (of the general structure **3**) and all posses a tetraene chain containing a substituted pyrrole ring on one end, with the other end of the chain attached to the position 6 of a substituted 2*H*-pyran-2-one ring.
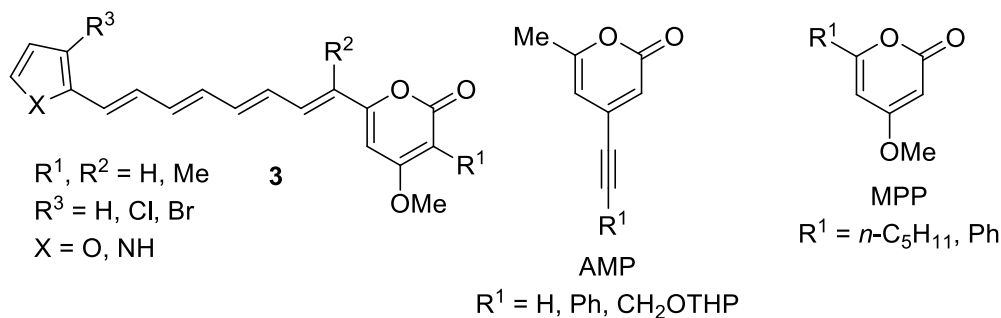

It was also demonstrated that 4-alkynyl-6-methyl-2*H*-pyran-2-ones (AMP) efficiently inhibit the growth of A2780 human ovarian carcinoma and K562 human chronic myelogenous leukemia cell lines at the micromolar level.[10]

Substituted 4-methoxy-6-pentyl-2*H*-pyran-2-one (MPP, R^1 = *n*-C$_5$H$_{11}$) derivatives were found to be produced by the fungus *Pestalotiopsis guepinii* that is the causal agent of the so-called "twig-blight", one of the most serious diseases of hazelnut trees (*Corylus avellana*) in Turkey and consequently one of the main causes of yield loss.[11] 4-Methoxy-6-phenyl-2*H*-pyran-2-one (MPP, R^1 = Ph) was found in the inedible bitter tooth mushroom (*Sarcodon scabrosus*).[12] All these cases vividly illustrate the importance of 2*H*-pyran-2-ones and the need for research in the field of their transformations.

2. Syntheses of 2*H*-Pyran-2-ones

There are many possible ways for the synthesis of 2*H*-pyran-2-ones **4**, one of the more traditional ones can be retrosynthetically represented as the hydrolysis of the ester bond in the lactone ring, therefore as the starting material offering hydroxyacid **5** or its tautomeric form **5'** (Scheme 2).[13]
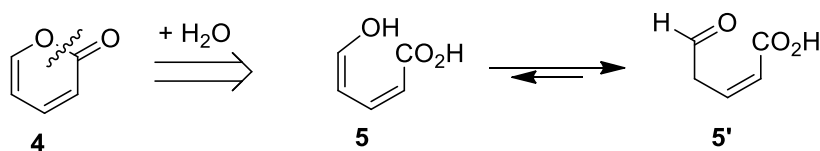
Scheme 2

Such a direct approach was recently applied in the case of the synthesis of (+)-dodoneine, isolated from *Tapinanthus dodoneifolius*, a parasitic plant growing on the sheanut trees in West Africa and exhibiting a vasorelaxant effect on preconstricted rat aortic rings. The final step of the synthesis is the construction of the dihydro-2*H*-pyran-2-one ring executed in two steps *via* the generation of a *Z*-configured α,β-unsaturated ester **6** followed by an acid-catalyzed intramolecular transesterification (lactonization) to yield (+)-dodoneine (Scheme 3).[14]
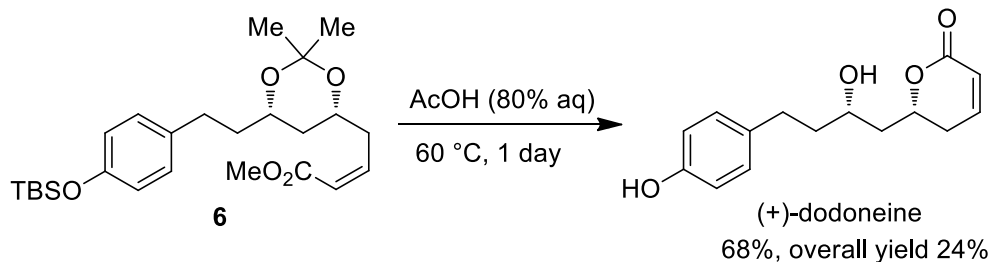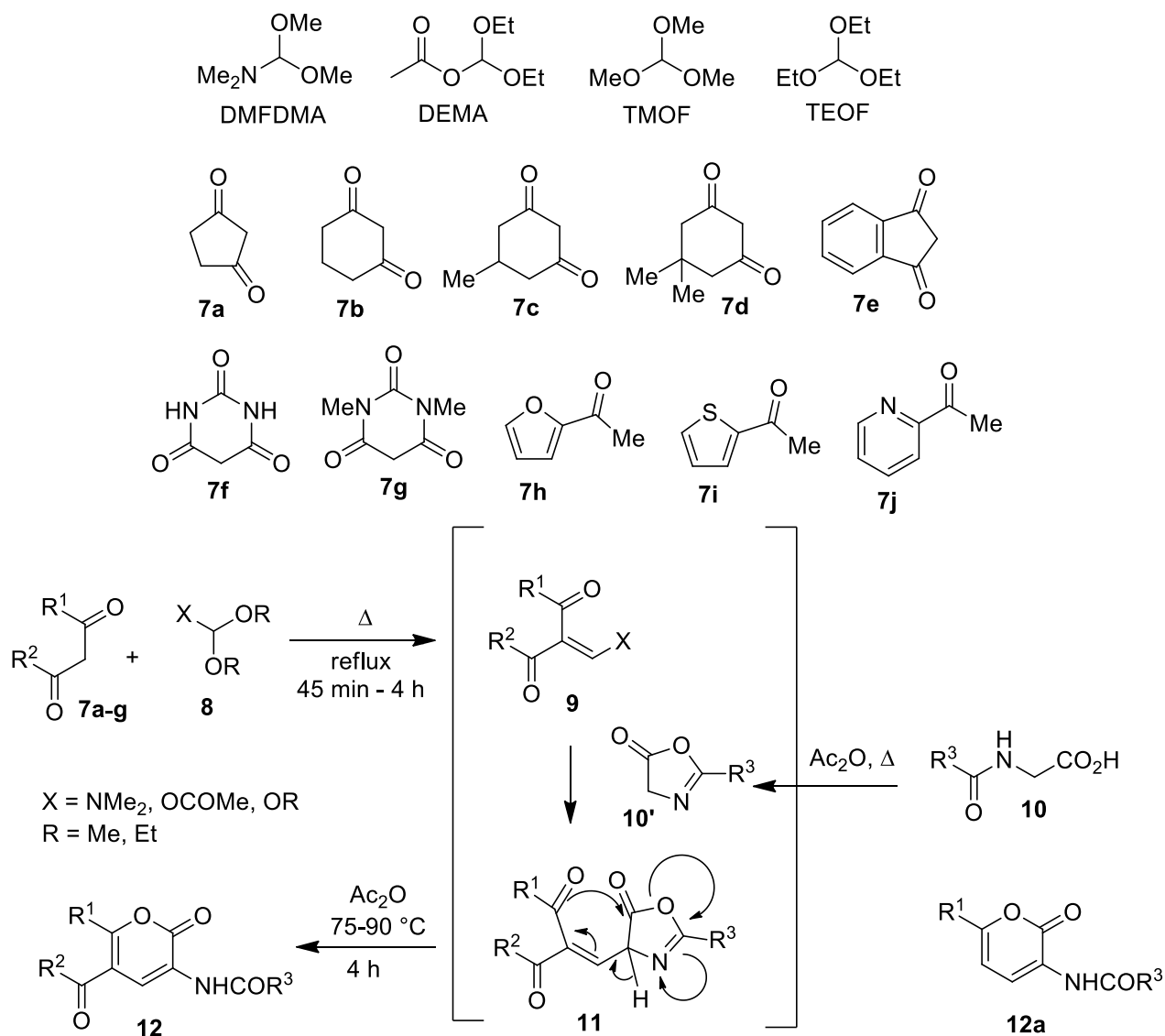
Scheme 3

Similarly, intramolecular translactonization of 4-hydroxy-6-methyl-2*H*-pyran-2-one and 4-hydroxycoumarin enabled the synthesis of substituted coumarin derivatives under conventional (reflux) conditions and under microwave irradiation.[15,16]

However, for the practical purposes in many cases a far more efficient way toward pyran-2-one derivatives is desirable. One such approach is represented by a one-pot synthesis starting from *N*-acylglycine **10**, an appropriate C$_1$-synthon **8** (such as *N,N*-dimethylformamide dimethyl acetal (DMFDMA), diethoxymethyl acetate (DEMA), trimethyl orthoformate (TMOF) or triethyl orthoformate (TEOF)) and a compound **7** possessing an active methylene group, such as acyclic 1,3-diketones, β-ketoesters, cyclic 1,3-diketones (cyclopenta-1,3-diones (**7a**), cyclohexa-1,3-diones (**7b**), 5-methylcyclohexane-1,3-dione (**7c**), 5,5-dimethylcyclohexane-1,3-dione (**7d**)),

cyclic 1,3-dioxo compounds (indane-1,3-dione (**7e**)) or heterocyclic 1,3-dioxo compounds (barbituric acid (**7f**) and 1,3-dimethylbarbituric acid (**7g**)).[17] This is a two-step procedure, where in the second step the intermediate **9** reacts with *N*-acylglycine in its cyclic oxazolone form **10'** yielding the intermediate **11** which is transformed into the final 2*H*-pyran-2-one derivative **12** (Scheme 4). These syntheses are generally conducted at elevated temperatures (conventional heating in an oil bath or reflux) in acetic anhydride, however there was also some promising development in the application of microwaves for this purpose.[18] This approach is in certain cases applicable even when the methylene group of **7** is less activated, i.e. not possessing two adjacent carbonyl groups, but only one; such were the cases where acetone, 2-acetylfuran (**7h**), 2-acetylthiophene (**7i**), 2-acetylpyridine (**7j**) etc. were used instead of **7a**–**g**, yielding 5-unsubstituted 2*H*-pyran-2-ones **12a**.[17f,g,18]
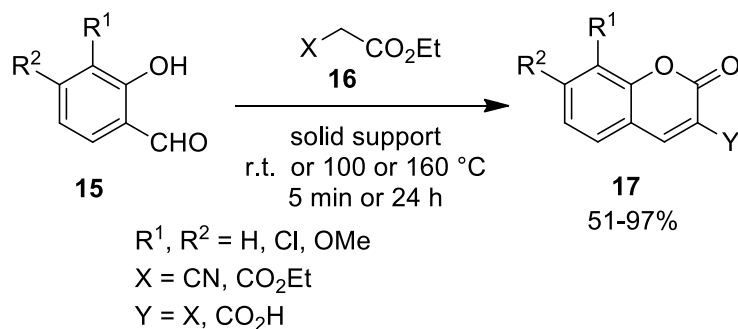
Scheme 4

Boháč and co-workers[19] have recently published a useful synthesis of 2*H*-chromen-2-one derivatives **14** starting from 4-substituted 2-hydroxybenzaldehydes **13**, succinic anhydride and sodium succinate under microwave irradiation (250–500 W, 18–50 min) (Scheme 5). The authors report that the microwave-assisted transformations proceed more smoothly and that they provide better yields than those carried out by conventional heating (where 1.5–5 h were necessary).

R OH CHO
13

→ sodium succinate, MW (250-500 W), 18-50 min →

R O O CO₂H
**14**
31-61%

+ side products (dimerization)
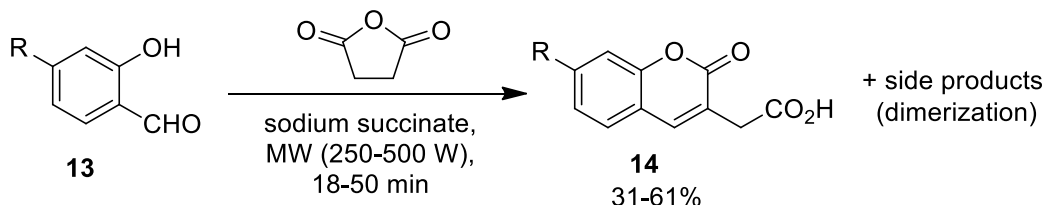
Scheme 5

2*H*-Chromen-2-one derivatives **17** were also prepared by a Knoevenagel condensation of suitable carbonyl compounds (substituted 2-hydroxybenzaldehydes **15**) and active methylene derivatives in the presence of inorganic supports (on alumina at room temperature, or on KSF clay at 100 or 160 °C); in some cases in addition to the condensation also the hydrolysis of one CO₂Et group of the starting material **16** occurred (Scheme 6).[20]

R¹ R² OH CHO
15

X CO₂Et
16

→ solid support r.t. or 100 or 160 °C 5 min or 24 h →

R¹ R² O O Y
17
51-97%

R^1, R^2 = H, Cl, OMe
X = CN, CO₂Et
Y = X, CO₂H

Scheme 6

A novel synthetic approach toward dihydro-2*H*-pyran-2-one **21** was described by Nair and co-workers proceeding *via* a homoenolate annulation between 4-methoxycinnamaldehyde (**18**) and methyl vinyl ketone (**19**) in THF at room temperature (Scheme 7). It was found that this synthesis is more efficient upon the addition of ionic liquid 1,3-bis(methanesulfonyl)-imidazolium chloride (**20**) (15 mol%) and application of DMAP (4-dimethylaminopyridine) or DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as the base (20 mol%).[21] The result was somewhat

surprising as the homoenolate annulation of α,β-unsaturated ketones (chalcones) in other cases provided substituted cyclopentenes.
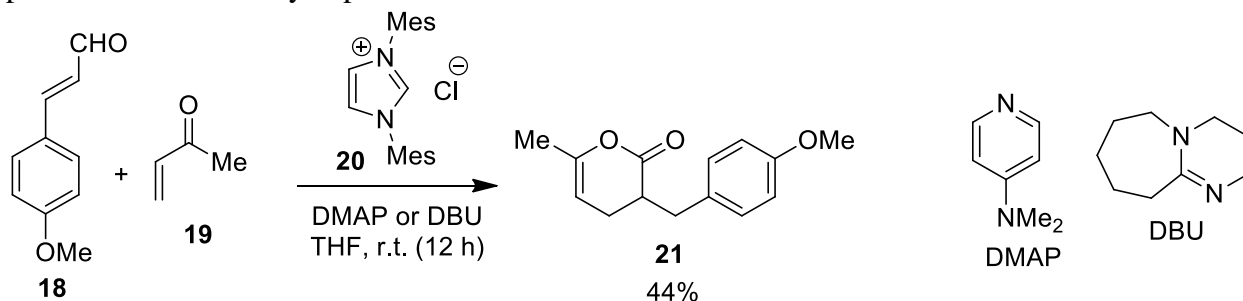
Scheme 7

An interesting approach to the preparation of a 2*H*-pyran-2-one ring was recently demon-strated in the case of the synthesis of (–)-spicigerolide (**23**), a natural product isolated from the plant *Hyptis spicigera*, which was used in traditional Mexican medicine to treat gastrointestinal disturbances, skin infections, wounds and insect bites. The final step of the synthesis consists of a ring-closing metathesis of **22** effected by the second-generation Grubbs ruthenium catalyst (2 mol%) (Scheme 8).[22] Similar approach, albeit with the application of the first-generation Grubbs catalyst, was applied by Falomir, Marco and co-workers for the synthesis of (+)-dodoneine.[23]
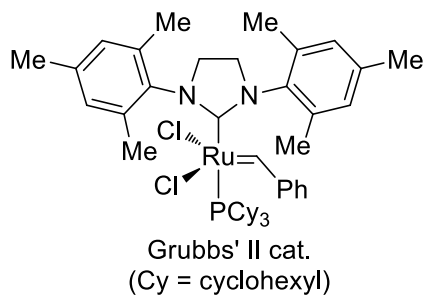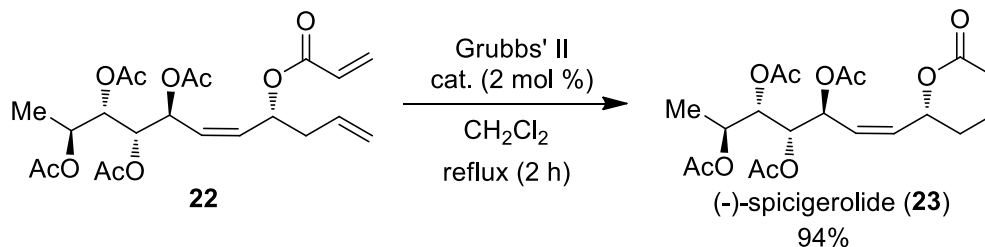
Scheme 8

3. Diels–Alder Reactions with 2*H*-Pyran-2-ones

Even though 2*H*-pyran-2-ones[2] **24** are somewhat aromatically stabilized, they are appropriate diene components in a variety of Diels–Alder reactions. Due to slightly different reaction pathways, one has to distinguish between two general versions of the cycloadditions taking place on **24** (or their fused derivatives): with alkynes **25** or with alkenes **28** as dienophiles.[16f] In the former case, the molecule of the alkyne **25** (groups R^5 could be different) acting as the dienophile is in the first reaction step cycloadded to the 2*H*-pyran-2-one diene system **24** therefore yielding a 2-oxabicyclo[2.2.2]octa-5,7-diene-3-one **26** (Scheme 9). Such adducts (**26**) contain a CO_2 bridge, which is eliminated in a very facile retro-hetero-Diels–Alder reaction forming a benzene ring **27** as the final product. This retro-cycloaddition (**27** → **26**) was found to be inevitable in all cases described so far; even under very mild reaction conditions (e.g. under high pressure at room temperature) the CO_2 is spontaneously eliminated. In fact, because of their instability 2-oxabicyclo[2.2.2]oct-5,7-diene-3-ones **26** have not yet been isolated and described in the literature.
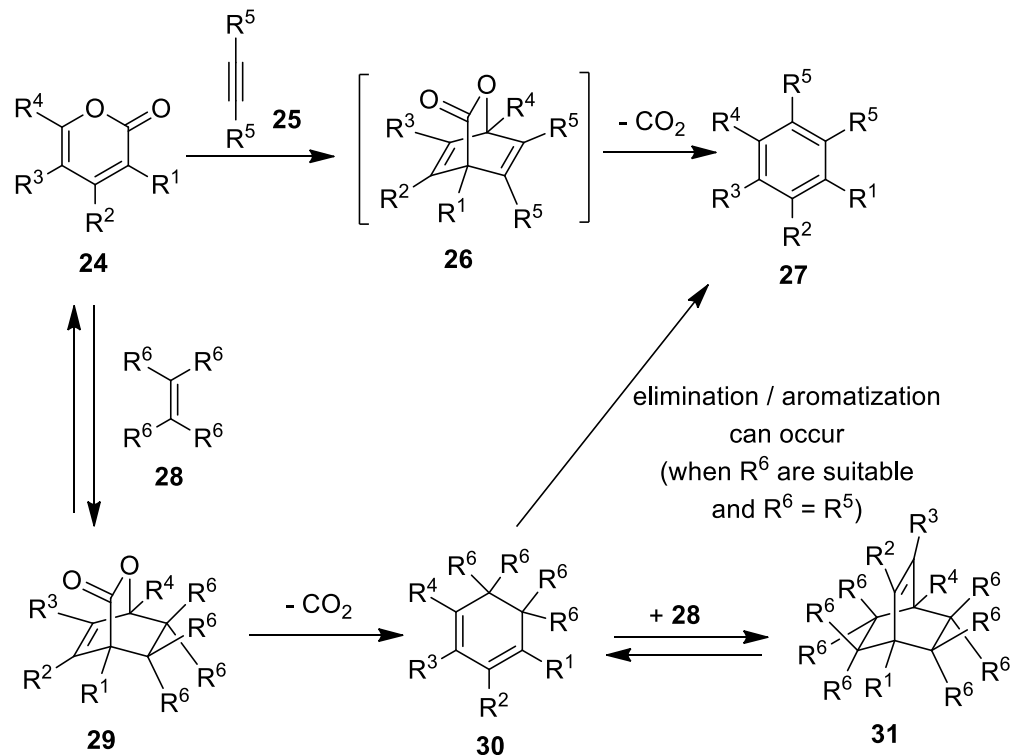
Scheme 9

The cycloaddition of alkenes **28**, on the other hand, offers a greater variety of products: the initial cycloadduct **29** (2-oxabicyclo[2.2.2]oct-5-en-3-one) is more stable than its analog **26** obtained with alkynes and can be in some cases even isolated (Scheme 9). However, often the reaction conditions applied for the first cycloaddition step (i.e. **24** → **29**) also result in the elimination (again *via* the retro-hetero-Diels–Alder reaction) of the CO_2 from **29**, yielding

cyclohexadiene (dihydrobenzene) systems **30**. The latter can also be in some cases isolated, however, they often display high reactivity and therefore undergo further transformations: either serving as a new diene and reacting with a new molecule of the dienophile **28** forming bicyclo[2.2.2]octene systems **31** ("double" cycloadducts), or an aromatization step (via oxidation or elimination if suitable groups are present) takes place yielding benzene derivatives **27** (analogous to those obtained with alkynes).

In many of the above-described cases high regio- and stereoselectivity is observed. Analogous transformations as presented above (Scheme 9) can also be carried out with fused pyran-2-ones (see below).

3.1. Alkynes as dienophiles

A variety of alkynes was already applied as effective dienophiles for Diels–Alder reactions with substituted 2H-pyran-2-ones.[24] We have focused our research on the application of 3-acylamino-derivatives **32** to yield the corresponding products **35**, such as highly substituted anilines **35**, dialkyl phthalates (**35**, $R^5 = R^6 = CO_2R$), biphenyl (**35**, $R^6 = Ph$) and terphenyl (**35**, $R^3 = Ar$, $R^6 = Ph$) systems (Scheme 10).[25] The cycloadditions were often conducted under conventional thermal reaction conditions. Relatively high temperature needed in these particular cases was successfully achieved under reflux conditions in high-boiling solvents, especially decalin (*cis,trans*-decahydronaphthalene, b.p. 189–191 °C) and tetralin (1,2,3,4-tetrahydronaphthalene, b.p. 207 °C) were found to be the most applicable.

decalin   tetralin
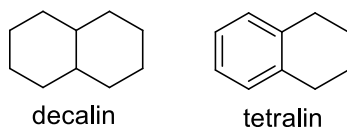
Microwave irradiation as a way of achieving the necessary activation energies combined with the use of closed vessels in focused microwave reactors was found to be one of the most successful ways to avoid the use of those high-boiling solvents. Namely, it is possible to conduct such transformations either in toluene, water or even as neat reactions, thereby significantly simplifying the isolation procedures and increasing the purity and yields of the products.
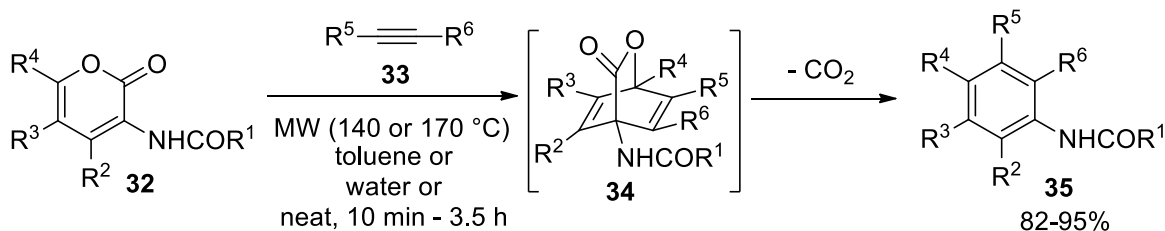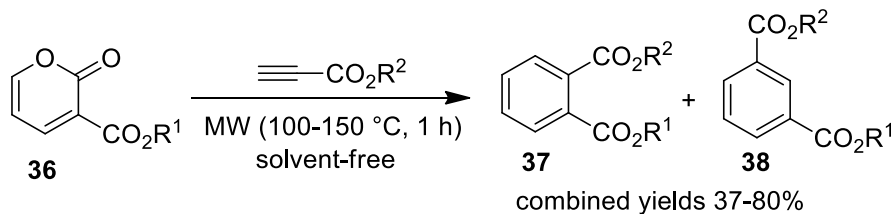

Scheme 10

When one of the reaction components is volatile (or prone to sublimation) the neat conditions, however, are connected with an additional problem. In such cases the volatile reactant tends to evaporate from the lower (hotter) part of the reaction vessel to the upper (colder) parts, where it condenses and is therefore no longer available for the reaction. This problem can be avoided by the use of a larger excess of the volatile component, but such an approach is not recommended, especially where expensive reagents are used. A much better way to circumvent this problem is to add a minimum amount of an appropriate neutral liquid additive possessing a boiling point close to the reaction temperature; *n*-butanol is often used).[25c,31d] Of course, this liquid evaporates as well and also condenses on the upper surfaces of the vessel, but due to its generally lower viscosity it tends to flow down the walls of the reaction vessel, thereby returning the condensed reagent to the seat of the reaction. With this precaution the necessary excess of the reagent can generally be lowered to a few ten percents.

It is of interest to note that cycloadditions of unsymmetrically substituted acetylenes with a hydrogen substituent on one side of the triple bond (**33**, R^5 = H) generally proceed in a regioselective manner yielding aniline products containing *para*-positioned hydrogen atoms (*e.g.* **35**, R^2 = R^5 = H) (Scheme 10).[25] With other alkynes **33**, such as *N,N*-diethylpropynamine and ethyl but-2-ynoate, both regioisomers were obtained providing a rewarding field for an experimental and computational research of their regioselectivity.[26] In the case of *N,N*-diethylpropynamine used as a dienophile, the results obtained point to a polar and asynchronous two-step mechanism, where 2*H*-pyran-2-ones act as electrophiles. Less polar and more synchronous concerted mechanism was found in the case of ethyl but-2-ynoate, most probably due to the presence of the electron-withdrawing carboxylic groups decreasing the nucleophilic character of the dienophile. Additionally, we have determined the effects of the 5-substituent (with 3-benzoylamino-2*H*-pyran-2-one derivatives) on the reactivity: for phenylacetylene as a dienophile we found that 5-acetyl and 5-benzoyl derivatives are far more reactive than 5-(4-methoxyphenyl) derivative. On the other hand, diethyl acetylenedicarboxylate and ethyl propynoate showed the inversed reactivity pattern.[25b] On the basis of these reactivity data for these transformations taking place *via* polarized asynchronous concerted transition states and possibly also *via* the formation of zwitterionic intermediates (a polar two-step mechanism) it was possible to classify them according to their electron demand.

Loupy and co-workers[27] have found that cycloadditions of various alkynes (alkyl propiolates and dialkyl acetylenedicarboxylates) with 3-alkoxycarbonyl-2*H*-pyran-2-ones **36** under solvent-free conditions in general do not proceed regioselectively but instead provide mixtures of **37** and **38** (Scheme 11). The authors made a strict comparison between conventional heating and microwave-assisted conditions. Furthermore, they have discussed the eventual occurrence of a specific microwave effect on the case of 3-methoxycarbonyl-2*H*-pyran-2-one.
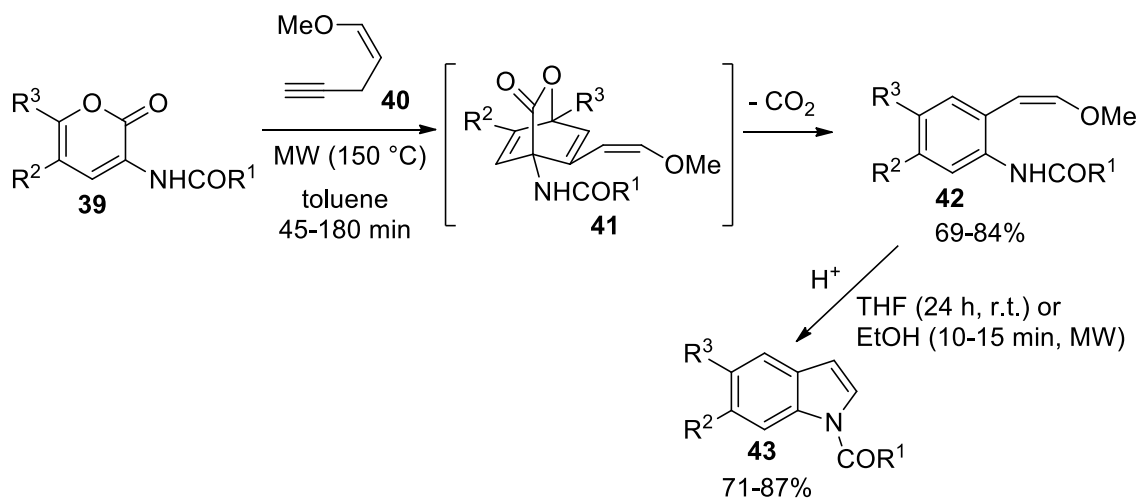
Scheme 11

In some cases it was demonstrated that triple-bond containing dienophiles (e.g. cyclohexyne and cyclooctyne derivatives, hetaryne analog of 2-chloropyridine and indolyne) can be formed *in situ* from simple precursors and immediately used as efficient partners for a variety of cycloadditions, including those with 2*H*-pyran-2-ones, additionally enabling a concise synthesis of ellipticine.[28]

ellipticine
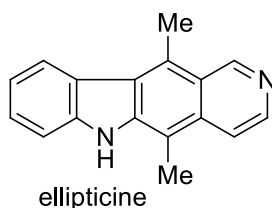
Synthesis of indoles. Further interest in the cycloaddition of alkynes was illustrated by the application of (*Z*)-1-methoxybut-1-en-3-yne (**40**) as the dienophile,[29] in this case the triple bond of the dienophile **40** preferentially cycloadds to the 2*H*-pyran-2-one skeleton **39** (under microwave irradiation, 45–180 min at 150 °C) yielding benzene derivatives **42** with a strategically positioned 2-methoxyethenyl moiety (Scheme 12). Namely, cycloadducts **42** can be easily cyclized into the corresponding substituted indoles **43** by the application of a catalytic amount of a dilute acid (e.g. HCl). This pathway represents a novel and straightforward synthetic route towards 1,5,6-trisubstituted indoles **43** and it enables access to indoles with substitution patterns on the six-membered ring that would be difficult to achieve *via* other methodologies.[30]

Scheme 12

3.2. Alkenes as dienophiles

Formation of 2-oxabicyclo[2.2.2]oct-5-en-3-ones 29. Alkenes **28**, with their wider variety of products that can be obtained in cycloadditions with 2H-pyran-2-one derivatives **24** (Scheme 9),[31] offer even broader research field than alkynes (c.f. section 3.1). The primary cycloadducts **29** (2-oxabicyclo[2.2.2]oct-5-en-3-ones), that are obtained with alkenes **28**, are in some cases of appreciable stability and can therefore even be isolated (in contrast to the primary adducts obtained with alkynes), as is shown by the examples (see Scheme 16) of various vinyl moieties containing dienophiles yielding **44** and **45**. Their structures were confirmed by X-ray diffraction analyses (Scheme 13).[32]


endo-**44**
R[3] = Et, Cy

exo-**45**

endo-**45**

n = 1, 3
R[1] = Ph, 2-chloro-3-pyridyl, 2-furyl, 3,4,5-(MeO)$_3$-C$_6$H$_2$
R[2] = COMe, COPh
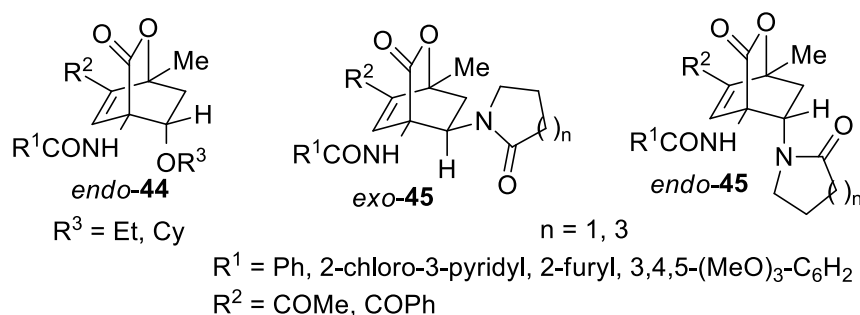
Scheme 13

The preparation of such 2-oxabicyclo[2.2.2]oct-5-en-3-ones **29** is feasible especially in those cases where the reactions are taking place under mild conditions (room temperature or at high pressures) or when the electronic demands of the dienophile and diene are correctly matched by the way of appropriate selection of the substituent patterns. 3-Phenylsulfenyl- and 3-phenylsulfonyl-2H-pyran-2-ones were shown by Posner and co-workers[33] to react with electron-rich and electron-poor dienophiles affording such bicyclic lactones suitable as precursors for the syntheses of many natural products and biologically active compounds. Encouraging were also the results obtained by Afarinkia and co-workers[34] while investigating reactions of chloro- and bromo-substituted 2H-pyran-2-ones and related systems with substituted acrylates, fumarates, maleates and their derivatives as dienophiles. The reactions were conducted at ambient temperature, under gentle heating (70–80 °C) or under high-pressure conditions. The regio- and stereochemical preferences of these thermal cycloadditions were investigated computationally (density functional theory calculations with B3LYP/6-31G basis set) providing results that were in agreement with the experimentally observed selectivities.

Formation of cyclohexadienes. Even the cyclohexadiene systems **30** (Scheme 9), which are formed in the next reaction step *via* a retro-hetero-Diels–Alder reaction (elimination of CO_2 from the 2-oxabicyclo[2.2.2]oct-5-en-3-ones **29**) can be in some special cases isolated (see below),[32]

but generally[35] they are of far lesser stability and tend to spontaneously aromatize into the final substituted benzene systems.

Formation of bicyclo[2.2.2]octenes. The other possible reaction pathway stemming from the crucial cyclohexadiene intermediate **30** (Schemes 9 and 14) is a second cycloaddition of a new molecule of the dienophile **46**, yielding bicyclo[2.2.2]octenes **47** as examples of double cycloadducts.[36] Many such cases were described starting from maleic anhydride or *N*-substituted maleimides (of the general structure **46**) as dienophiles and various 3-acylamino-2*H*-pyran-2-ones taking place either under conventional reflux conditions or in closed vessels with the microwave-assisted heating yielding **47**. Here generally four stereoisomers can be expected: two containing a plane of symmetry (i.e. *exo,exo*-**47** and *endo,endo*-**47**) and a pair of enantiomeric asymmetric products (*endo,exo*-**47** and *exo,endo*-**47**).
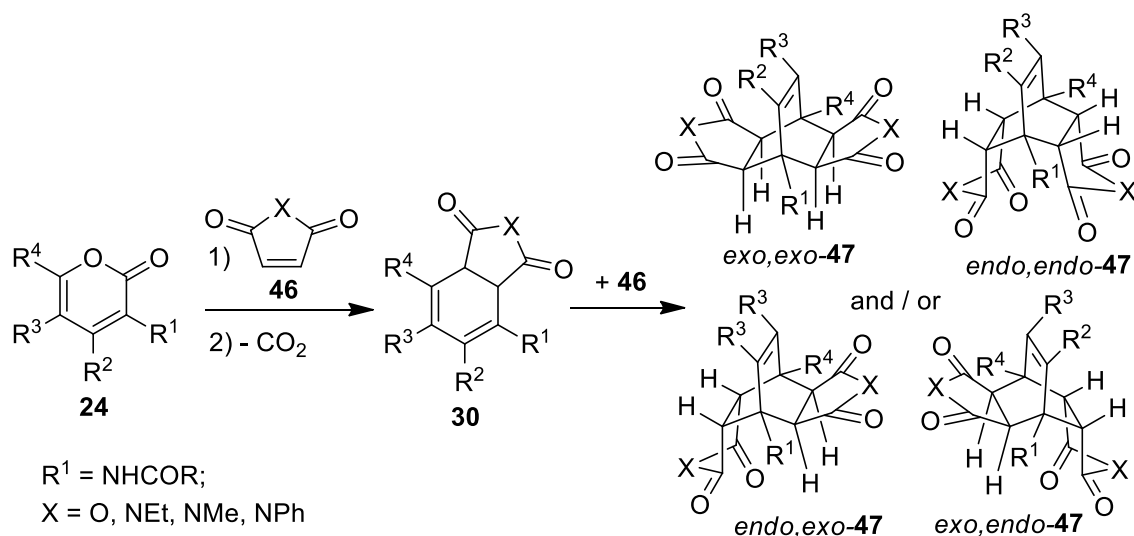
Scheme 14

Thermal cycloadditions of the majority of the 2*H*-pyran-2-one derivatives resulted exclusively in the symmetric products *exo,exo*-**47**. This type of symmetric product is in agreement with the expected stereostructures of the energetically favored transition states.[37] However, in special cases where severe steric hindrance exists between the two reacting partners, it was suspected that the second cycloaddition step could take place *via* a different stereo-chemical course. Indeed, such asymmetric *endo,exo*-bicyclo[2.2.2]octenes **50** were obtained when an eight-membered ring was fused to the starting 2*H*-pyran-2-one skeleton (i.e. **48**) and the dienophile applied was an *N*-substituted maleimide **49** possessing enough steric hindrance. We found that the methyl substituent (**49**, R = Me) was the smallest among those examined, to provide such an effect (Scheme 15).[37] In contrast, when maleic anhydride (**51**) cycloadded to the fused **48**, symmetric *exo,exo* adducts **52** were again produced, clearly demonstrating the need for both partners to provide sufficient steric hindrance during the stereochemically crucial reaction

step and consequently to change the stereoselectivity of the bicyclo[2.2.2]octene adduct (Scheme 15). Previously such asymmetric *endo,exo* products were accessible only *via* photochemical conditions.[38] Symmetric adduct **52** can be further transformed with aniline into the corresponding symmetric *exo,exo* derivative **53** that can be thermally isomerized into asymmetric *endo,exo* product **50** (R = Ph) (the same as obtained directly with the cycloaddition of **49**). This isomerization clearly shows that the asymmetric *endo,exo* product **50** is thermodynamically more stable than its symmetric *endo,exo* counterpart **53**. These results were further corroborated by computations at the DFT level.[37]
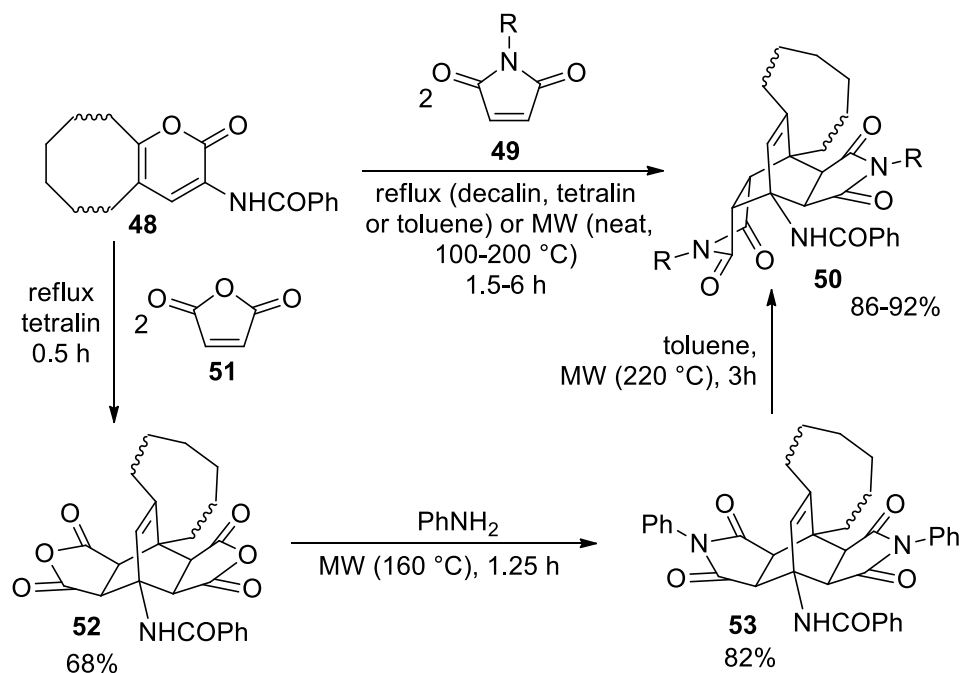
Scheme 15

Formation of isoindole derivatives. The last cycloaddition reaction step of the alkene (i.e. **30** → **31**) (Scheme 9) can be, at least theoretically, reversible, therefore preserving a certain concentration of the cyclohexadiene intermediate **30** in the mixture throughout the reaction course. Bearing in mind that oxidation (aromatization **30** → **27**) (Scheme 9) of the cyclohexadiene intermediate is generally irreversible, it was often experimentally found that in such reactions (with *N*-substituted maleimides **49** used as dienophiles) the bicyclo[2.2.2]octenes **59** represent the kinetically preferred products, whereas the aromatized isoindoles **58** are thermodynamically favored (Scheme 16).[31b] Therefore, longer reaction times and higher temperatures generally cause the oxidation to occur, consequently yielding the corresponding isoindole products **58**. When suitable dehydrogenation catalysts are applied this oxidation can be the exclusive reaction path. In the case when fused pyran-2-ones **54** (R^2, R^3 = [CH$_2$]$_n$ or –C(O)–[CH$_2$]$_n$–) Rh/C was used as a dehydrogenation catalyst,[31b] whereas in the cases of other

substituted 2*H*-pyran-2-ones **54** activated charcoal Darco KB was found to be the best choice.[31f] Further studies have shown that the most important factor influencing the dehydrogenation activity of the catalyst is its specific surface area. It has also been demonstrated that the dienophile (i.e. *N*-substituted maleimide **49**) additionally acts as the sink for the hydrogen eliminated from the cyclohexadiene intermediate **56**. Compound **49** is thereafter transformed into the corresponding *N*-substituted succinimide **57**.
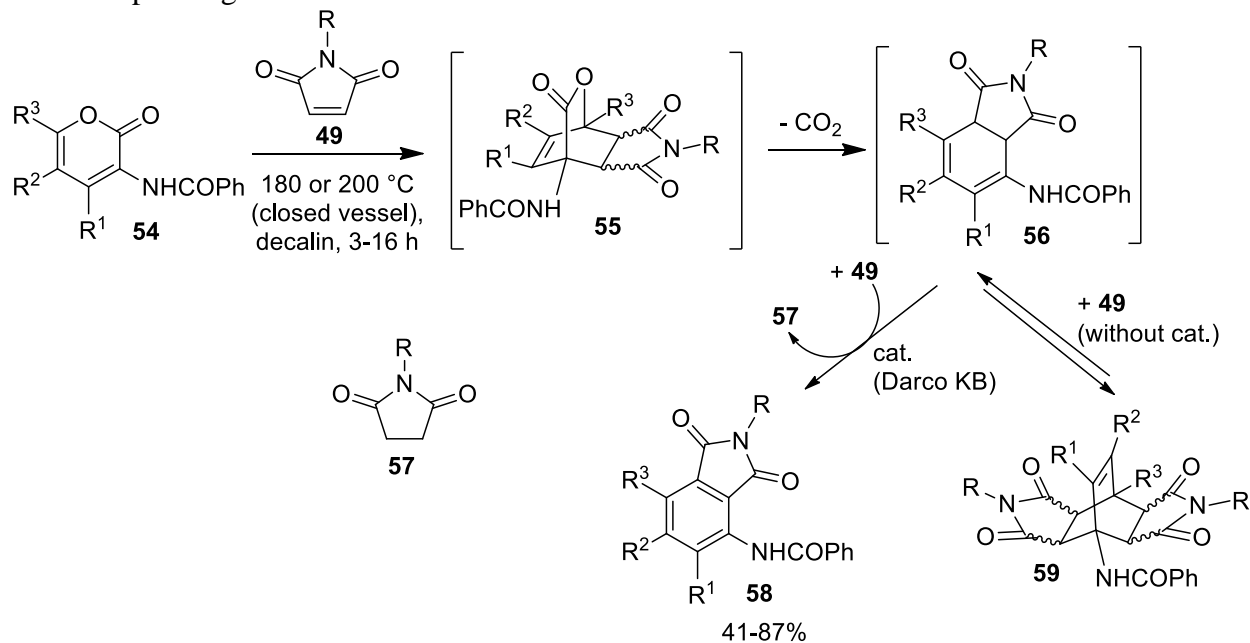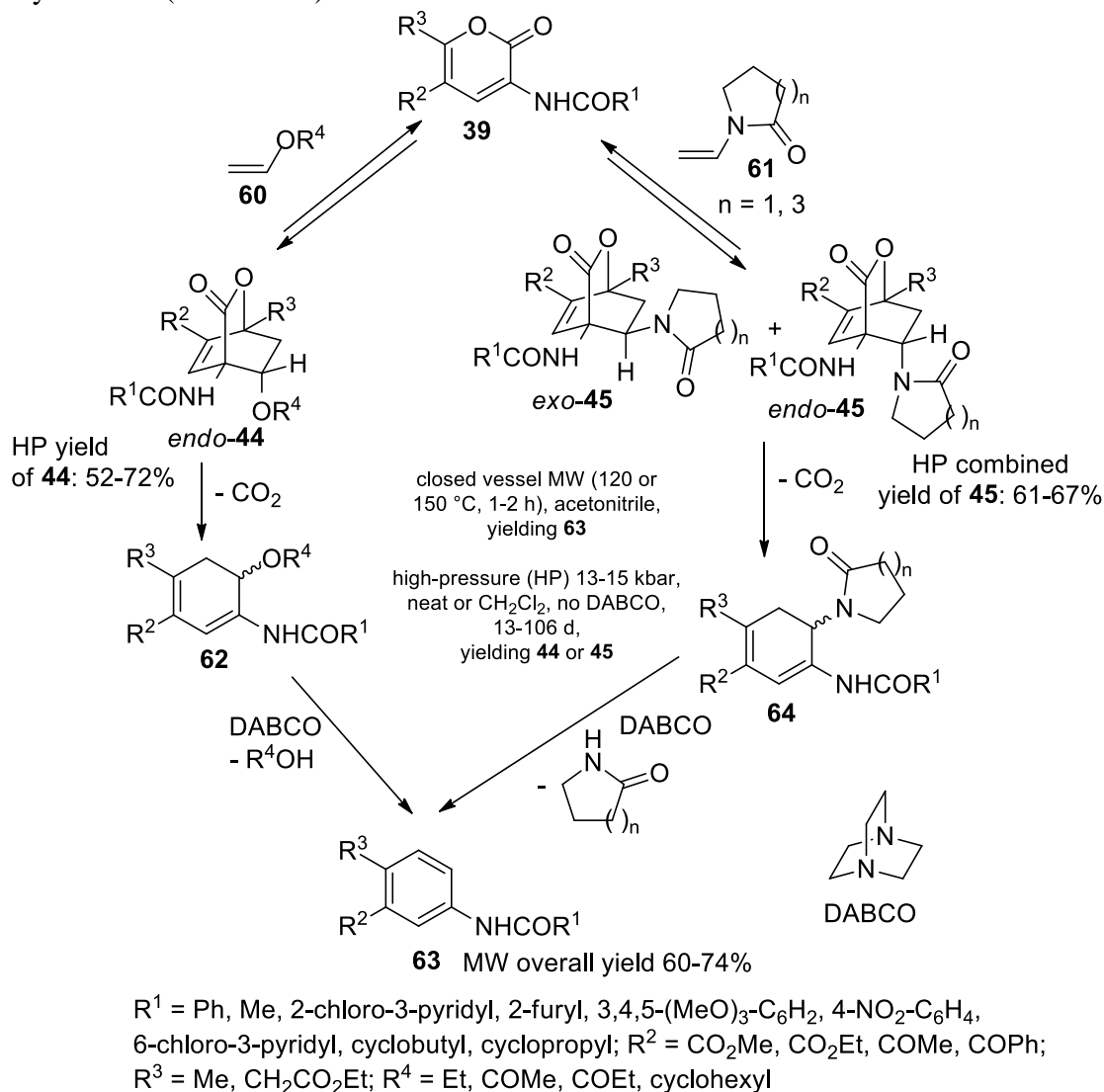

Scheme 16

In some cases, where aromatization is energetically very favorable, the heterogeneous dehydrogenation catalyst might not be needed at all; however, there is still the need for the presence of some other molecule possessing a suitable double bond to act as the hydrogen sink. Tsuboi and co-workers, for example, have described some elegant cases of cycloaddition of various 3-hydroxy-2*H*-pyran-2-ones with 1,4-quinones, which were used as dienophiles and concomitantly enabled the aromatization into the final naphtho- and anthra-quinones.[39] In some other examples aromatization is achieved by the elimination of a small, stable molecule, such as ethanesulfinic acid, as described by Haider *et al*.[40]

Cycloadditions of vinyl-containing dienophiles. Sometimes it would be useful if acetylene could be used as the dienophile. However, because of its gaseous nature and negligible polarization it is very unreactive and therefore often unsuitable for cycloadditions as the dienophile. Therefore, some synthetic equivalents of acetylene would be of certain interest: vinyl-moiety containing ethers and esters **60** as well as amides **61** proved to be suitable masked equivalents of acetylene readily reacting as dienophiles with a variety of electron-deficient substituted 2*H*-pyran-2-ones **39** (Scheme 17).[32,41] The initially formed 2-oxabicyclo[2.2.2]oct-5-en-3-ones **44** and **45** could be isolated only in the cases where the cycloadditions took place at high pressure (13–15 kbar) and at room temperature; the necessary reaction times were therefore

rather long – *ca.* 15 days. It is of additional interest that the stereoselectivity of the cyclo-additions depended upon the dienophiles used: ethyl vinyl ether (**60**, R^4 = Et) (and other dienophiles **60**) yielded exclusively *endo* adducts **44**, whereas with 1-vinyl-2-pyrrolidone (**61**, n = 1) and *N*-vinylcaprolactam (**61**, n = 3) (both with the vinyl moiety attached to a nitrogen atom) mixtures of both *endo* and *exo* adducts **45** were observed, the *exo* adduct predominating in the majority of cases (Scheme 17).

R^1 = Ph, Me, 2-chloro-3-pyridyl, 2-furyl, 3,4,5-$(MeO)_3$-C_6H_2, 4-NO_2-C_6H_4, 6-chloro-3-pyridyl, cyclobutyl, cyclopropyl; R^2 = CO_2Me, CO_2Et, COMe, COPh; R^3 = Me, CH_2CO_2Et; R^4 = Et, COMe, COEt, cyclohexyl
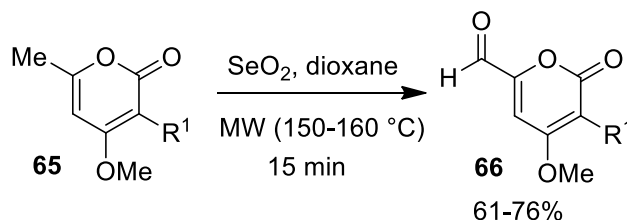
Scheme 17

When these cycloadditions (Scheme 17) were conducted under microwave irradiation, the resulting reaction temperature caused the elimination of CO_2 from **44** and **45** *via* the retro-hetero-Diels–Alder reaction. The cyclohexadienes **62** and **64** produced proved to be of low stability and were prone to spontaneous aromatization yielding the final aromatic systems **63** corresponding to those that would be obtained by the application of acetylene as the dienophile. The reaction

towards such aromatic systems **63** was found to be further accelerated by the application of a suitable base acting as an organocatalyst. Among the bases examined DABCO (1,4-diaza-bicyclo[2.2.2]octane) was shown to be the most appropriate; additionally it was proved that DABCO has no effect on the cycloaddition step (i.e. **39** → **44** and **39** → **45**) and that it acts only in the last elimination step (formation of **63**). The same synthetic strategy of using ethyl vinyl ether (**60**, R^4 = Et) as a masked equivalent of acetylene was later extended also to the cases of fused pyran-2-ones, where only final, aromatized products of type **63** were isolated.[42]

Application of a vinylated sugar (an appropriately protected D-glucofuranose derivative) as the dienophile for a cycloaddition with 3-methoxycarbonyl-2*H*-pyran-2-one afforded either the CO_2-bridged primary adduct (after 6 days at 65 °C) or a cyclohexadiene system (after 2 days at 100 °C) amenable for the further transformation into a carbasugar-sugar pseudodisaccharide.[43]

4. Selected examples of other transformations of 2*H*-pyran-2-one derivatives

One of the key steps for the preparation of biologically important compounds belonging to the gymnoconjugatin, auxarconjugatin and isorumbrin classes (see chapter 1) was a microwave-assisted oxidation of a 6-methyl group on a 2*H*-pyran-2-one ring **65** into the corresponding aldehyde moiety taking place with SeO_2 in dioxane (at 150–160 °C) (Scheme 18).[9] Instead of using conventional heating in a sealed tube, as was reported earlier,[44] Lam, Hua and Wu with co-workers[9] decided to use microwave irradiation; in this way reaction times were shortened and yields of the products **66** improved.
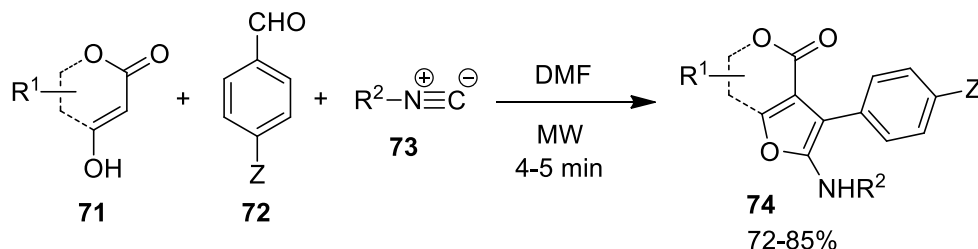

Scheme 18

4-Hydroxy-6-methyl-2*H*-pyran-2-one (**69**) can be used as an efficient partner for a three-component reaction with *N*-substituted isatins **67** and 1,3-dicarbonyl compounds **68** catalyzed by an appropriate Lewis acid yielding products **70** (Scheme 19 also presents the suggested mechanism).[45] Stephenson and co-workers have investigated many possible Lewis acids (including $TiCl_4$, $BF_3 \cdot OEt_2$ and $SnCl_4$, the last being found to be the most efficient) and various conditions (including conventional heating in 1,2-dichloroethane at 60 °C or with microwave irradiation at 80 °C in the same solvent). The most appropriate were found to be the microwave conditions enabling the decrease of the necessary reaction times from 12–20 h to just 80 min and in most cases providing the products **70** with increased yields.
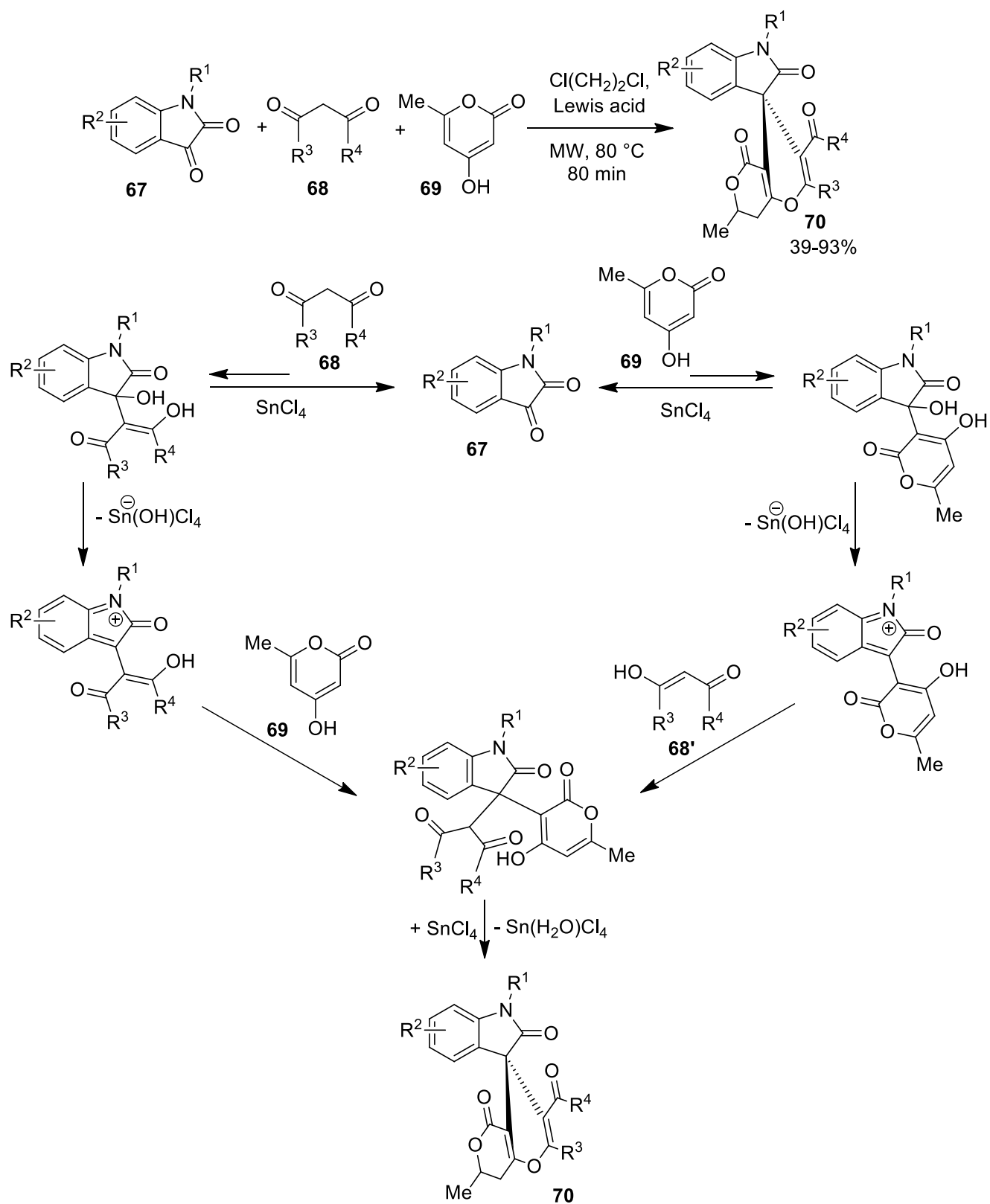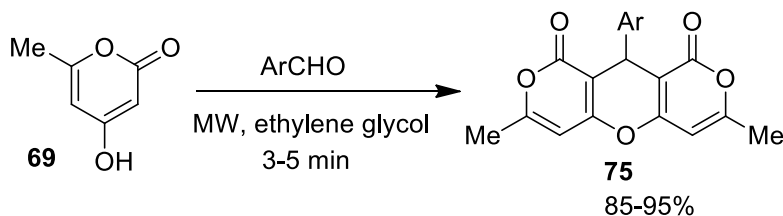
Scheme 19

Furopyrimidines and furopyranones as well as furocoumarins (the latter two represented by the general structure **74**) can be prepared by a three-component solvent-free condensation between various 2*H*-pyran-2-ones or coumarins **71**, substituted benzaldehydes **72** and isonitriles **73** on montmorillonite K10 as the solid support in DMF (Scheme 20). The otherwise necessary reaction times (14–16 h for furopyranones and 16–24 h for furocoumarins) were drastically reduced to just 4–5 min with the application of microwave irradiation.[46]

Scheme 20

Furopyranones and furocoumarins similar to those above were also obtained by the cyclization of 4-hydroxy-2*H*-pyran-2-ones or related coumarins with substituted benzaldehydes and nitriles in DMF under microwave irradiation for 3 min.[47]

Tu *et al.* have reported the condensation of arylaldehydes with two molecules of 4-hydroxy-6-methyl-2*H*-pyran-2-one (**69**) under microwave irradiation in refluxing ethylene glycol yielding tricyclic systems **75** in 4–5 min with yields generally higher than those previously reported (Scheme 21).[48]

Scheme 21

Pyrazolecarboxaldehydes were also used for reaction with 4-hydroxy-6-methyl-2*H*-pyran-2-one and a related 4-hydroxycoumarin catalyzed by Zn(proline)$_2$ as a Lewis acid under solvent-free conditions (or alternatively in water).[49] However, the expected Knoevenagel condensation products were not detected and instead of them pyrazolopyrones were produced. With the application of microwave irradiation, the authors were able to decrease the necessary reaction times from 45–120 min (conventional heating in the aqueous medium) to 5–9 min with the concomitant increase of yields.

Beifuss *et al.*[50] have investigated the use of substituted α,β-unsaturated aldehydes **76** for microwave-assisted domino Knoevenagel condensations/6π-electron electrocyclization with 4-hydroxy-2*H*-pyran-2-one derivatives **77**. The transformation takes place in ethyl acetate in the presence of β-alanine and under microwave irradiation yielding a set of 2*H*,5*H*-pyrano[4,3-*b*]pyran-5-ones **78** (Scheme 22).
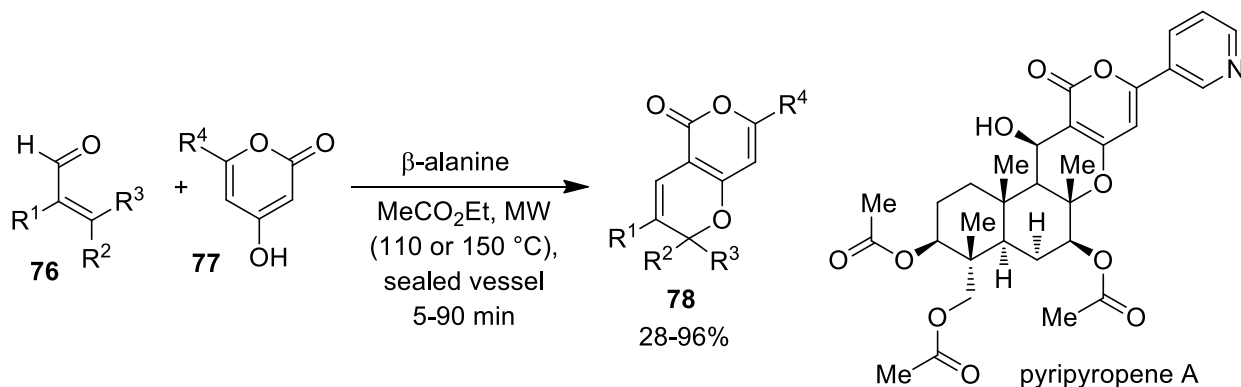
Scheme 22

The temperature attained with microwave irradiation was 150 °C; however, when CaSO$_4$ was used as the additive only 110 °C was needed. Reaction times of microwave-accelerated reactions varied between 5 and 90 min and were significantly shorter than those needed under thermal conditions at 80 °C (up to 25 h). Albeit the obtained yields of **78** were in some cases lower than under conventional conditions, the microwave approach offers significant time savings and thus enables more rapid access to large libraries of such heterocyclic systems **78** that are related to natural products of the pyripyropene family (Scheme 22).

Stoyanov and Ivanov[51] have published a transformation between 4-hydroxycoumarin (**79**) or 4-hydroxy-6-methyl-2*H*-pyran-2-one (**69**) and a set of substituted amines including morpholine under microwave-irradiation (850 W, 1.5–10 min). It is noteworthy that the fused pyran-2-one moiety of the coumarin **79** did not open during this transformation and therefore the 2*H*-pyran-2-one-moiety-containing product **80** was obtained. On the other hand, the 2*H*-pyran-2-one ring **69** was transformed into the 2-pyridone ring **81** (Scheme 23). It should be noted that these reactions were carried out in a closed vessel in an ordinary kitchen microwave oven, so the reaction parameters (temperature, pressure) are not reported; this might lead to certain problems with the reproducibility.
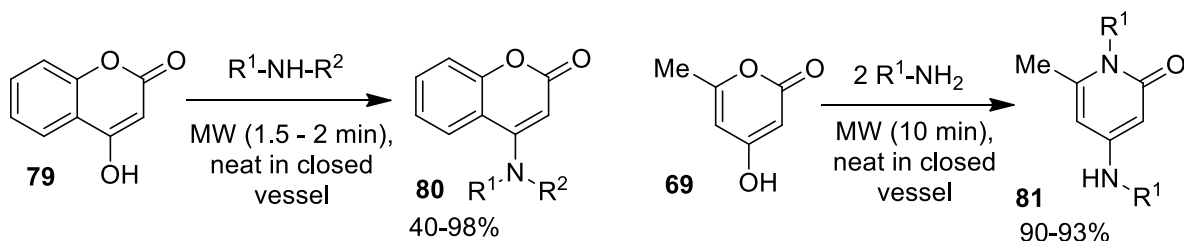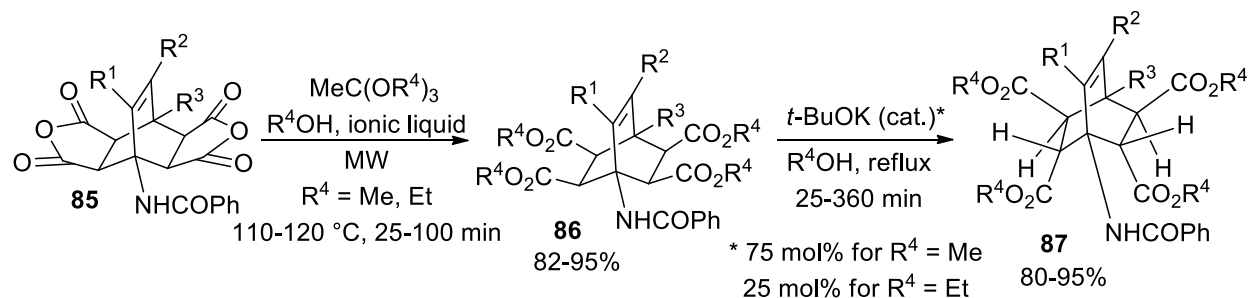
Scheme 23

4.1. Transformations of bicyclo[2.2.2]octenes

Bicyclo[2.2.2]octenes of type **82**[36] that are easily accessible by the Diels–Alder reactions of a variety of 2*H*-pyran-2-ones and appropriate *N*-substituted maleimides or maleic anhydride represent very rewarding substrates for the investigations of the regio- and stereoselectivity of hydrogenation reactions in the presence of suitable heterogeneous catalysts: various LDH (layered double hydroxides)-supported Pd and Rh salts were applied to study the chemoselectivity: the hydrogenation can take place at the double bond; alternatively acetyl group can be reduced to the 1'-hydroxyethyl group (i.e. formation of **83** versus **84**) (Scheme 24).[31c,52] Additionally, silica sol-gel heterogenized synphos modified Pt nanoclusters[53] and iron oxide colloids[54] were evaluated and successfully applied for an analogous hydrogenation. It is important to mention that hydrogenations of these bicyclo[2.2.2]octenes under standard conditions proceed poorly, at best.
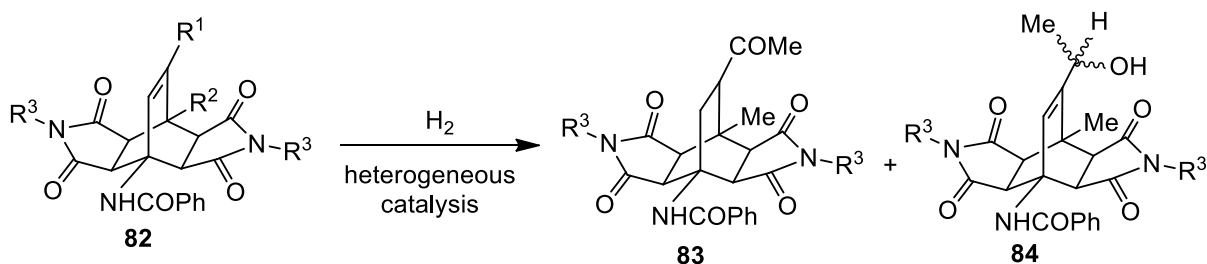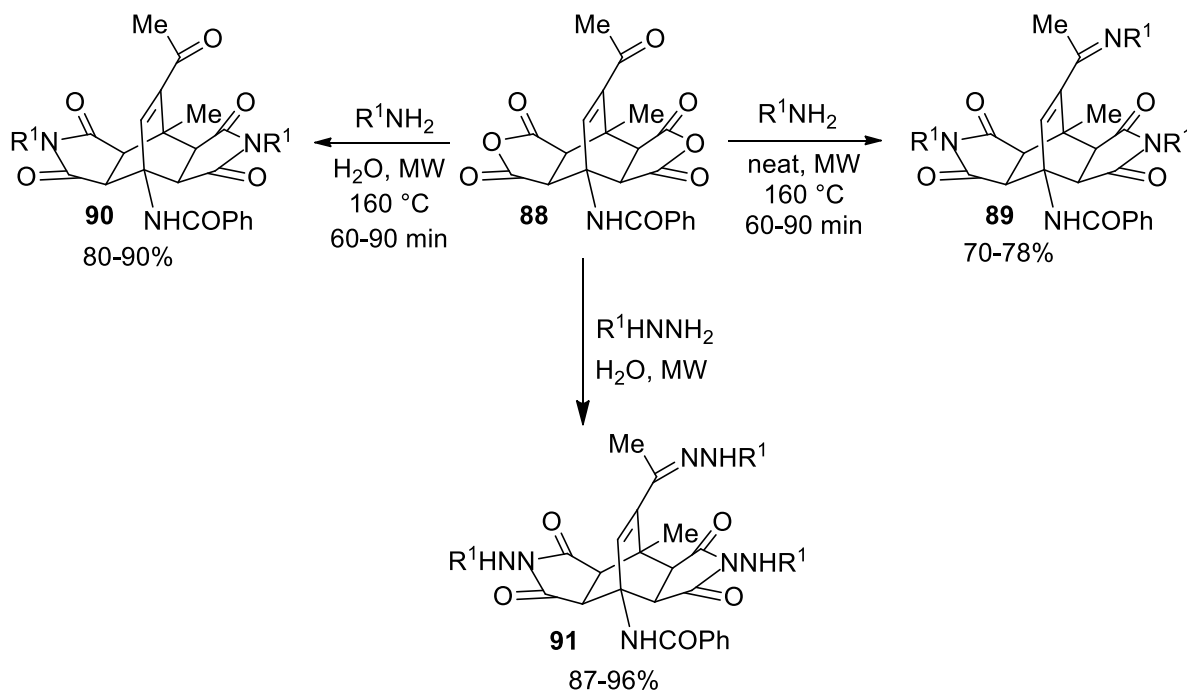

Scheme 24

Bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydride derivatives **85** (obtained by simple cycloaddition between 2*H*-pyran-2-ones and maleic anhydride (**51**)) can be efficiently converted into the corresponding tetraesters **86** by microwave-assisted and ionic-liquid-catalyzed transformation (Scheme 25).[55] Base-catalyzed isomerization of these tetraesters **86** takes place with the retention of symmetry and yields the products **87** that are appropriate substrates for catalytic hydrogenation. This hydrogenation proceeds under far milder conditions (5 h at room temperature, 3 bar of H₂ and with standard Pd/C as the catalyst) as were necessary for the above mentioned bicyclo[2.2.2]octenes **82** (analogous to those before the isomerization) indicating that the isomerization (**86** → **87**) strongly decreases the steric hindrance around the double bond.

Scheme 25

Additionally, bicyclo[2.2.2]octenes, such as **85**, resulting from the cycloaddition of maleic anhydride are also interesting substrates for derivatizations with amines[56] as well as with hydrazine and its derivatives.[57] We have focused special attention to those bicyclo[2.2.2]octenes that incorporate acetyl moiety. When **88** reacts with amines the resulting products differ according to the conditions applied: neat reaction conditions (with an addition of a minor amount of a non-polar liquid, such as toluene) under microwave irradiation yield the product **89** (representing an example of a succinimide derivative with the acetyl group transformed into an imine moiety) (Scheme 26). On the other hand, similar reaction of **88** carried out in an aqueous suspension leads to the product **90**, which is an example of a succinimide derivative with the acetyl group remaining unchanged. Transformations with hydrazine and its substituted derivatives, on the other hand, provided derivatives **91** with the acetyl group transformed into the corresponding hydrazone moiety also in the case when water was used as the solvent.

Scheme 26

5. Conclusions

We have presented 2*H*-pyran-2-one derivatives as naturally occurring and biologically important compounds; furthermore a very versatile one-pot synthesis of many 3-acyl-2*H*-pyran-2-one derivatives was considered in the light of some other more recent preparation procedures. Then we turned our attention to the application of 2*H*-pyran-2-ones as dienes useful for a plethora of Diels–Alder reactions with alkynes and alkenes (with special consideration to maleic anhydride and *N*-substituted maleimides) discussing the regio- and stereoselectivities observed. A novel preparation of substituted indoles and the application of vinyl-moiety containing dienophiles as masked synthetic equivalents of acetylene are also presented. Cycloadditions of 2*H*-pyran-2-ones often yield bicyclo[2.2.2]octene derivatives that are interesting targets for further reactions: hydrogenation, transformations with amines and hydrazines, isomerizations etc. The introduction of contemporary synthetic tools, including principles of green chemistry and the microwave irradiation, keeps the field of synthesis and transformations of 2*H*-pyran-2-one a very vital research area and we suppose that novel results will appear in the near future.

6. Acknowledgements

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Authors, please provide the last page of the reference number 53.

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Krištof Kranjc was born in Kranj, Slovenia, in 1975 and studied chemistry at the Faculty of Chemistry and Chemical Technology, University of Ljubljana where he obtained his Diploma in 1999 under the supervision of Professor Marijan Kočevar. He continued with his postgraduate studies at the same institution, where he finished his Ph.D. degree in 2003 under the supervision of Professor Marijan Kočevar. Since then he is continuing with his research in the fields of cycloaddition reactions with special emphasis on the application of green reaction conditions (aqueous and neat reactions), microwave-assisted synthesis and high-pressure research.

Marijan Kočevar was born in Slovenia in 1949. He graduated in chemistry from the University of Ljubljana in 1974, and finished his M.Sc. (1978) and Ph.D. (1982) degrees under the supervision of Professor Miha Tišler. He became an Assistant Professor in 1983, Associate Professor in 1988, and Professor in 1997 at the University of Ljubljana, where he is currently Professor of Organic Chemistry at the Faculty of Chemistry and Chemical Technology. His research interests include heterocyclic chemistry, amino acids, especially unsaturated amino acids, oxidations and reductions, cycloaddition reactions, structural investigations in solution, catalysis, green chemistry, and high-pressure chemistry. He was a member of the management

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