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A novel one-pot synthesis of N,6-disubstituted 1,3,5-triazine-4,6-diamines from isothiocyanates and amidines

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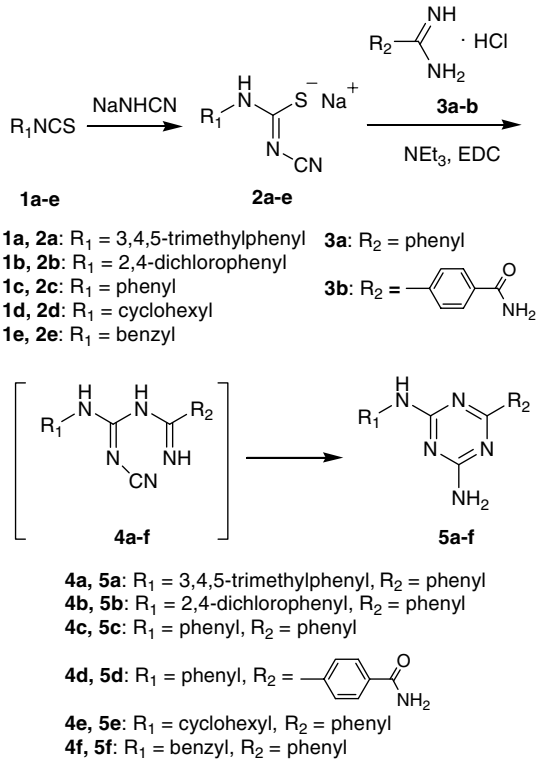
Abstract—A novel one-pot procedure for the preparation of N,6-disubstituted-1,3,5-triazine-2,4-diamines and its scope of application are demonstrated with a number of examples. The new procedure involves the treatment of isothiocyanates with sodium hydrogencyanamide, followed by amidines in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

N,6-Disubstituted-1,3,5-triazine-2,4-diamines have often been found to be synthetic targets as chemotherapeutic agents.[1–5] Previous synthetic methods for such compounds mainly relied on two routes, each requiring two or three steps. One route starts with cyanuric chloride, which can sequentially be reacted with Grignard reagents,[1,6] ammonia, and amines. The utility of this procedure is limited by the fact that Grignard reagents are highly reactive and therefore prevent versatile functionality for further elaboration. The other route involves the reaction of substituted biguanides with acid chlorides,[7,8] anhydrides,[9] or carboxylates.[3–5] This procedure appears more general. However, substituted biguanides usually need to be prepared from dicyandiamide and amines. The preparation occasionally requires harsh conditions and the products are extremely water soluble, making product isolation difficult. In this letter, we report a facile, one-pot procedure for the preparation of the title compounds from isothiocyanates, sodium hydrogencyanamide, and amidines in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC).

We previously reported a novel, one-pot synthesis of 1,2,4-triazole-3,5-diamine derivatives from isothiocyanates, sodium hydrogencyanamide, and mono-substituted hydrazines in the presence of EDC.[10] It was envisioned that this methodology could be extended to the preparation of N,6-disubstituted-1,3,5-triazine-2,4-diamines, by replacing mono-substituted hydrazines with amidines. Thus, 3,4,5-trimethylphenyl isothiocyanate (**1a**) was reacted with commercially available sodium hydrogencyanamide in DMF to provide *N*-cyanothiourea sodium salt **2a** (Scheme 1). Without



Scheme 1.

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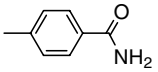
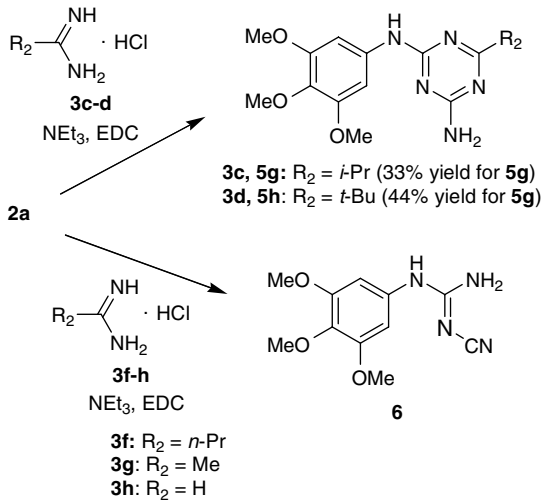
isolation, **2a** was treated with benzamidine hydrochloride (**3a**) at rt in the presence of triethylamine and EDC. Thirty minutes later, **2a** was completely consumed, giving rise to two products in a ratio of 5:1. Both products had the desired mass. This ratio reversed to 1:8.6 after the mixture was heated at 75 °C for 1 h. After an additional 1 h of heating, the initially more polar product was completely converted to the less polar one. The final product was isolated by flash chromatography in 71% yield (Table 1) and confirmed to be 1,3,5-triazine-2,4-diamine **5a**[11] by comparison with an authentic sample, prepared by a known procedure.[1] The more polar, less stable product is believed to be intermediate **4a**, though it was not isolated due to its instability. In a similar manner, 2,4-dichlorophenyl isothiocyanate (**1b**) was reacted with sodium hydrogencyanamide to generate *N*-cyanothiourea sodium salt **2b**. When **2b** was treated with benzamidine hydrochloride (**3a**), triethylamine, and EDC at rt for 1 h, **4b** and **5b** formed in a ratio of 4:1, respectively. However, when the mixture was heated to 75 °C for an additional 1 h, **5b**[12] was the only product detected with the desired mass. The isolated yield of **5b** was 54%. In the interest of developing synthetic methodology, it is not imperative for the second part of the one-pot procedure to begin at rt. Elimination of the initial rt treatment gave similar yields. For example, heating **2c**, the adduct of phenyl isothiocyanate (**1c**) and sodium hydrogencyanamide, with benzamidine (**3a**) in the presence of triethylamine and EDC at 75 °C for 3 h resulted in the formation of **5c**[13] in 72% yield. Similarly, **5d**[14] was obtained from **1c** and **3b** in 65% yield. Cycloalkyl and alkyl isothiocyanates proved to work as demonstrated by cyclohexyl isothiocyanate and benzyl isothiocyanate. The products **5e** and **5f** were isolated in 50% and 44% yields, respectively. The structure of **5f** was again confirmed by comparison with an authentic sample, prepared by a known procedure.[1]

Table 1. Isolated yields of **5a–f**

Product	Yield (%)	R_1	R_2
5a	71	3,4,5-Trimethylphenyl	Phenyl
5b	54	2,4-Dichlorophenyl	Phenyl
5c	72	Phenyl	Phenyl
5d	65	Phenyl	
5e	50	Cyclohexyl	Phenyl
5f	44	Benzyl	Phenyl

Further examination of the scope of the synthetic methodology revealed that aliphatic carbamidines behaved differently in the reaction and the outcome appeared to depend on the nature of the aliphatic groups. When *N*-cyanothiourea sodium salt **2a** was treated with isobutyramidine hydrochloride (**3c**) in the presence of triethylamine and EDC at rt for 30 min (Scheme 2), multiple peaks appeared as judged by LC–MS.[15] Two peaks had the desired mass, but they accounted for only 4.3% and 9.6% of the total UV active components, respectively. Interestingly, when the mixture was heated



Scheme 2.

to 75 °C for 1 h, the reaction became much cleaner with only one peak corresponding to the desired mass. Product **5g**[16] was obtained in 33% yield. *t*-Butyl carbamidine hydrochloride (**3d**) performed similarly to isobutyramidine hydrochloride (**3c**) to afford **5h**[17] in 44% yield. However, when butyramidine hydrochloride (**3f**), triethylamine, and EDC were mixed with **2a** at rt, a very clean reaction occurred within 40 min to give *N*-cyanoguanidine **6**[18] in 80% yield. The structure of **6** was confirmed by comparison with an authentic sample prepared by a known synthetic method.[19] It was further found that acetamidine hydrochloride (**3g**) and formamidine hydrochloride (**3h**) also gave product **6** exclusively under the same conditions.

The isolation of the single product **6** from the reactions of **2a** with **3f–h** prompted us to re-examined the reactions of **2a** with **3c** and **4d** and the examples in Scheme 1. The formation of *N*-cyanoguanidine **6** or its analogues as by-products appeared to be general in those reactions, but they were minor. For example, the ratios of **6** to **5g** and **5h** in the reactions of **2a** with **3c** and **3d** were 1:8 and 1:11, respectively, by LC–MS.[15] The ratio of **6** to **5a** in the reaction of **2a** with **3a** was 1:12.

The mechanism by which the common product **6** was formed exclusively with amidines **3f–h** is not exactly clear at this point. One possibility is that once inter-

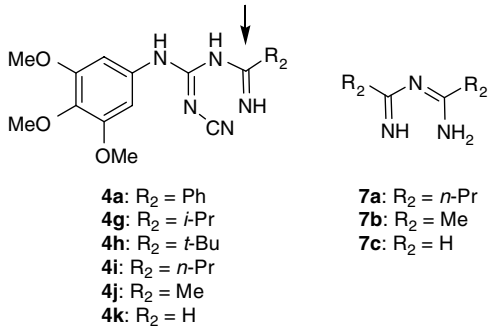


Figure 1.

mediate **4i–k** formed, they underwent electrophilic reactions with unreacted amidines **3f–h** at the position denoted with an arrow before intramolecular cyclizations could occur (Fig. 1). The by-products from such reactions would be **7a–c** that could also participate in the conversion of **4i–k** to **6** in the same manner. If by-products **7a–c** were not stable, they would likely decompose back to the starting amidines **3f–g**. In the case of **4a**, **4g,** and **4h**, the steric hindrance provided by phenyl, *i*-propyl, and *t*-butyl might have impeded such electrophilic reactions significantly, and therefore, 1,3,5-triazine-2,4-diamine derivatives **5a**, **5g,** and **5h** were generated as the major products. Benzamidine is also less nucleophilic than amidines **3f–h** to initiate the side reaction, and this may also play a role in determining the extent of by-product **6** in the case of **4a**.

In summary, a convenient synthetic procedure for the preparation of N,6-disubstituted-1,3,5-triazine-2,4-diamines from isothiocyanates, sodium hydrogencyanamide, and amidines has been reported in this letter. This procedure possesses the advantages of a one-pot operation that requires only mild conditions. The new protocol appears to be general with isothiocyanates (both aromatic and aliphatic) and aromatic carbamidines. With aliphatic carbamidines, the outcome of the procedure is apparently determined by steric hindrance. More hindered aliphatic carbamidines give the desired product, while less hindered aliphatic carbamidines lead to *N*-cyanoguanidines.

A representative procedure demonstrated by the preparation of **5b**: To a solution of 2,4-dichlorophenyl isothiocyanate (0.215 g, 1.00 mmol) in dry DMF (5 mL) was added sodium hydrogencyanamide (68.6 mg, 1.05 mmol) at room temperature in one portion. The mixture was heated at 60 °C for 50 min before triethylamine (0.31 mL, 2.22 mmol), benzamidine hydrochloride (0.235 g, 1.50 mmol), and EDC (0.240 g, 1.25 mmol) were added at room temperature. The mixture was stirred at rt for 30 min and then at 75 °C for 1 h. On cooling to rt, the mixture was diluted with ethyl acetate (80 mL), washed sequentially with water (25 mL) and 10% LiCl solution (25 mL), and dried over anhydrous $MgSO_4$. The solution was concentrated under vacuum, and the residue was subjected to flash chromatography (silica gel, 30% ethyl acetate/hexane) to afford **5b** (0.180 g, 54% yield) as a pale yellow solid.

References and notes

1. Pitts, W. J.; Guo, J.; Dhar, T. G. M.; Shen, Z.; Gu, H.; Watterson, S. H.; Bednarz, M. S.; Chen, B.-C.; Barrish, J. C.; Bassolino, D.; Cheney, D.; Fleener, C. A.; Rouleau, K. A.; Hollenbaugh, D. L.; Iwanowicz, E. *J. Bioorg. Med. Chem. Lett.* **2002**, *12*, 2137–2140.
2. Hanessian, S.; Sgarbi, P. W. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 437–443.
3. Hajiduk, P. J.; Dinges, J.; Schkeryantz, J. M.; Janowick, D.; Kaminski, M.; Tufano, M.; Augeri, D. J.; Petros, A.; Nienaber, V.; Zhong, P.; Hammond, R.; Coen, M.; Beutel, B.; Katz, L.; Fesik, S. W. *J. Med. Chem.* **1999**, *42*, 3852–3859.
4. Kosáry, J.; Kasztreiner, E.; Rablóczky, G.; Kürthy, M. *Eur. J. Med. Chem.* **1989**, *24*, 97–99.
5. Irikura, T.; Abe, Y.; Okamura, K.; Higo, K.; Maeda, A.; Morinaga, F.; Shirai, G.; Hatae, S. *J. Med. Chem.* **1970**, *13*, 1081–1089.
6. Hirt, R.; Nidecker, H.; Berchtold, R. *Helv. Chim. Acta* **1950**, *33*, 1365–1369.
7. Yuki, Y.; Sakurai, S.; Kakurai, T.; Noguchi, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2130–2134.
8. Shapiro, S. L.; Isaacs, E. S.; Parrino, V. A.; Freedman, L. *J. Org. Chem.* **1961**, *26*, 68–74.
9. Alkalay, D.; Volk, J.; Bartlett, M. F. *J. Pharm. Sci.* **1976**, *65*, 525–529.
10. Liu, C.; Iwanowicz, E. J. *Tetrahedron Lett.* **2003**, *44*, 1409–1411.
11. Compound **5a**: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.41 (1H, s), 8.33 (2H, d, $J = 6.9$ Hz), 7.56–7.49 (3H, m), 7.28 (2H, s), 7.18 (2H, br s), 3.80 (6H, s), 3.63 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.5, 167.4, 164.8, 152.9, 137.1, 136.4, 132.9, 131.8, 128.6, 128.1, 98.0, 60.4, 56.1.
12. Compound **5b**: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.91 (1H, s), 8.25 (2H, d, $J = 6.9$ Hz), 7.83 (1H, d, $J = 8.7$ Hz), 7.69 (1H, s), 7.57–7.44 (4H, m), 7.15 (2H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.7, 167.6, 136.9, 135.4, 131.8, 129.6, 129.5, 129.2, 128.9, 128.7, 128.2, 127.8.
13. Compound **5c**: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.55 (1H, s), 8.33 (2H, d, $J = 6.7$ Hz), 7.85 (2H, d, $J = 7.9$ Hz), 7.58–7.49 (3H, m), 7.31 (2H, dd, $J = 7.8$, 7.8 Hz), 7.16 (2H, br s), 7.00 (1H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.6, 167.5, 165.0, 140.3, 137.1, 131.8, 128.8, 128.6, 128.1, 122.3, 120.3.
14. Compound **5d**: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.53 (1H, s), 8.28 (2H, d, $J = 8.4$ Hz), 8.00 (1H, s), 7.93 (2H, d, $J = 8.4$ Hz), 7.77 (2H, d, $J = 7.9$ Hz), 7.41 (1H, s), 7.24 (2H, dd, $J = 7.8$, 7.8 Hz), 7.16 (2H, br s), 6.93 (1H, t, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.9, 167.8, 167.5, 164.9, 140.2, 139.6, 137.1, 128.8, 127.9, 127.8, 122.4, 120.3.
15. LC–MS conditions: Column: Phenomenex 5u C18 4.6×50 mm; Solvent A: 10% MeOH—90% H_2O—0.1% TFA; Solvent B: 90% MeOH—10% H_2O—0.1% TFA; Gradient time: 4 min; Detecting wavelength: 254 nm.
16. Compound **5g**: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.22 (1H, s), 7.23 (2H, s), 6.97 (2H, br s), 3.75 (6H, s), 3.60 (3H, s), 2.66 (1H, m), 1.20 (6H, d, $J = 6.9$ Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 182.4, 167.2, 164.8, 153.0, 136.6, 132.8, 98.0, 60.6, 56.2, 39.8, 21.3.
17. Compound **5h**: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.14 (1H, s), 7.24 (2H, s), 6.90 (2H, br s), 3.75 (6H, s), 3.61 (3H, s), 1.26 (9H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 184.4, 167.1, 164.6, 152.8, 136.6, 132.6, 97.7, 60.4, 56.0, 38.8, 29.2.
18. Compound **6**: ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.99 (1H, s), 6.95 (2H, s), 6.64 (2H, s), 3.76 (6H, s), 3.64 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.9, 153.1, 134.4, 134.0, 117.7, 100.1, 60.4, 56.1.
19. Iwanowicz, E. J.; Watterson, S. H.; Liu, C.; Gu, H.; Mitt, T.; Leftheris, K.; Barrish, J. C.; Fleener, C. A.; Rouleau, K.; Sherbina, N. Z.; Hollenbaugh, D. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2931–2934.