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Direct synthesis of arenecarboxamides through Friedel–Crafts acylation using ureas

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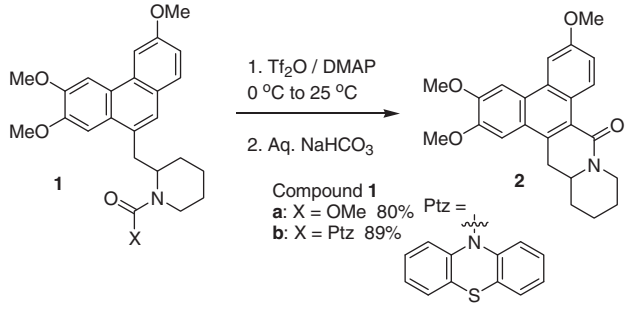
ABSTRACT

The reaction of urea derivatives that contain the phenothiazine unit with trifluoromethanesulfonic anhydride in the presence of electron-rich aromatic compounds leads to the formation of arenecarboxamides. The reaction has been successfully demonstrated for several inter- and intramolecular systems.

Friedel–Crafts acylation reaction has proven to be one of the most valuable reactions for the preparation of aromatic ketones, and is presented as a fundamental reaction in every introductory organic chemistry textbook. Friedel–Crafts acylation has proven less effective for the preparation of other types of carbonyl compounds. In a recent total synthesis of the phenanthroindolizidine alkaloids antofine and cryptopleurine, the intramolecular Bischler–Napieralski reaction of carbamate derivative **1a** (Scheme 1) to afford lactam **2** accomplished the final ring closure.[1] However, the urea analog **1b** could be prepared in a higher enantiomeric purity than carbamate **1a**. The phenothiazine urea was chosen as a synthetic intermediate in anticipation that the urea group would be hydrolyzed to the free amine, a well-known precursor to cryptopleurine.[2] Urea hydrolysis normally occurs only under harsh conditions, however a reported oxidative hydrolysis unique to phenothiazine ureas occurs under relatively mild conditions.[3] Oxidative hydrolysis of urea **1a** failed. Out of desperation to finish the synthesis, urea **1b** was subjected to the same conditions employed for the carbamate-based ring closure. This reaction readily afforded the desired lactam **2** in even higher yield than the established process employing carbamates.[4]

The number of examples where ureas participate in the Friedel–Crafts reaction is highly limited. The urea carbonyl group is minimally electrophilic[5] and if the urea is unsymmetrical there is a chemoselectivity issue. Reports involving the direct conversion



Scheme 1.

of ureas to aromatic carboxamides include: (1) a process based on the Fries rearrangement of *N*-phenyl ureas,[6] (2) C-aminoacylation of phenoxides using a magnesium/aluminum oxide catalyst at 230 °C,[7] (3) intramolecular cyclization of in situ generated (carbodiimide + acylurea) acylguanidines,[8] (4) intramolecular reactions using N-2-pyridylureas using $POCl_3$/PPTS at 138 °C,[9] (5) intramolecular cyclization of an *N*-phenyl urea at 270–280 °C,[10] (6) cyclization of N-pyrroloureas at 260–280 °C,[11] and (7) a four-membered ring 'diisocyanate' undergoing an intramolecular reaction.[12] In addition several papers that involve the aminoacylation of aryllithiums have also been reported.[13] During this investigation an alternate breakthrough approach employing triflic acid at 50 °C was reported and successfully demonstrated for the synthesis of many

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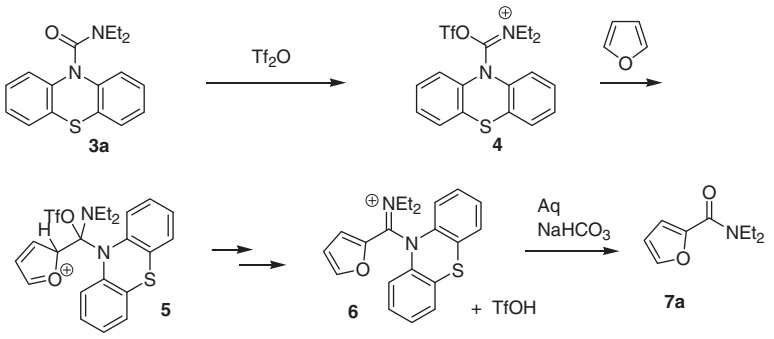
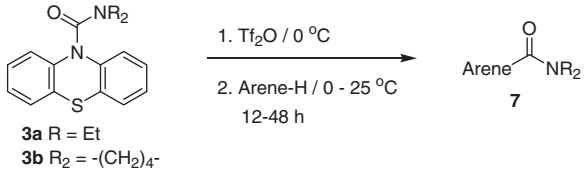
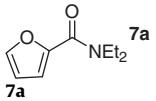
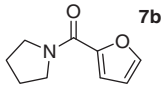
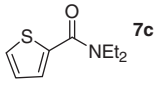
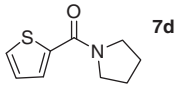
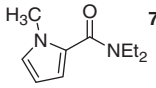
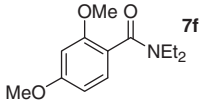
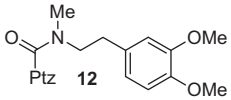
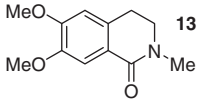


Scheme 2.

Table 1
Friedel–Crafts acylation of arenes using N-phenothiazine ureas



Entry[a]	Arene-H	Urea	Conditions[b]	Amide product	Yield[c]
1	Furan	**3a**	B	 **7a**	67
2[d]	Furan	**3a**	A	**7a**	70
3	Furan	**3b**	B	 **7b**	31
4	Thiophene	**3a**	A	 **7c**	68
5	Thiophene	**3b**	B	 **7d**	80
6	*N*-Methylpyrrole	**3a**	A	 **7e**	57
7	1,3-Dimethoxybenzene	**3a**	A	 **7f**	40
8	1,3-Dimethoxybenzene	**3a**	B	**7f**	63
9[e]	 **12**	N/A	A	 **13**	90

[a] For detailed experimental and photocopies of ^{1}H and ^{13}C NMR spectra (using the higher yielding method) see the Supporting information.
[b] Conditions: A—no DMAP, B—3 equiv DMAP, and 4–5 equiv of Tf_2O.
[c] Isolated yields.
[d] For the procedure, see Ref. 18.
[e] For the procedure see Ref. 19.

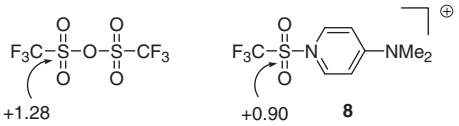


Figure 1. Charge at S for Tf_2O and the DMAP adduct.

primary arenecarboxamides[14] and one secondary arenecarboxamide. The arenecarboxamide forming reaction in Scheme 1 is thus potentially very useful due to the rarity of the transformation and the relatively harsh conditions required in studies to date, coupled with the ready availability of the requisite starting materials. The phenothiazine urea reactants are easily prepared from the reaction of amines with inexpensive phenothiazine carbonyl chloride. In this manuscript the scope and limit of the reaction in Scheme 1 will be delineated.

Initial studies involved examination of the intermolecular reaction between urea derivative **3a**[15] (Scheme 2), triflic anhydride,