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An Efficient Hydration of Cyanamides to Substituted Ureas with Acetaldoxime as an Effective Water Surrogate

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Hydration of nitriles to amides is important in both academic and industrial points of view.[1] The hydration reaction was performed usually in the presence of a strong acid or base catalyst, but these methods suffer from drastic conditions and over-hydrolysis problem.[2] Recently palladium and indium-catalyzed hydrations of nitrile to amide were developed by us using acetaldoxime as an effective water surrogate.[3a-c] Chang and co-workers also reported a similar hydration using acetaldoxime.[3d-f] We used aqueous EtOH or toluene as solvent for the Pd(II)-catalyzed hydration[3b,c] and toluene in the $InCl_3$-catalyzed reaction.[3a] The weakly-activated nitrile by $Pd(OAc)_2$ or $InCl_3$ can be attacked easily by acetaldoxime to produce amide and acetonitrile as a by-product, *via* the six-membered transition state.

Hydration of cyanamides (RNHCN or R_2NCN) to the corresponding substituted ureas is an important chemical transformation.[4,5] Substituted ureas are found in many natural products, and the synthesis of ureas remains of great interest owing to their wide applications in pharmaceutical and agrochemical industry.[4-6] The synthetic approaches of substituted ureas can be classified as follows:[4-6] (i) reaction of amines with phosgene or its less hazardous substitutes; (ii) reaction of amines with isocyanates; (iii) insertion of CO into amino compounds;[6c,d] (iv) acid or base-catalyzed hydration of cyanamides.[4,5] The hydration of nitrile moiety in cyanamide could be easier than that of organonitriles (R-CN) due to the electron-withdrawing nitrogen atom; however the reported hydration methods still required harsh reaction conditions including the use of HF-pyridine complex,[4a] H_2SO_4,[4b,e] H_2O_2/NaOH,[4c] and HCl.[4d] We envisioned that the nitrile group in cyanamide could be easily hydrated with acetaldoxime as a water surrogate in the presence of $InCl_3$, as shown in Scheme 1.

As a model substrate, *N*-cyanoaniline (**1a**) was prepared by cyanation of aniline with cyanogen bromide (BrCN) as reported.[7] The hydration conditions were examined with **1a**, and the results are summarized in Table 1. The hydration of **1a** with acetaldoxime (2.0 equiv) in toluene at room temperature provided a moderate yield of phenylurea (**2a**, 77%) even in the absence of $InCl_3$ (entry 1). The reaction at elevated temperature (70 °C) showed lower yield of **2a** (entry 2) due to the formation of aniline and some intractable side products. The use of larger excess amounts of acetaldoxime (5.0 equiv) at slightly elevated temperature (40 °C) raised the yield to 85% (entry 3). However, the yields (52 - 85%) in three entries were not satisfactory. The reaction of **1a** in the presence of $InCl_3$ (3 mol %) was completed within 30 min even at room temperature to afford a high yield of **2a** (entry 4). In comparison, the reaction without acetaldoxime in aqueous ethanol did not produce any trace amounts of product (entry 5).[8]

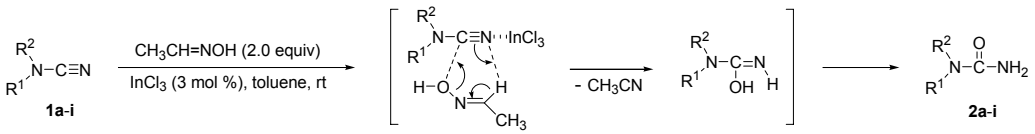
Thus we chose the conditions in entry 4 (Table 1), and carried out the hydration of cyanamide derivatives, as summarized in Table 2. Various cyanamides derived from arylamines (entries 1-4 and 8), alkyl amines (entries 5-7 and 9), primary amines (entries 1-3, 6, and 7), and secondary amines (entries 4, 5, 8, and 9) produced the corresponding substituted ureas in good to excellent yields (88 - 96%). Most of the entries produced the corresponding ureas at room temperature within 30 min; however hydrations of **1d**, **1h**, and **1i** were carried out at slightly elevated temperature (30 - 40 °C) for 2 h.

In summary, an efficient hydration method of various cyanamides to substituted ureas is disclosed using acetaldoxime as an effective water surrogate. The reaction was carried out in

Table 1. Optimization of reaction conditions with *N*-cyanoaniline (**1a**)

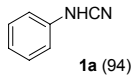
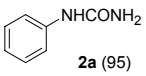
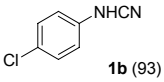
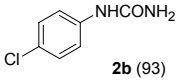
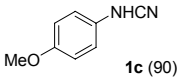
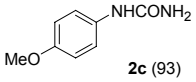
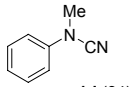
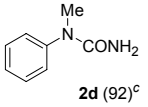
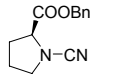
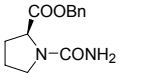
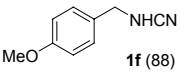
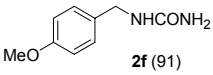
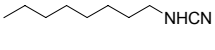
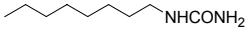
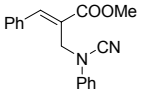
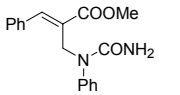
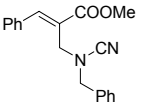
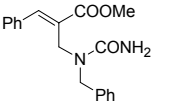
Entry	Conditions	Yield (%)[a]
1	CH_3CH=NOH (2.0 equiv), toluene, rt, 10 h	77
2	CH_3CH=NOH (2.0 equiv), toluene, 70 °C, 2 h	52
3	CH_3CH=NOH (5.0 equiv), toluene, 40 °C, 2 h	85
4	CH_3CH=NOH (2.0 equiv), $InCl_3$ (3 mol %), toluene, rt, 30 min	95
5	no CH_3CH=NOH, aq EtOH, rt, 24 h[b]	0

[a]Isolated yield of phenylurea (**2a**). [b]Compound **2a** was observed in trace amount (< 5%) under refluxing conditions.



Scheme 1

Table 2. Hydration of various cyanamides

Entry	Cyanamide (%)[a]	Product (%)[b]	mp (°C)
1	 **1a** (94)	 **2a** (95)	143 - 145
2	 **1b** (93)	 **2b** (93)	204 - 206
3	 **1c** (90)	 **2c** (93)	166 - 167
4	 **1d** (94)	 **2d** (92)[c]	80 - 81
5	 **1e** (96)	 **2e** (95)	77 - 78
6	 **1f** (88)	 **2f** (91)	110 - 112
7	 **1g** (92)	 **2g** (88)	100 - 101
8	 **1h** (93)	 **2h** (94)[c]	134 - 135
9	 **1i** (86)	 **2i** (96)[c]	148 - 149

[a]Conditions of *N*-cyanation: BrCN (2.0 equiv), $NaHCO_3$, PhH, rt, 2 h. [b]Conditions: CH_3CH=NOH (2.0 equiv), $InCl_3$ (3 mol %), toluene, rt, 30 min. [c]Slight warming (30 - 40 °C) for 2 h.

toluene at room temperature in the presence of a catalytic amount of $InCl_3$.

Experimental Section

Typical Procedure for the Synthesis of *N*-Cyanamide 1e. To a stirred mixture of L-proline benzyl ester hydrochloride (241 mg, 1.0 mmol) and $NaHCO_3$ (252 mg, 3.0 mmol) in benzene (2 mL) was added cyanogen bromide (212 mg, 2.0 mmol), and the reaction mixture was stirred at room temperature for 2 h. After the usual aqueous workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 10:1:1), compound **1e** (221 mg, 96%) was isolated as colorless oil. Other cyanamides were prepared similarly, and the known cyanamides **1a**,[7d] **1b**,[7a] **1c**,[7a] **1d**,[7d] **1f**,[7e] and **1g**[7f] were characterized by comparison their IR, ^{1}H NMR and/or melting points with the reported data. The spectroscopic data of unknown cyanamides **1e**, **1h**, and **1i** are as follows.

Compound 1e: 96%; colorless oil; IR (film) 2214, 1744, 1449 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88-1.98 (m, 2H), 2.03-2.13 (m, 1H), 2.16-2.29 (m, 1H), 3.48 (dt, J = 9.0 and 7.2 Hz, 1H), 3.57-3.64 (m, 1H), 4.26 (dd, J = 8.4 and 4.2 Hz, 1H), 5.21 (s, 2H), 7.33-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.18, 30.11, 51.12, 62.20, 67.44, 115.79, 128.23, 128.51, 128.62, 134.99, 170.42; ESIMS *m*/*z* 231 (M^++H). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.98; H, 6.34; N, 12.02.

Compound 1h: 93%; white solid, mp 81 - 82 °C; IR (KBr) 2220, 1715, 1630, 1597, 1499 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 3H), 4.54 (s, 2H), 7.04-7.13 (m, 3H), 7.29-7.44 (m, 7H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.62, 52.54, 112.47, 116.12, 123.75, 124.73, 128.94, 129.18, 129.53, 129.81, 133.85, 139.88, 146.87, 166.67; ESIMS *m*/*z* 293 (M^++H). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.12; H, 5.54; N, 9.79.

Compound 1i: 86%; colorless oil; IR (film) 2208, 1713, 1632, 1447 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.87 (s, 3H), 3.97 (s, 2H), 4.18 (s, 2H), 7.20-7.23 (m, 2H), 7.28-7.37 (m, 8H), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.03, 52.38, 55.72, 117.28, 125.85, 128.46, 128.48, 128.71, 128.75, 129.14, 129.42, 133.86, 134.54, 145.75, 167.07; ESIMS *m*/*z* 307 (M^++H). Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.41; H, 6.17; N, 9.09.

Typical Procedure for the Hydration of 1e. To a stirred mixture of **1e** (115 mg, 0.5 mmol) and acetaldoxime (60 mg, 1.0 mmol) in toluene (1.5 mL) was added $InCl_3$ (3 mg, 3 mol %) and stirred at room temperature for 30 min. Most of **2e** was deposited during the reaction, and the solid product was filtered and washed with CH_2Cl_2 to afford analytically pure product, 82 mg. Additional **2e** (36 mg) was isolated from the washings and filtrates by column chromatography (CH_2Cl_2/EtOAc/MeOH, 25:3:1). Total amount of **2e** was 118 mg (95%).[9] Other urea derivatives were prepared similarly and characterized by comparison their IR, ^{1}H NMR and/or melting points with the reported data.[5c,6e,6g,9]

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8. The reaction of **1a** in aqueous EtOH did not produce **2a** even in the presence of acetaldoxime, and the reason is not clear at this stage. The hydration of cyanamide can be performed under solvent-free conditions. As an example, the reaction of **1a** and acetaldoxime (3.0 equiv) at room temperature in the presence of $InCl_3$ (3 mol %) afforded **2a** in 91% yield.
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