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ARTICLE TYPE

Friedel-Crafts-type reactions with ureas and thioureas

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5 Despite the relatively low reactivities of urea and thiourea functional groups towards nucleophilic attack, we have found Published on 22 June 2012 on http://pubs.rsc.org | doi:10.1039/C2CC34062C conditions in which they are useful substrates in Friedel-Crafts reactions. The Brønsted superacid, triflic acid, promotes these reactions and a mechanism is proposed 10 involving dicationic, superelectrophilic intermediates. Known since the 1870s, Friedel-Crafts reactions involve the reactions of cationic electrophiles with arene nucleophiles.¹ They commonly involve reactive intermediates such as acyl cations,

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carbocations, carboxonium ions, iminium ions, and other 15 species.² These reactions are of great practical value, being used to produce chemical feedstock, synthetic intermediates, and fine chemicals. Recently, we reported several new methods of accomplishing Friedel-Crafts acylation using amides.³ Amides have not generally been considered viable substrates for Friedel-

20 Crafts chemistry primarily because the strong amide bond prevents cleavage to the acyl cation. Moreover, resonance interactions are thought to raise the energy of the LUMO at the carbonyl group - inhibiting direct nucleophilic attack. In our acylations using amides, we utilized the high reactivities of 25 dicationic superelectrophiles. Amide activation involved charge-

charge repulsive effects and diminished amide resonance.³ Ureas or carbamides are another functional group known for low reactivity towards nucleophiles. This stability is evident by the remarkably slow hydrolysis rates of ureas.⁴ Indeed, the ureas 30 represent perhaps the weakest of all carbonyl-centered electrophiles. Not surprisingly, there have been no previous

- reports of ureas being using in Friedel-Crafts chemistry, as arenes are also very weak nucleophiles. Recent work by Hutchby et al. has shown that ureas may undergo activation by N-protonation
- 35 leading to cleavage and solvolysis reactions.⁵ The proposed mechanism invokes cleavage of the urea to an isocyanate and nucleophilic attack by the solvent (methanol) to provide carbamate products. Since isocyanates are known to be useful in Friedel-Crafts-type reactions (giving amide products),⁶ we sought
- 40 to determine if ureas could provide aromatic amides through analogous chemistry. In the following Communication, we describe Friedel-Crafts-type reactions with urea and thiourea substrates.

Previously, Shudo and co-workers had demonstrated the high 45 reactivities of species bearing nitro-substituted aryl groups when the reactions are done in superacidic media.⁷ We reasoned that nitrophenyl-substituted ureas might exhibit an enhanced level of electrophilic reactivity by virtue of the electron withdrawing

effects of the aryl group. Our studies began with cyclizations of 50 phenethylamine-based ureas (eq 1). The urea substrates (1-2) were readily prepared by the reactions of phenethylamine and the appropriate aryl isocyanate. When 1-phenethyl-3-phenylurea (1) is reacted with CF3SO3H at 50°C, only the starting material is found in the product mixture. In contrast, the same reaction with

⁵⁵ 1-(2-nitrophenyl)-3-phenethylurea (2) provides nearly а quantitative yield of 3,4-dihydroisoquinolin-1(2H)-one (3). The same product (3) is obtained in 85% yield with use of the 1-(4nitrophenyl)-3-phenethylurea. Clearly, the nitro group can have a profound effect on the reactivity of N-phenylureas.

- Following these conversions, a series of ureas (4-10) were prepared for cyclization reactions (Table 1).⁸ Simple alkyl and phenyl substituted derivatives (4-6) undergo cyclizations to give the respective heterocyclic products (11-13). In an effort to prepare other diverse structures, the branched derivatives (7-9) 65 were also reacted in superacid. Although the methyl-substituted urea (7) reacted smoothly to provide compound 14 in good yield, the (S)-prolinol-derived urea 8 did not give a 3,4dihydroisoquinolin-1(2H)-one but rather cyclized to the
- benzylsubstituted oxazolidinone (15). Since the hydroxyl group is 70 a stronger nucleophile than a phenyl group, cyclization occurs at the hydroxymethyl and product 15 is formed. The desired 3,4dihydroisoquinolin-1(2H)-one ring may be formed however, if the hydroxyl group is blocked the nicotinoyl group. Thus, compound 9 undergoes cyclization to provide heterocycle 16 in 75 good yield. Under the acidic reaction conditions, the pyridyl ring is completely protonated and the ester exhibits little or no nucleophilic reactivity, allowing for cyclization at the phenyl group. Finally, urea 10 also provides the cyclization product, isoindolin-1-one 17, although the yield is somewhat lower than ⁸⁰ the reactions giving 3,4-dihydroisoquinolin-1(2H)-ones. In addition to the reactions of ureas, several thiourea substrates were examined and also found to provide the cyclization products (eq 2). The phenethylamine-derived thiourea 18 gives the 3,4dihydroisoquinoline-1(2H)-thione (21) in fair yield, while the 85 tolyl and chlorophenyl derivatives (19-20) provide the respective
- heterocycles (22-23) in good yields.

Both urea and thiourea substrates were also found to undergo intermolecular reactions in reactions with benzene. For example, N-phenylbenzamide (28) is produced in 68% yield from the urea

90 24 (Table 2). The piperidinyl urea 25 also gives products from carboxamidation of benzene (29) and toluene (30), though the yields are somewhat low. Surprisingly, the urea from benzylamine (26) provides nearly a quantitative yield of

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triphenylmethanol (**31**) from reaction with benzene in triflic acid. The thiourea **27** also provides a Friedel-Crafts-type product with benzene, as the thioamide **32** is isolated in 53% yield. Finally, 1,3-bis-(4-nitrophenyl)urea (**33**) reacts with benzene in triflic acid s to give benzophenone (**34**) in good yield (eq 3). This conversion likely involves formation of the amide **35** - a compound which is

- likely involves formation of the amide 35 a compound which is known to provide benzophenone in high yield under the reaction conditions.^{3e}
- For the reactions of the urea substrates, a mechanism is 10 proposed involving protonation of the nitro group and urea nitrogen, cleavage to the protonated isocyanate, followed by reaction with the arene nucleophile (Scheme 1). To examine this mechanism, theoretical calculations were done to study the reaction of urea 24 with acid.⁹ Urea substrates are relatively 15 strong bases. The pKa values for protonated ureas range from about +2 to $-2.^{10}$ As one of the strongest Brønsted acids, ¹⁰ triflic acid should completely protonate the urea substrates and equilibria would be established with deprotonated superelectrophilic species. Thus, urea 24 would form the 20 monocation 36 by protonation of the carbonyl oxygen. A second protonation at the nitro group leads to dication 37 – the most stable dicationic species. Hutchby's recent work demonstrated that protonation of the urea nitrogen may lead to cleavage reactions.⁵ Equilibration with the O,N-diprotonated species **38** is 25 estimated to require +11.3 kcal/mol of energy and the transition state leading to carbon-nitrogen bond cleavage (39) is about +17.3 kcal/mol above dication 37. At the reaction temperature of 60°C, this should be a readily surmountable barrier. Previous studies have shown that dicationic superelectrophiles tend to 30 favor reaction steps that separate or jettison charge from the multiply charged ions.¹² Cleavage to the monocations (protonated o-nitroaniline 40 and isocyanate 41) serves this purpose. Product 28 is then formed by a Friedel-Crafts-type reaction of the 41 and the arene nucleophile. Presumably, a similar mechanism operates 35 for the intramolecular reactions and the conversions involving thioureas. It is not presently clear how triphenylmethanol 31 arises from urea 26, but a possible route involves some type of
- ⁴⁰ We have found that urea and thiourea substrates will participate in superacid catalysed Friedel-Crafts-type reactions. Both intra and intermolecular reactions have been demonstrated, although the intramolecular conversions were generally more efficient. This is a particularly good synthetic route to 3,4the divergence of the second synthetic route to 3,4-

cleavage reaction to liberate the benzyl cation.

⁴⁵ dihydroisoquinolin-1(2H)-ones and related thiones. A mechanism is proposed involving formation of diprotonated, superelectrophilic intermediates and cleavage to isocyanate-type electrophiles.

50 Notes and references

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60 ‡ Dedicated to Professor George A. Olah on the occasion of his 85th

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Table 1. Products and yields from reactions of ureas (4-10) with CF₃SO₃H.



^aIsolated yields. ^bReaction with 16 eq CF₃SO₃H, CH₂Cl₂, 50°C.

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Table 2. Products and yields from reactions of substrates (24-27) with CF_3SO_3H and benzene or toluene.

^alsolated yields. ^bCF₃SO₃H, C₆H₆, 50°C. ^cCF₃SO₃H, toluene, 50°C.

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Scheme 1. Proposed mechasnim with calculated relative free energies (kcal/mol) in solution for M06/6-31G(d) optimized structures of intermediates and transition state (39) for urea 24 cleavage. Alternative reaction path with tetrahedral intermediate 42.

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