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Friedel–Crafts alkylation of benzene with α,β-unsaturated amides ☆

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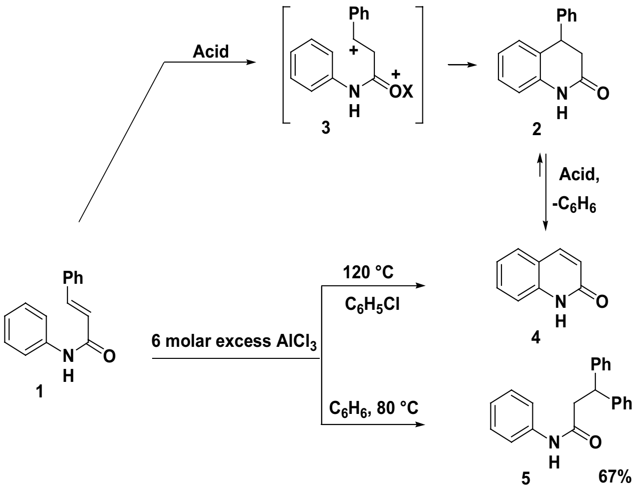
Abstract—A variety of α,β-unsaturated amides ($RHC{=}CH_2CONR'_2$, R = H, Me, Ar; R′ = H or Et) readily condense with benzene at room temperature in the presence of an excess of aluminum chloride to give the corresponding 3-phenylpropionamides in excellent yields. This simple, one-pot procedure proved to be efficient and very clean. The mechanism of these and related reactions is discussed and the participation of superelectrophilic dicationic intermediates is suggested.

Despite their broad utility in organic chemistry, little work has been done to evaluate amides in their reactivity toward weak nucleophiles such as arenes. Their reactions in Friedel–Crafts type chemistry are unusual and mostly known for Bischler–Napieralski and related methods of preparation of heterocyclic compounds.[1] The use of amides has serious limitations because of competing hydrolysis and other acid catalyzed reactions.

To develop the electrophilic reactivity of amides we suggest to subject them to superelectrophilic[2] (dicationic) activation under superacidic conditions. Recent years have seen the appearance of productive synthetic approaches involving superacidic activation of naphthols, quinolinols, isoquinolinols, and a variety of other heterocyclic and polyfunctional compounds.[3] Similar activation of amides could involve their O-protonation[4] or O-complexation[5] with Lewis acid with subsequent additional protonation of closely situated appropriate functional groups.

Thus, it was recently shown, that cinnamanilide **1** cleanly undergoes intramolecular cyclization in triflic acid (CF_3SO_3H) to give quinolinone **2** in good yield.[6] It was postulated, that superelectrophilic activation involved O,C-diprotonation of **1** to produce dications **3** (X = H) (Scheme 1). Similar reaction also occurred under classical Friedel–Crafts procedures at elevated temperature to give **2** in lower yields due to its subsequent reversible conversion into carbostyril **4**.[6,7] The latter reaction is predominant, for example, upon treatment of **1** with excess $AlCl_3$ in chlorobenzene.[8] Remarkably, similar treatment of **1** in benzene gives mostly product **5** due to competing intermolecular reaction (Scheme 1).[8]

Given the reactivity of amide **1**, it seemed likely that a variety of α,β-unsaturated amides, in general, would



Acid = CF_3SO_3H, H_2SO_4, Polyphosphoric acid, $AlCl_3$, $AlBr_3$;

X = H or $\bar{Al}_nCl_{3n}$ or $\bar{Al}_nBr_{3n}$

Scheme 1.

Keywords: Friedel–Crafts; Alkylation; Superelectrophile; Aluminum chloride; Amide.

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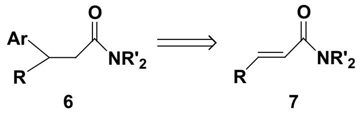
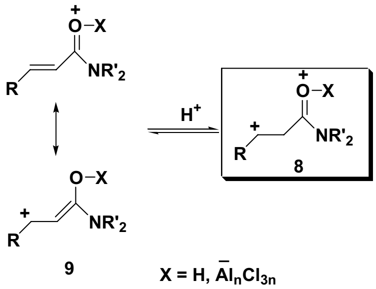


Scheme 2.

give intermolecular reactions, analogous transformation **1** → **5**, with aromatic compounds. Electrophilic reactions of α,β-unsaturated acids, aldehydes, ketones, nitriles, sulfones, and sulfonates with aromatics are known, offering an access to the corresponding β-arylated derivatives.[9] Due to their importance as pharmacophores, various syntheses of β-arylpropionamides **6** have been reported, but they suffered from multistep procedures or low yields.[10] To simplify the synthesis of such useful intermediates, we reasoned that readily available α,β-unsaturated amides **7** and appropriate aromatic compounds ArH could be direct precursors toward **6** (Scheme 2).

In this communication, we describe our preliminary results showing that compounds **7** indeed react with benzene upon activation by strong acids to give the corresponding derivatives **6** (Table 1). The reaction takes place under mild conditions (at room temperature) and appears to be fast in the presence of 2–3 molar excess of $AlCl_3$. This procedure is very clean and in most cases gives products **6** in quantitative yield.[11] It was also demonstrated that the same reaction is initiated by triflic acid (Ho = −14.1[12]), but not as efficiently. This result is in agreement with earlier observations: the efficiency of electrophilic activation upon action of excess aluminum halides is comparable to that of such strong acids as $CF_3SO_3H–SbF_5$ (Ho ∼ −18.5[12]) and even $HF–SbF_5$ (Ho < −20[12]).[3a–c] This effect can be related to the ability of excess of aluminum halides to produce with water (usually present in 'dry' commercially available materials) highly acidic protonic superacids, such as $HAlHal_4$ and $HAl(OH)Hal_3$ (Hal = Cl, Br) in low concentration.[12,13] For comparison, $HBr–AlBr_3$ system (Ho ∼ −17.5[12]) has been claimed to be a 10^3 times stronger acid than triflic acid.

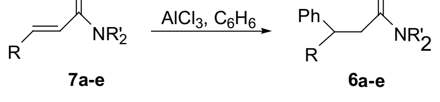


Scheme 3.

The reaction mechanism, proposed, at least in case of compounds **7c–e**, suggests the formation of superelectrophilic dicationic intermediates such as α-C-protonated complexes **8** ($X = Al_nCl_{3n}^-$) or analogues O,C-diprotonated dications **8** (X = H) in low concentration (Scheme 3). Similarly, dicationic species **3** may be considered as key alkylating intermediates in reaction **1** → **5** (Scheme 1). In our opinion, consideration of these reactions as 'traditional' Friedel–Crafts alkylation involving only the intermediacy of monocationic species **9** cannot explain all the experimental results, such as: (i) the lower reactivity in triflic acid, which is acidic enough to exhaustive O-protonation of the amides; (ii) higher reactivity of **7d**, than that of **7a–b**, whereas the latter should produce significantly stronger monocationic electrophiles **9**; (iii) moreover, we have found, that precursors **7c–e**, in contrast to **7a–b**, readily react (for several hours at room temperature) with *o*-dichlorobenzene, which due to poor nucleophilicity[14] is known to be inert toward usual C-electrophiles. For this reason we suggest that the reactive intermediate is the dicationic species **8** (R = Ar) probably in equilibrium with corresponding monocations **9**.

On the other hand, when we dissolved compound **7e** in triflic or fluorosulfuric (Ho = −15.1[12]) acids, ^1H and ^{13}C NMR spectra[15] of the solutions showed its total conversion in O,C-diprotonated dication **8** (R = *p*-$MeOC_6H_4$; R′ = X = H). The spectra exhibit the signal of the CH_2 group at δ 4.6 ppm in proton NMR and δ 36 ppm in the carbon NMR. The proton spectrum also

Table 1. Reactions of amides **7a–c** with benzene in the presence of 2.5 molar excess of $AlCl_3$ at 25 °C[a]



Entry	R	R′	α,β-Enamide	Reaction time (h)	β-Phenylamide	Yield (%)[b]
1	H	H	**7a**	2[c]	**6a**	99
2	CH_3	H	**7b**	3	**6b**	93
3	Ph	H	**7c**	4	**6c**	97
4	Ph	C_2H_5	**7d**	0.5[d]	**6d**	100
5	*p*-$MeOC_6H_4$	H	**7e**	5[e]	**6e**	98

[a] The ratio of the reagents and the reaction conditions are not completely optimized.

[b] The yields are of isolated, pure products.

[c] For comparison, the reaction carried out upon action of 10 molar excess of triflic acid gave only 17% conversion of **7a** into **6a** after 20 h.

[d] Upon action of 7 molar excess of triflic acid the reaction requires 15 h to obtain **6d** in quantitative yield.

[e] 5 Molar excess of $AlCl_3$ was used.

shows the signal of the hydrogen bound to carbonyl oxygen at δ 10.6 ppm and the signal of the amino hydrogens at δ 8.7 ppm (HSO_3F, −80 °C), that is similar to chemical shifts for O-protonated amides.[4a] The chemical shifts of signals assigned to the benzylic site of the dication are in accord with those reported for analogous benzylic dicationic systems.[16] Similar O,C-diprotonation of α,β-unsaturated ketones[17] and nitro compounds[18] in superacids have been described earlier. The involvement of such dications (or analogous protonated complexes with aluminum halides) as plausible reaction intermediates also have been discussed.[17–19] Recently, alkylation of aromatics with α,β-unsaturated carboxylic acids was performed in triflic acid and intermediacy of dicationic species suggested.[20]

It is worth to note, that the utility of $AlCl_3$ as cheap and convenient alternative to strong protic (super)acids is probably underestimated. Whereas the presence of small amounts of base (water) decreases drastically the acidity of superacid,[21] traces of humidity are rather beneficial to the reactivity of aluminum halides, which may be used without special dryness of starting materials or solvent and do not require inert gas atmosphere.

In conclusion, we have demonstrated that the reaction of α,β-unsaturated amides with aromatics initiated by strong Lewis or Bronsted acid can be a convenient alternative to known preparations of 3-arylpropionamides. We suggest that dicationic electrophiles, such as those directly observable by low-temperature NMR when α,β-unsaturated amides are dissolved in liquid superacids, are a convenient rationale in accord with the reaction mechanism.

Acknowledgements

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