The use of ionic liquid catalysis in the synthesis of steroid derivatives

The main goals of the present project involved the development of ionic liquid based catalytic systems for the synthesis of known and novel steroid derivatives with potential pharmaceutical applications. The biological activity of some of these products, as well as steroids synthesised in our group previously, was also tested in collaboration with research groups in Pécs and Szeged.

Because of the great variability of their structure and due to other favourable properties, such as stability, wide liquid range, low vapour pressure, *etc.*, ionic liquids (ILs) became alternative reaction media for many organic reactions. By the introduction of acidic/basic groups, they can be used as catalysts or may play the dual role of catalyst and solvent. At the same time, depending on the structural features, they have higher or lower toxicity and although their price decreased in the past few years, they are still more expensive compared to organic solvents or simple acid/base catalysts. One important feature of ILs is however that they are potentially recyclable in most of the applications. Thus both the costs and the production of wastes can be reduced even compared to the use of 'classic' methodology. Another option is to immobilise the ILs on a solid support to prepare a SILP (supported ionic liquid phase) that may retain some of the advantages of the original IL, such as catalytic properties or stabilisation effect on metal catalysts. That means that in all of the synthetic reactions investigated during the project a great emphasis has been placed not only on catalytic activity but also on the recyclability of IL-based catalysts. With the exception of ILs **F** and **G** (Figure 1), all ILs were prepared in our lab.

1. Catalytic reactions in the presence of acidic ILs

Various acidic ILs were synthesised and tested in acid catalysed reactions. Brønsted acidity of ILs **A-E** is due to the presence of the SO_3H group in the side chain of the cation, ILs **F- I** are acidic because of the C-H acidity of the C(2)-H of the cation, while **J** has a Lewis acidic anion. Beside the usual imidazolium- or pyridinium core, ILs with the less toxic morpholinium cation **(C-E**) were also prepared.

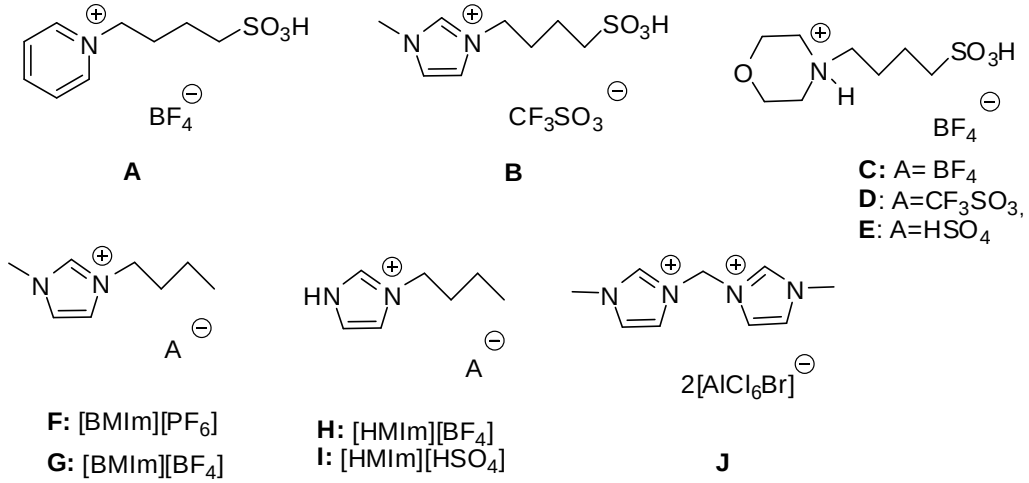
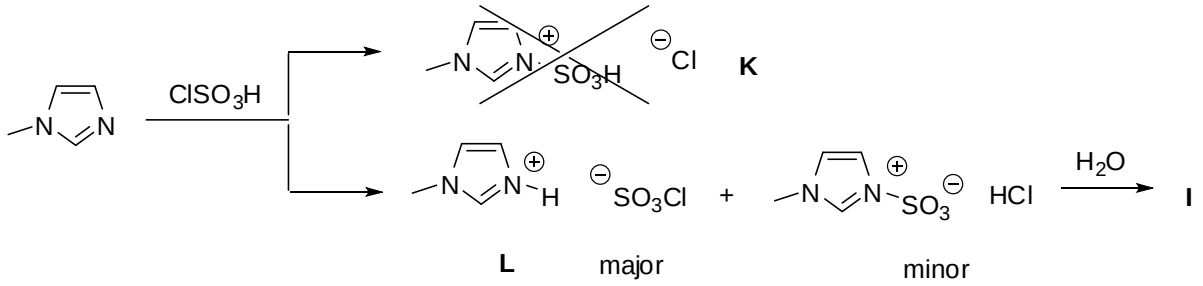


Figure 1. Acidic ILs tested in catalytic reactions

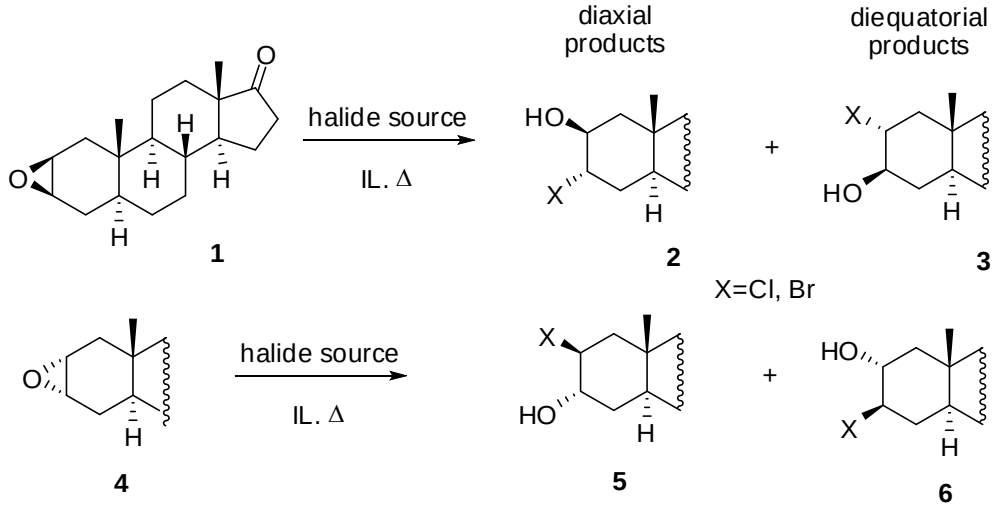
A real structure of an acidic IL obtained by the chlorosulfonation of 1-methylimidazole was clarified. Although a great number of publications had appeared on organic reactions catalysed by the chlorosulfonation product, the possibility of the formation of the assumed 1-

methyl-3-sulfonic acid imidazolium chloride (**K**) [1] seemed to be questionable. Based on X-ray crystallography and NMR spectroscopy, including ^{1}H-, ^{13}C-, ^{17}O- and ^{15}N-^{1}H HSQC measurements, chlorosulfonation was proved to lead mainly to 1-methylimidazolium chlorosulfate ([HMIm]$^{+}$[SO_3Cl]$^{-}$, **L**)) [2]. Formation of the zwitterionic (minor) product is probably due to the SO_3 contamination of chlorosulfonic acid. Also. ^{1}H- and ^{17}O-NMR experiments supported a fast hydrolysis of the primarily formed compounds to [HMIm][HSO_4] (**I**) in the presence of traces of water.



1.1. Ring-opening of steroid 2,3-epoxides with metal halides

Beyond catalyst recyclability, a complete change in selectivity could be achieved with the help of ILs in the ring opening of 2β,3β- (**1**, Scheme 1) and 2α,3α epoxy-5α-androstane-17-one (**4**) with halide reagents ($AlCl_3$, TMSCl, LiCl and LiBr) [3]. The reaction was investigated using imidazolium ILs **G** and **H** in the dual role of solvent and catalyst. Under usual acid-catalysed conditions, the reaction leads to the kinetically controlled diaxial product (**2** or **5**) (as it is formulated by the Fürst-Plattner rule). The application of the IL was shown to result in an increase in the amount of the unusual diequatorial halohydrins **3** or **6** especially at temperatures above 100°C. With a careful choice of reaction conditions the latter derivatives could be produced with 43-96% selectivity depending on the nature of the halide ion. Moreover the usual diaxial products (**2**, **5**) could also be isolated in 70-85% yields by a proper change in the temperature and steroid/reagent ratio. (It should be mentioned that similarly to the reactions catalysed by inorganic acids, only the diaxial products could be obtained with IL **B**).The reusability of IL **G** was demonstrated in the synthesis of both types of products. Based on quantum chemical calculations, the effect of the IL could be explained by the stabilization of the transition state leading to the diequatorial products.



Scheme 1. Ring opening of steroid epoxides with halides in ILs

1.2. Beckmann rearrangement and reductive alkylation

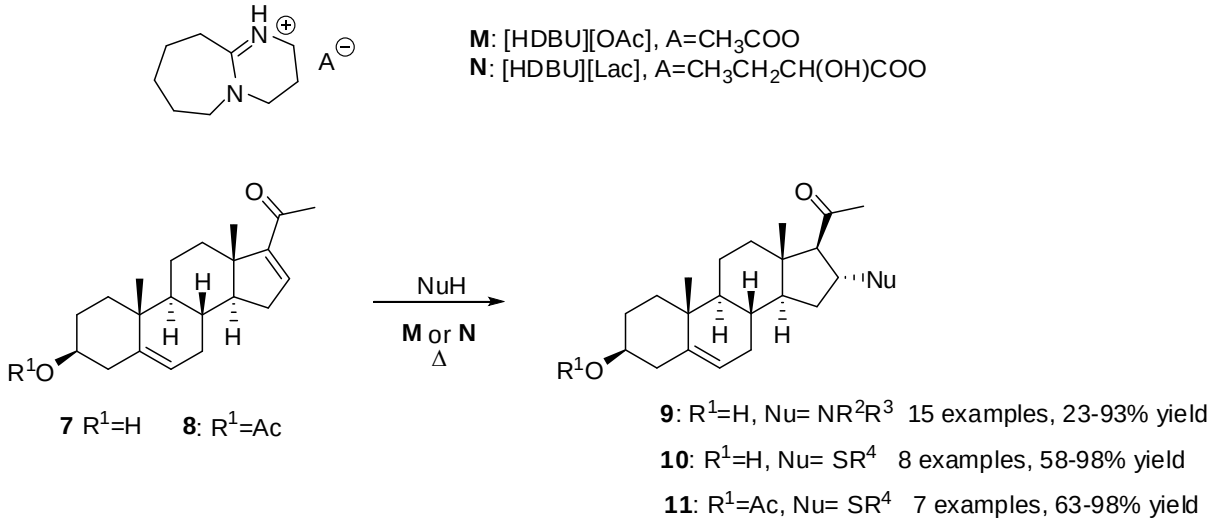
Beckmann rearrangement of steroidal oximes was investigated in the presence of various acidic ionic liquids. Conversions and isolated yields were found to fall behind those obtained under standard conditions. However the main problem was the loss of activity that was observed during the recycling of the ionic liquid that makes this methodology too expensive. A BSc thesis (by Alexa Vörös) was written based on the results, but further attempts seemed to be aimless as catalytically active ILs (e.g. **E** and **F**) underwent a noticeable change (from colourless to dark brown) during the reaction that shows decomposition.

Poor results were obtained in case of reductive alkylation of 5α-androstan-17-one with *N*-methylindol as well. Although ILs **A**-**D** catalysed the reaction and led to the product with 25-60% isolated yield, the IL could not be reused. Based on the results, an MSc thesis was prepared (by Enikő Nagy).

2. Hetero-Michael additions in the presence of DBU-based ionic liquids

DBU-based ionic liquids, such as [HDBU][OAc] (**M**, Scheme 2) or [HDBU][Lac] (**N**) (Lac: lactate) may play a dual role in Michael additions: the acidic hydrogen of protonated DBU can form a hydrogen bond with the carbonyl oxygen of the substrate, while the anion can increase the electron density on the nucleophile reaction partner either via deprotonation or H-bond formation [4].

The efficiency of IL **M** as the catalyst and solvent was proved in the synthesis of 15 different 16α-amino-pregnenolone derivatives (**9**) in the aza-Michael addition of 16-dehydropregnenolone (**7**) and aliphatic, aromatic and heteroaromatic amines [5]. Primary and cyclic secondary amines gave the products in excellent yields. Aromatic amines were less reactive and steric bulk had a decisive effect on the outcome of the reaction: acyclic secondary amines showed poor reactivity. Less reactive amines had to be used in excess (up to tenfold), depending on their reactivity. Recyclability of the IL was also proved. After extraction of the products with diethyl ether, the IL was reused three times efficiently. A decrease of activity was observed only during the fifth run, this could be explained by a small loss of ionic liquid upon reuse. Due to the poor solubility of some of the products in ether, especially those incorporating an imidazole ring, some reactions were carried out in IL **N**. This IL showed similar activity but allows the use of toluene for the extraction of the product.



Scheme 2. Hetero-Michael additions in the presence of ILs

The same ILs were also applied in thio-Michael additions [6]. Both aliphatic and aromatic thiols showed good reactivity and the products (**10** or **11**) could be obtained in 59-97% yields (with the exception of a mercaptopyridine derivative) even using the nucleophiles in equimolar amount. In contrast to conventional inorganic base catalysts, IL **M** tolerates the presence of ester functional groups in the substrate, so 16-dehydropregnenolone acetate (**8**) could also be converted into the corresponding products **11**. It should be mentioned that this observation proves that the hydrolysis of the 3-acetoxy group of the same substrate in aza-Michael additions can be attributed not to the IL catalyst/solvent but to the amine reaction partners. The IL showed good recyclability, it could be used in five subsequent runs without a noticeable loss of activity.

3. Application of reversible ionic liquids for the isolation of steroid products of base catalysed reactions

Instability of imidazolium- and quaternary ammonium ionic liquids under basic conditions might lead to the formation of undesirable side products [7], so the application of ILs such as [BMIm]OH, Bu_4NOH, [BMIm][OAc] at temperatures that is usually necessary for the conversion and even dissolution of steroidal substrates is not always favourable. At the same time, the concept of reversible ionic liquids, introduced by Jessop [8], can still be used for the recycling of the base catalysts. Among other organic bases, guanidines can form ILs in the presence of alcohols and carbon dioxide. In contrast to 'normal' ILs, these derivatives can be decomposed (can be switched back from their ionic form into their molecular form) by expelling CO_2 at high temperature. According to the original idea, at the end of the base catalysed reaction where the base serves not only as catalyst but also as solvent [9], methanol and CO_2 are added to the reaction mixture and the product is extracted by an apolar solvent. Then CO_2 (and methanol) is removed and the base catalyst/solvent is reused. In the present project this methodology was used in the Claisen-Schmidt condensation of various steroidal substrates and in the aza-Michael reaction of 16-dehydropregnenolone using heteroaromatics as *N*-nucleophiles.

3.1. Claisen-Schmidt condensation of carbonyl compounds

In order to obtain an efficient recyclable catalytic system, the following requirements should be fulfilled: i) the base should be strong enough to catalyse the reaction, ii) it should form an ionic liquid in the presence of an alcohol and CO_2, iii) this ionic liquid should not be dissolved by the solvent used for the extraction of the product and iv) CO_2 should be removable without the decomposition/evaporation of the base and preferably, the alcohol component. During this work, several base+alcohol systems (Figure 2) were tested but only a few were found to satisfy all the requirements.

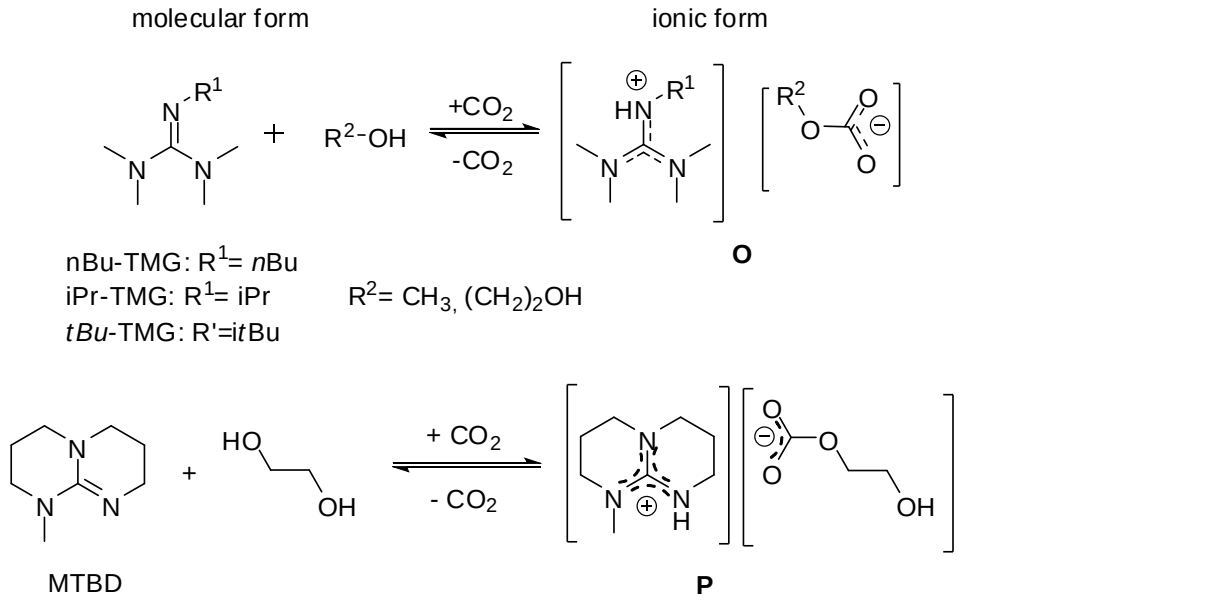
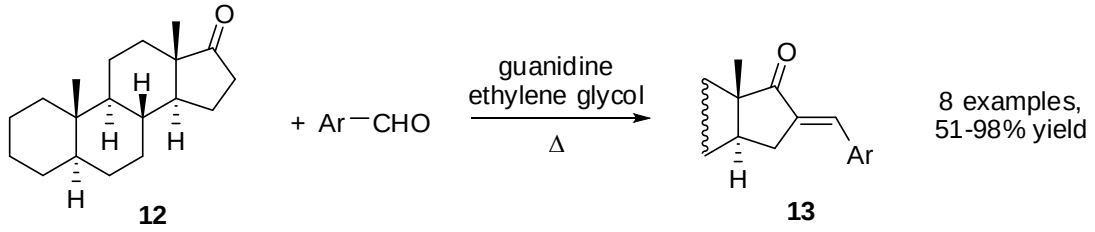
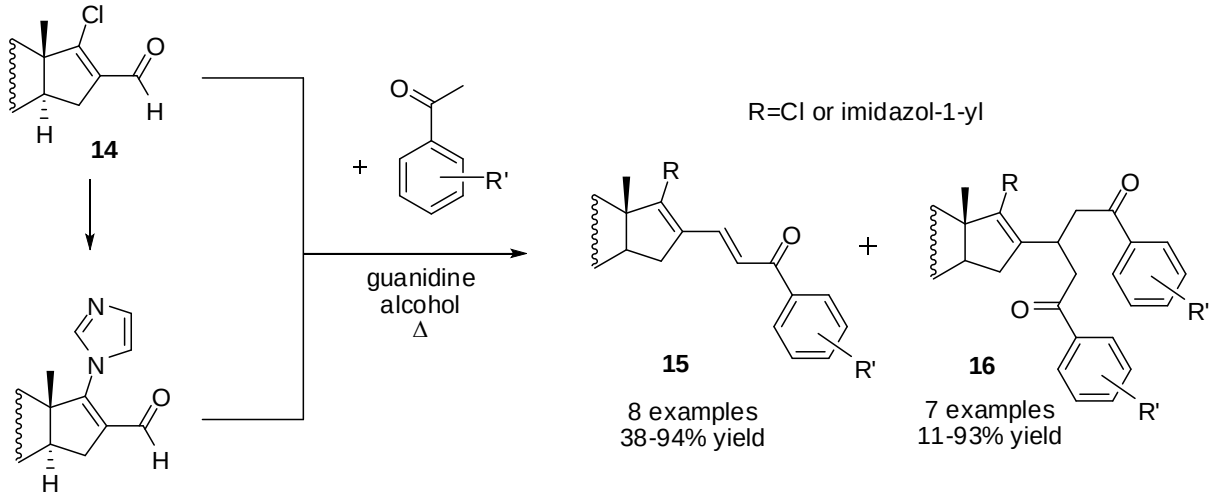


Figure 2: Guanidine base—alcohol mixtures investigated for reversability and catalytic activity

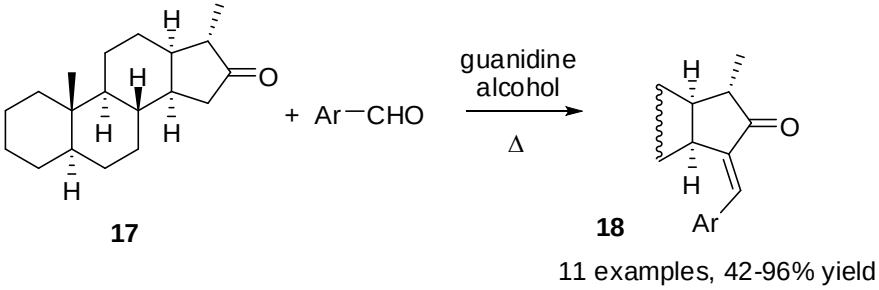
Condensation of three types of steroidal substrates were explored: the 17-keto compound **12** (Scheme 3) [10], 16-formyl derivatives bearing androstane or estrane skeleton **14** (Scheme 4) [11] and the 13-epi-derivative **17** (Scheme 5) [12].



Scheme 3. Claisen-Schmidt condensation of 17-keton (**12**) and aromatic aldehydes



Scheme 4. Claisen-Schmidt condensation of 16-formyl steroids and aryl-methyl ketones



Scheme 5. Claisen-Schmidt condensation of 16-keto-13-epi-steroid (**17**) and aromatic aldehydes

The results of the catalytic experiments in the three types of reactions can be summarised as follows:

i) The catalytic activity of guanidine bases increased in the order nBu-TMG < iPr-TMG < tBu-TMG < MTBD. E g. in case of the 16-formyl derivatives **14**, good conversion could be achieved only at 50-60 °C in the presence of nBu-TMG, while similar results were obtained at room temperature with tBu-TMG under otherwise identical conditions. Also, the condensation products of the much less reactive 13-epi-16-keto derivative **17** could be synthesised in low yields using nBu-TMG, while total conversion of the substrate was observed in short reactions with tBu-TMG or MTBD.

ii) The alcohol component had been shown to accelerate the condensation, so its presence was absolutely necessary not only during the separation step to form the IL, but also in the catalytic reaction. Although condensation of steroid **12** could be performed using methanol as the alcohol component, the results were poorly reproducible with conversions varying between 74-99%. It was assumed that a partial and uncontrollable evaporation of MeOH took place even at 50 °C.

iii) Ethylene glycol was thought to be a good choice for the alcohol component, as in principle, it could be recycled together with the guanidine base in contrast to methanol. Moreover, during the reaction of the least reactive substrate **17**, the application of diols as alcohol components was found to be absolutely necessary to attain good results. Quantum chemical calculations supports the assumption that diols are capable of forming two simultaneous H-bonds with the steroidal ketone that facilitates deprotonation of the α-CH, the first step of the condensation reaction.

The formation and reversibility of the ILs **O**, **P** were also investigated. The alcohol component had to be used in twofold excess compared to the base in order to achieve its total conversion to the corresponding guanidinium ion by the addition of CO_2. The structure of the new ILs and the formation of the non-symmetrical alkylcarbonates from ethylene glycol under the present conditions were proved by NMR spectroscopy. The assignment of the bands of IR spectra was supported by quantum chemical calculations.

CO_2 could be expelled relatively easily from ILs with methanol as the alcohol component by heating the IL in vacuum. The process was followed by conductivity measurements. At the same time, some of the ILs obtained from methanol (*e.g.* that formed with tBu-TMG) were miscible with toluene, the only apolar solvent that could be used for the extraction of the steroidal products. From this point of view, ethylene glycol was more suitable making it possible to isolate the products easily. At the same time, the IL formed from tBu-TMG,

ethylene glycol and CO_2 was too stable and could not be switched back into its molecular form without the loss of the original components.

As a summary, it can be concluded that the nBu-TMG/ethylene glycol mixture is suitable to carry out condensation of substrates **12** and **14**, while the application of the more expensive MTBD (together with ethylene glycol as the alcohol component) is absolutely necessary for the conversion of the less reactive 13-epi-steroid **17**. The recyclability of these base/alcohol mixtures was proved in all types of reactions: they retained their catalytic activity in at least five subsequent runs.

3.2. Aza-Michael addition of N-heterocyclic amines on 16-dehydropregnenolone

We encountered some problems in the IL catalysed aza-Michael reaction of 16-dehydropregnenolone (**7**) with imidazole (and other heterocyclic amines) namely poor solubility of the product in toluene that hindered the extraction of the product and the necessity to use the reagent in 5-10-fold excess to obtain good conversion (see section 2). As 1,1,3,3-tetramethyl-guanidine (TMG) is known to form ILs with weak proton donors, such as imidazole [13, 14] or pyrazole [14], moreover, these ILs are capable to capture CO_2 reversibly via the formation of carboxylates, a guanidine-catalysed reaction with catalyst recycling based on CO_2 absorption-desorption was envisaged (Figure 3).

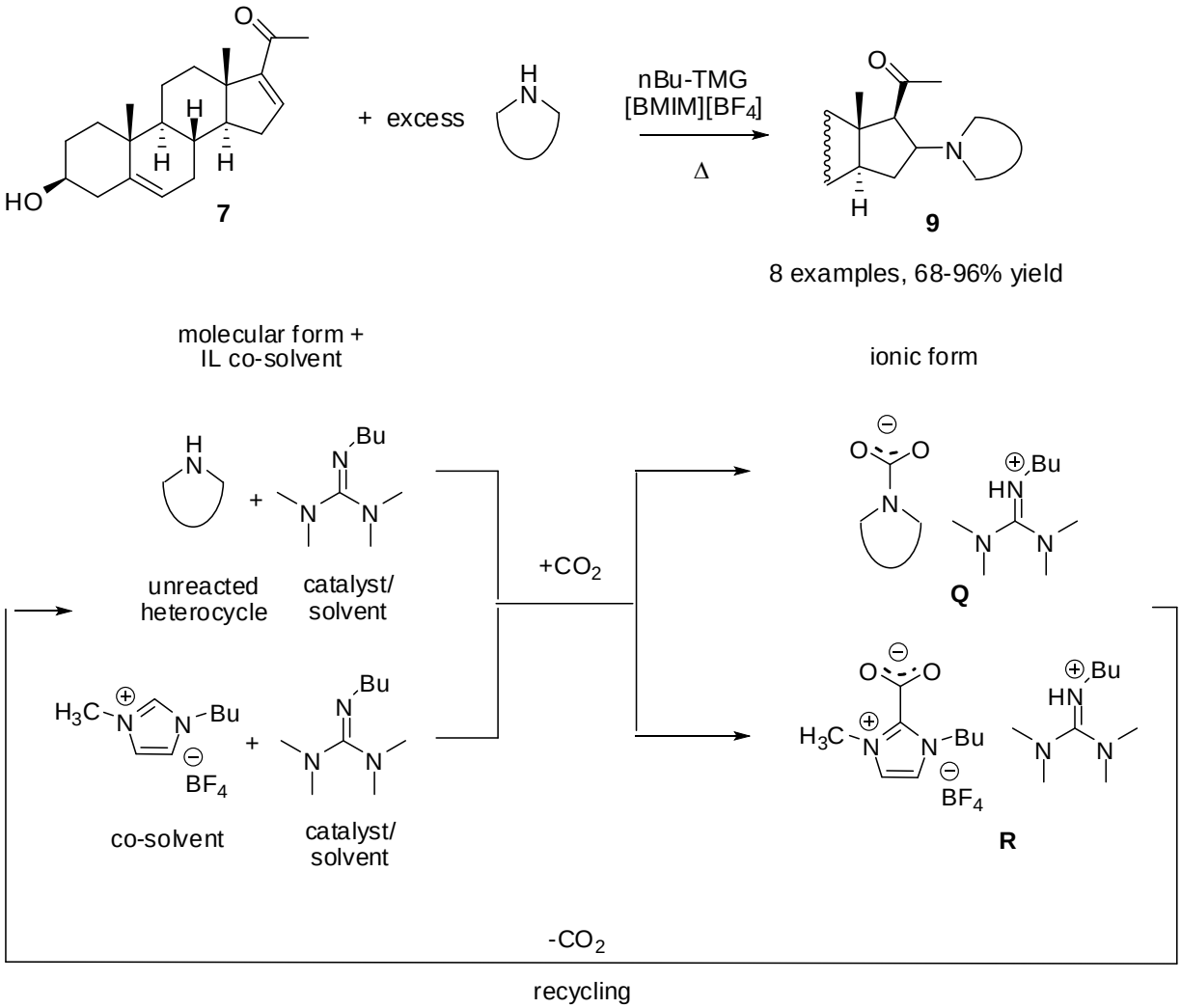


Figure 3. Excess reagent and catalyst recycling in the aza Michael additions of *N*-heterocycles

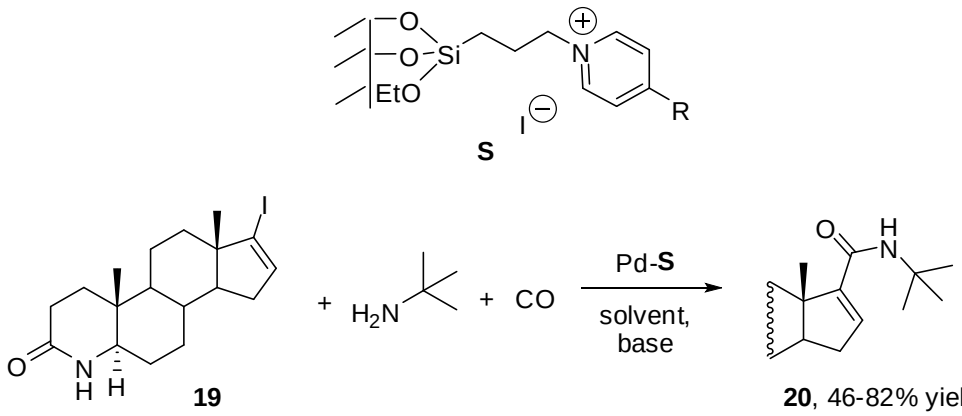
Similarly to the Claisen-Schmidt condensation, the guanidine base, nBu-TMG served as catalyst and solvent. In principle, the recycling of both the guanidine catalyst and the unreacted *N*-heterocycle could be achieved based on the formation of IL **Q**. At the same time, according to our observations, complete deprotonation of the *N*-heterocycle could not be realised in the presence of one equivalent of the guanidine base, moreover, if the latter was used as the solvent it had to be present in excess. So recycling of the base had to be worked out. The solution was the addition of an IL, [BMIm][BF_4] that had been reported to chemisorb CO_2 in the presence of a strong base with the formation of the ionic compound **R** [15]. That means that at the end of the reaction, the reaction mixture contains the product (**9**) (and some unreacted steroid **7**), the excess of the reagent, the guanidine base and [BMIm][BF_4]. After converting the non-steroidal components into a mixture of **Q** and **R** in the presence of CO_2, the steroids can be extracted with an apolar solvent. Then after the removal of CO_2, the excess reagent and the guanidine base can be recovered and reused. In the repeated reaction an equimolar mixture of steroid and reagent can be used. In order to develop the correct methodology, detailed investigations were carried out to determine the optimal ratio of steroid/*N*-heterocycle/guanidine base/[BMIm][BF_4] to avoid leaching of the *N*-heterocycle or the guanidine base during extraction. The reversible formation of ionic species **Q** and **R** were followed by NMR measurements. The method was used successfully for the reaction of various *N*-heterocycles, such as imidazole, benzimidazole, pyrazole, 1,2,3- and 1,2,4-triazoles, indazole and is under development for indole and carbazole. Recyclability of the system was proved in each case. Part of the results was summarised in a BSc thesis (by Boglárka Szele) and a manuscript is under preparation to be submitted [16].

4. Application of metal catalysts immobilised on supported ionic liquid phases

The application of immobilised metal complexes/salts may combine the advantages of homogeneous and heterogeneous catalysts. They retain the possibility to modify the environment of the catalytically active metal, and at the same time make the catalyst easily separable from the reaction mixture and readily recyclable. ILs are ideal modifiers of solid supports to prepare such heterogeneous catalysts: they can stabilise metal complexes and nanoparticles efficiently and they can be connected either by physisorption or chemisorption to the support. This methodology was used in two reaction types to convert steroidal substrates (among others) to products.

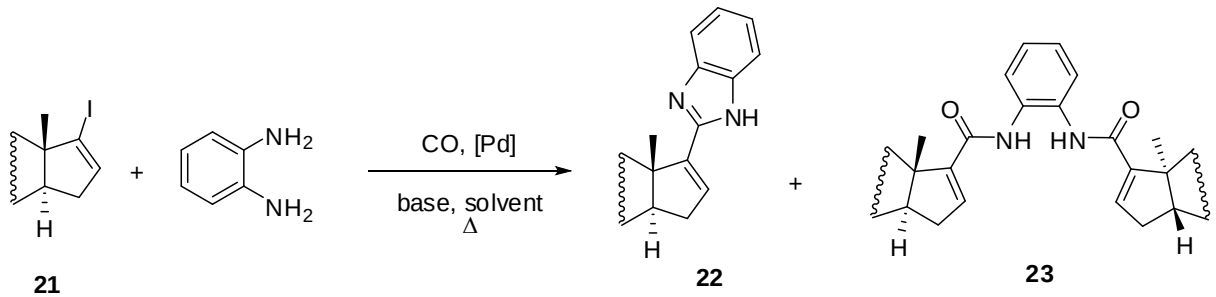
4.1. Pd-catalysed aminocarbonylation

It was shown that a considerably more efficient stabilisation of palladium particles could be achieved by a pyridinium SILP (**S**, Scheme 6) compared to its imidazolium and phosphonium counterparts. The presence of the grafted pyridinium cations on the surface of the support was found to result in the formation of highly dispersed Pd nanoparticles with their diameter in the range of 1-2 nm. Beside the aminocarbonylation of simple substrates and the synthesis of some active pharmaceutical ingredients, the conversion of steroidal iodoalkene **19** to amide **20**, an intermediate in the synthesis of the 5α-reductase inhibitor Finasteride [17] used in the treatment of benign prostatic hyperplasia, could be performed. The catalyst was recyclable in at least five subsequent runs, with a loss of only 0.02-2% of the original Pd load per run, depending on the reaction conditions [18].



Scheme 6. Heterogeneous catalytic aminocarbonylation of steroid **19** to produce an intermediate (**20**) of the synthesis of Finasteride

The same catalyst was tested in the synthesis of steroidal derivatives with a benzimidazole (**22**, scheme 7) moiety which potentially have antiandrogen effect. The synthetic method used in the preparation of the heteroaromatic ring involved palladium catalysed aminocarbonylation of various 17-iodo-steroids (**21**) in the presence of o-phenylenediamine and the subsequent intramolecular ring-closure. In contrast to the similar conversion of iodoarenes in the presence of the heterogeneous catalyst, the main product is the bis-amide (**23**) during the aminocarbonylation of steroidal iodoalkenes. The products could be isolated with yields up to 76%. Under homogeneous conditions these bisamides are the minor products beside the awaited benzimidazole derivatives. The results were summarised in an MSc thesis (by Máté Fonyó), the optimisation of reaction conditions and isolation processes are in progress.



Scheme 7. Synthesis of 17-benzimidazolyl steroids via aminocarbonylation of alkenyl iodides **21**

4.2. Cu-catalysed azide-alkyne cycloaddition

Heterogeneous copper catalysts were prepared by the deposition of CuI on a hybrid material consisting of silica and a polymer with imidazolium moieties (**T**). The solid materials were characterised by solid phase NMR-, FTIR-, Raman-, BET- and XPS measurements. The formation of Cu-carbene complexes was proved by Raman spectra and the results were supported by DFT calculations. The catalyst was used to prepare different triazole derivatives, among others five steroid derivatives of structures **24** and **25**. Good recyclability of the catalyst was proved in three consecutive runs for all pairs of substrates [19].

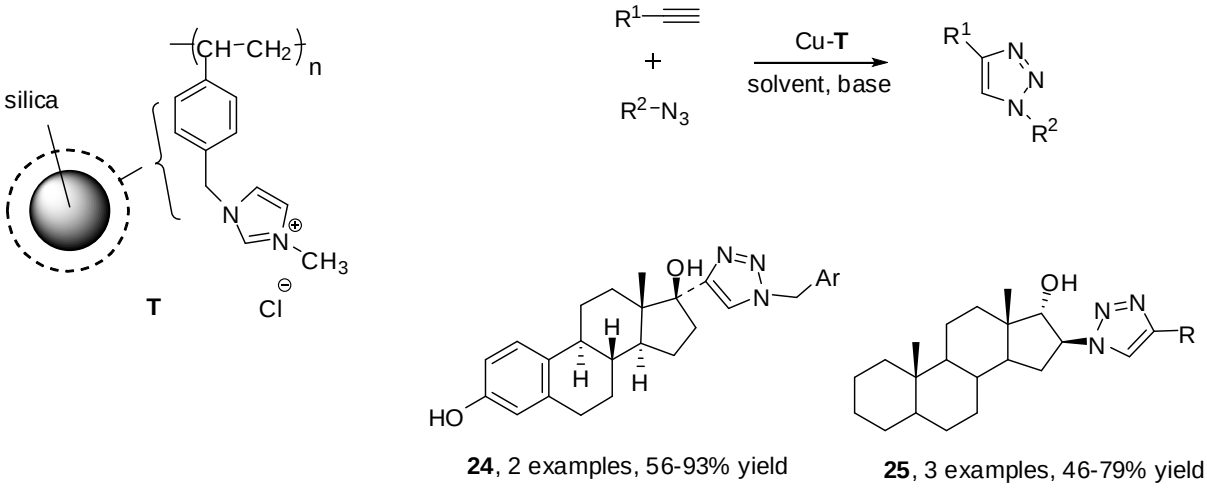


Figure 4. Structure of catalyst used in the CuAAC reaction and the triazole products.

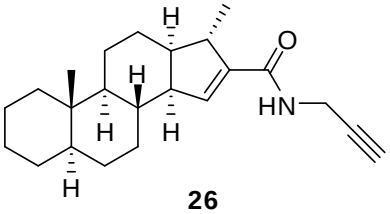
5. Biological studies

5.1. TRPV1 receptor inhibition studies

The synthesis of carboxamido steroid **26**, reported previously and involving an IL-catalysed rearrangement as the key step, was repeated to provide the necessary material for biological investigations. Compound **26** exerted prominent inhibitory effects on all investigated TRP channels located on primary sensory neurons, such as TRPV1, TRPA1, TRPM3 and TRPM8. The presence and the position of the carboxamido group were found to be important for this action. The first evidence was provided that steroid compound **26** was able to deplete cholesterol from the plasma membrane and exerted the same effect in 10 μM concentration as methyl β-cyclodextrin (MCD) in 1000-times higher concentration [20]. In vivo data provided the first evidence that steroid 26 exerted antinociceptive and antihyperalgesic effects. The maximal inhibitory effect observed in both TRPV1 and TRPA1 activation-induced nocifensive tests were similar to that of MCD, but in 150-fold lower concentrations. Furthermore, steroid 26 proved to be effective also on RTX-evoked mechanical hyperalgesia that was not affected by MCD [21].

5.2. Enzyme inhibition studies

The potential inhibitory effect of diverse previously synthesised triazolyl-ferrocene steroids on key enzymes of the estrogen biosynthesis was investigated. Inhibition of human aromatase, steroid sulfatase (STS) and 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) activities was investigated with in vitro radiosubstrate incubations. 17α-Triazolyl-ferrocene derivatives of 17β-estradiol exerted outstanding inhibitory effect and experiments demonstrated a key role of the ferrocenyl moiety in the enhanced binding affinity. Submicromolar IC_{50} and K_i parameters enrol these compounds to the group of the most effective STS inhibitors published so far [22].



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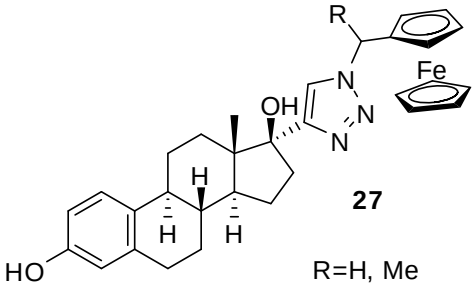

27

R=H, Me

Some aza-Michael adducts (**9**) were tested against the in vitro $C_{17,20}$- lyase activity of the rat testicular $P450_{17\alpha}$. The imidazole derivative was found to be the most potent inhibitor, displaying an IC_{50} value of 1.8 μM [5].

5.3. Cytotoxic activity

Thioether products (**10, 11**) were tested for cytotoxic activity on different breast cancer (MDA-MB-231, MCF7) cell lines. Interestingly, the triple negative (and more aggressive and less curable) MDA-MB-231 cell line showed higher sensitivity for most of the new compounds. The comparison of data obtained with 3-OH (**10**) and 3-OAc (**11**) compounds with the same 16-functionality showed greater toxicity of the former derivatives [6].

6. Concluding remarks

During the project, we succeeded in using recyclable catalytic systems based on ILs for acid-, base- or metal-catalysed reactions for the synthesis of steroids. These catalytic systems produced known and several new steroid derivatives with good to excellent yields. Based on biological activity tests, thioether compounds **10** that were found to be more effective on the triple negative (and more aggressive and less curable) MDA-MB-231 cell line, deserve further investigation. The synthesis and activity test of their sulfoxide and sulfone derivatives are planned. Further biological tests for the effect of carboxamide **26** are in progress, and optimisation of conditions for the multistep synthetic procedure is under way.

Besides the publications that have already appeared, the drafts of one manuscript [12] is almost ready and will be submitted soon. Also, another manuscript on the synthetic work concerning aza-Michael addition of *N*-heterocyclic amines on 16-dehydropregnenolone (section 3.2) is under construction [16]. As molecular and ionic forms of mixtures obtained with the 8 heterocycles were investigated carefully by NMR methods including low-temperature and 2D measurements, these results are planned to be submitted in a separate publication, being beyond the scope of a synthetic work.

The results formed the basis of 2 BSc and 6 MSc thesis projects. (In the present report only those are mentioned in the text the results of which have not been included in the publications, yet.) 2 PhD theses will also be submitted at the end of this year. Part of the work was presented by undergraduate students at the conferences of the Scientific Students' Associations.

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