Published in final edited form as:
Tetrahedron Lett. 2014 August 13; 55(33): 4541–4544. doi:10.1016/j.tetlet.2014.06.056.

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.

The 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 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 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

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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 °[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 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, and furan, which is inexpensive, volatile, and highly activated in electrophilic aromatic substitution reactions (Scheme 2).[16] Exactly the same conditions were employed as noted for the reaction in Scheme 1, which employed 4-5 equivalents of triflic anhydride and 3 equivalents of DMAP at 0° C followed by warming to room temperature.[4] Initially this reaction was tested using a very large excess of furan and produced the desired furancarboxamide derivative **7a** as the only furan-containing product. Later experiments employed 3-4 equivalents of furan and the reaction still worked effectively. Under the optimal conditions (see Table 1) furan amide **7a** was obtained in 67% yield. The proposed mechanism is depicted in Scheme 2. The active species, presumably iminium salt triflate **4**, was generated through reaction with triflic anhydride. Reaction of the activated arene then affords the arylated iminium salt **6** through electrophilic aromatic substitution, which is then converted to urea **7a** upon treatment with aqueous sodium bicarbonate.

After optimizing the reaction leading to amide **7a** we were somewhat perturbed by the unreliability of the process in some experimental runs. The reaction would occasionally proceed in low yield or completely fail. Analysis of the reaction mechanism reveals no obvious role for DMAP except for the possible neutralization of triflic acid in a very late reaction event. Although DMAP is commonly used to activate acylations and tosylations, its use as a triflic anhydride activator seems illogical since triflate is among the best known leaving groups. DMAP would more than likely de-activate triflic anhydride, and we thus hypothesized that only the small molar excess of triflic anhydride is actually doing anything. A DFT comparison of triflic anhydride and the cationic sulfonylpyridine **8** (Figure 1) revealed that the Mulliken atomic charge at sulfur is actually more positive in triflic anhydride (+1.28 compared to 0.90 in **8**).[17] To test this possibility, we examined the reaction with only a slight excess of triflic anhydride and no DMAP. In these cases, the reaction was successful using the same temperatures as previously established, and these latter conditions proved to be more reliable and less wasteful of triflic anhydride.

The reaction was next examined using a variety of substrates (see Table 1). The reaction appears to be restricted to very electron-rich aromatic ring systems. Furan, thiophene, N-methylpyrrole, and 1,3-dimethoxybenzene participated in the reaction to afford the arenecarboxamide in reasonable yield. The reaction did not work for toluene and ferrocene, thus only activated rings were tested. Toluene appeared to be inert, however reactions employing ferrocene developed intense blue color and no identifiable products. The more activated but more hindered compound 1,3,5-trimethoxybenzene failed. Both the diethylamine and pyrrolidine-derived ureas were successfully employed in the reaction. Failure was noted for the Weinreb urea. The intramolecular reaction in entry 9 as well as the one employed in the total synthesis in Scheme 1 both proceeded in excellent yield. The use of a primary amine derived system (**9**, Scheme 3) did not result in the amide but rather afforded a product that still contains the phenothiazine group, likely the amidine structure **11**. This compound was very resistant to any further hydrolysis attempts.[20]

In summary, we have demonstrated a new method that directly transforms electron rich aromatics into arene carboxamides. Precursor compounds are readily prepared from inexpensive phenothiazine carbonyl chloride and only the phenothiazine group is consumed in the urea-forming process. The method proceeds under mild conditions and complements a recently-reported method that has barely been examined for tertiary amide formation. The method does not require a prior metallation of the system to be successful.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the SCORE program of NIH (SC1GM083693) and the MARC program of NIH (5T34GM007667-36) for financial support of this research. We thank Bishnu Dhakal for assistance in the acquisition of spectral information.

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18. To a solution of compound 3a (298 mg, 1.0 mmol) and furan (204 mg, 3.0 mmol) in dichloromethane at 0 °C was added a 1.0M solution of trifluoromethanesulfonic anhydride in dichloromethane (1.5 mL, 1.5 mmol) dropwise over 10min. The solution was allowed to warm to room temperature and stirred for 48 h, after which time aqueous sodium bicarbonate solution was added and the mixture was stirred vigorously for additional 3 h. The reaction mixture was extracted using diethyl ether. The organic layer was washed with water and saturated aqueous sodium chloride consecutively. The washed organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the crude product was purified using column chromatography on silica gel using 2:1 hexane:ethyl acetate as eluent. The compound 7a was isolated as yellow oil (117 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (dd, 1H, J = 1.8, 0.9 Hz), 7.01 (dd, 1H, J = 3.5, 0.9 Hz), 6.47 (dd, 1H, J = 3.5, 1.8 Hz), 3.56 (br peak, 4H), 1.25 (br t, 6H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 148.7, 143.5, 115.7, 111.2, 41.3 (very broad), 13.1 (very broad). The spectral data were in agreement with those previously reported for this compound. Wang X, Wang DC. Tetrahedron. 2011; 67:3406–3411.
19. To a solution of compound 12 (101 mg, 0.238 mmol) in dichloromethane at 0 °C was added a 1.0M solution of trifluoromethanesulfonic anhydride in dichloromethane (0.357 mL, 0.357 mmol). The solution was allowed to warm to room temperature and stirred for 30 h, after which time aqueous sodium bicarbonate solution was added and the mixture was stirred vigorously for additional 3 h. The reaction mixture was extracted using diethyl ether. The organic layer was washed with water and saturated aqueous sodium chloride consecutively. The washed organic layer was dried over anhydrous sodium sulfate. The solvent was removed and the crude product was purified using column chromatography on silica gel using 2:1 hexane ethyl acetate as eluent. Compound 13 was isolated as an off-white solid (47 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (s, 1H), 6.63 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.54 (t, 2H, J = 6.7 Hz), 3.13 (s, 3H), 2.94 (t, 2H, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.9, 151.6, 147.7, 131.5, 122.0, 110.5, 109.5, 56.1, 56.0, 48.4. 35.2, 27.5. The spectral data were consistent with those previously reported for this compound. Said IM, Hamid NAA, Latif J, Din LB, Yamin BM. Acta Cryst. 2005; E61:o797–o798.
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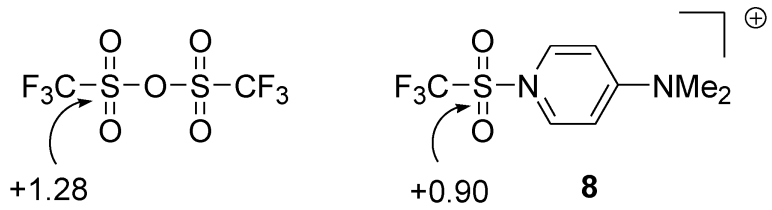
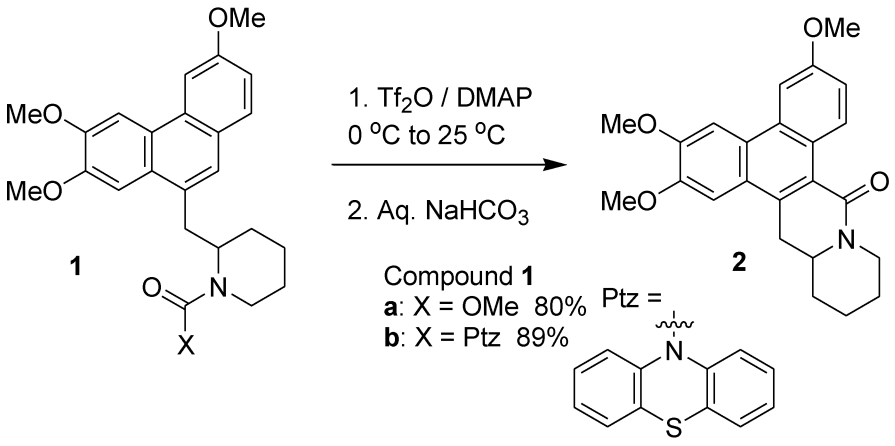
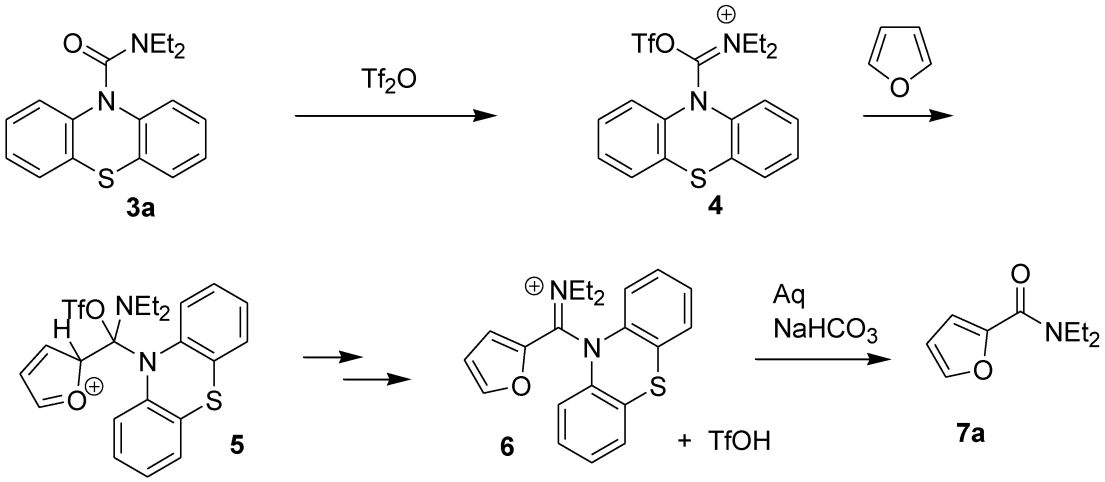


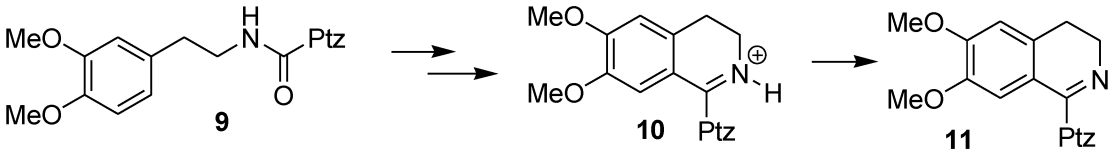
Figure 1.
Charge at S for Tf_2O and the DMAP adduct.



Scheme 1.



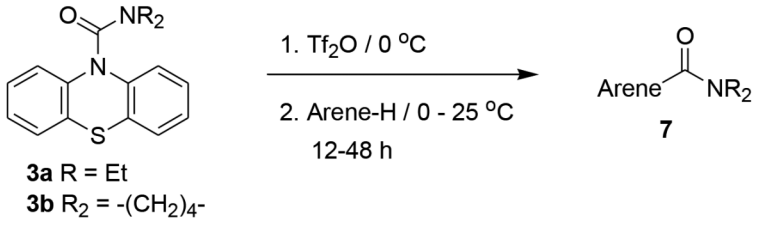
Scheme 2.

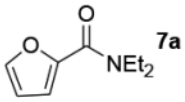
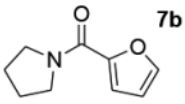
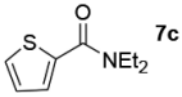
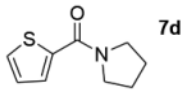
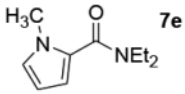
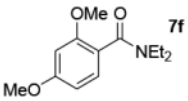
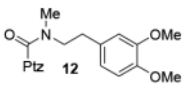
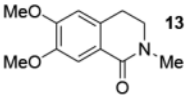


Scheme 3.

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 eq DMAP and 4-5 eq of Tf_2O.

[c] Isolated yields.

[d] For a procedure, see Reference 18.

[e] For a procedure see reference 19.