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# Novel two-step, one-pot synthesis of primary acylureas

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ABSTRACT

A new procedure for the synthesis of primary acylureas from cyanamide and a variety of carboxylic acids is described. Under mild reaction conditions, the products were obtained in good yield from commercially available starting materials.

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Both primary acylureas and primary amides are relatively hydrophilic moieties, which have been used as metabolically stable bioisosteres of carboxylates. However, primary acylureas, unlike primary amides, have the potential to form intramolecular hydrogen bonds as shown in Figure 1.[1] As a result of such interactions, small molecules derived from primary acylureas are likely to exhibit better permeability in cell-based assays than their primary amide counterparts. Because of their greater metabolic stability, aqueous solubility, and permeability, primary acylureas represent important functional groups in the field of medicinal chemistry.

Few studies have been reported for the synthesis of functionalized primary acylureas,[2] and better synthetic protocols which are efficient and do not require harsh reaction conditions are needed. One procedure recently reported in the literature (Eq. 1, Fig. 2) could potentially produce compound **4a** from **3a** (Eq. 2, Fig. 2). However, in our hands when the reaction was carried out at a high temperature (130 °C) for 10–24 h, only 17% of the desired product was isolated after repeated attempts (Eq. 2, Fig. 2). In this Letter, we report an efficient and general alternative method for the synthesis of primary acylureas from a variety of commercially available carboxylic acids (Eq. 3, Fig. 2).

Our study began with the coupling reaction of **3a** and cyanamide (Table 1, entry 1). We envisioned that the cyanamide would readily couple with the carboxylic acid in the presence of BOP (1.2 equiv) and DIEA (3 equiv), and that the hydrolysis step could then be performed in the same flask. Despite the lack of literature reports on the hydrolysis of *N*-acylcyanamide to the corresponding primary acylurea, we speculated that such a transformation could be accomplished under acidic conditions.[3] In our first attempt, **4a** was isolated in 37% yield (Table 1, entry 1). It is worth noting that mild heating was often necessary to hydrolyze the *N*-acylcyanamide, although higher reaction temperatures did not improve the yield. We were able to improve the reaction yield dramatically by allowing a longer reaction time in both steps (entry 1 vs entry 2, Table 1). Based on these

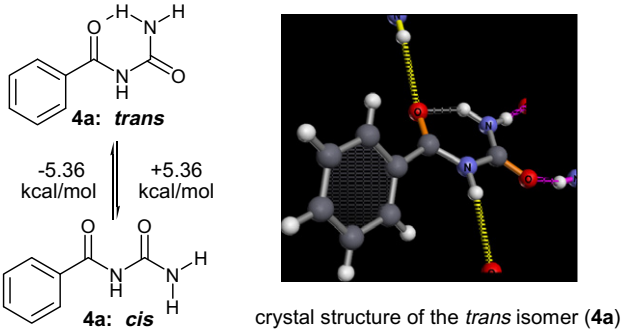


**Figure 1.** Evidence of intromolecular hydrogen bonding in **4a**.

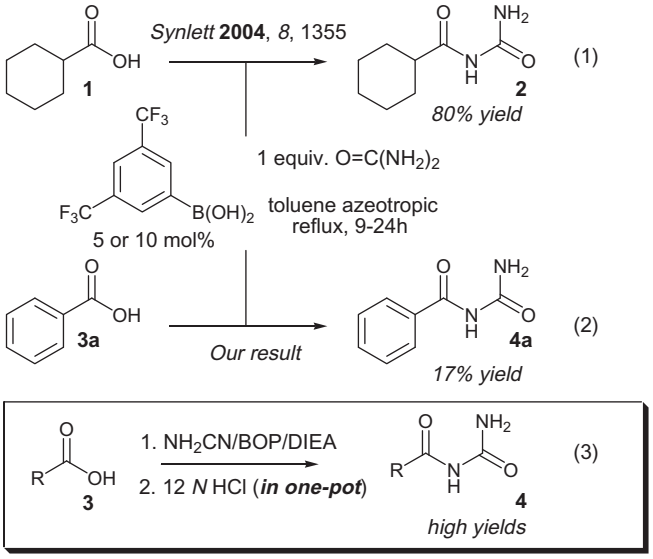


**Figure 2.** Recent studies on the synthesis of primary acylureas.

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**Table 1**
Primary acylureas **4a**–**k** produced via Eq. 3 in Figure 2

| Entry | Acids **3** | Reaction conditions step 1[a]→step 2[b] | Ureas **4** (Yield %)[c] |
|---|---|---|---|
| 1 | Benzoic acid **3a** | rt/3 h→50 °C/6 h (*Method **A***) | **4a** (37) |
| 2 | Benzoic acid **3a** | rt/16 h→50 °C/16 h (*Method **B***) | **4a** (84) |
| 3 | 4-Methoxybenzoic acid **3b** | **B** | **4b** (74) |
| 4 | 4-Chlorobenzoic acid **3c** | **B** | **4c** (71) |
| 5 | 4-Isopropyl benzoic acid **3d** | **B** | **4d** (77) |
| 6 | 6-Methylnicotinic acid **3e** | **B** | **4e** (65) |
| 7 | 2-Fluorobenzoic acid **3f** | rt/16 h→rt/16 h (*Method **C***) | **4f** (77) |
| 8 | 3-Nitrobenzoic acid **3g** | **C** | **4g** (72) |
| 9 | 1*H*-Indole-3-carboxylic acid **3h** | **C** | **4h** (31) |
| 10 | Cyclohexanecarboxylic acid **3i** | **C** | **4i** (88) |
| 11 | (*S*)-2-Phenylbutanoic acid **3j** | **B** | **4j** (86) |
| 12 | 1-Phenylcyclopropane carboxylic acid **3k** | **B** | **4k** (71) |

[a] The reactions were conducted in DMF with 1 equiv of **3**, 1.5 equiv of cyanamide, 1.2 equiv of BOP, and 3 equiv of DIEA.
[b] Concentrated HCl (12 N) was added.
[c] For detailed purification procedures see Ref. 4.

observations, the reaction times of entry 2 were used throughout the remainder of the study.[4] Reactions went smoothly at room temperature for entries 7–10 (Table 1).

A broad range of acids has been studied for this reaction and representative results are summarized in Table 1. For substituted benzoic acids, both electron donating (entries 3–5) and withdrawing groups (entries 7 and 8) were well tolerated. The reaction yields ranged from 71% to 77%. It is worth mentioning that the coupling reaction of 4-nitrobenzoic acid with cyanamide was not successful under the current reaction conditions. However, heterocyclic carboxylic acids such as 6-methylnicotinic acid (**3e**) and 1*H*-indole-3-carboxylic acid (**3h**) were converted into the desired products **4e** and **4h** in 65% and 31% yields, respectively (entries 6 and 9). The reaction also worked well with aliphatic carboxylic acids. In the case of cyclohexanecarboxylic acid (**3i**), the reaction gave **4i** in excellent yield (entry 10). (*S*)-2-Phenylbutanoic acid (**3j**) provided the corresponding acylurea **4j** in 86% yield (entry 11). The sterically hindered 1-phenylcyclopropane carboxylic acid (**3k**) was well tolerated to give **4k** in 71% yield (entry 12).

In summary, we have developed a novel method for the synthesis of primary acylureas from cyanamide and a variety of carboxylic acids. The combination of mild reaction conditions and wide substrate scope makes this protocol both useful and practical. Currently, this methodology has been successfully applied in our medicinal chemistry efforts to generate biologically active primary acylurea derivatives. These results will be reported in due course.

## Acknowledgment

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## References and notes

1. Computer modeling and the crystal structure suggest that the trans isomer is the preferred conformation. The initial conformational energies for both rotomers were minimized using the OPLSAA-2005 force field in Macromodel (version 9.7, Schrodinger, LLC, New York, NY, 2009). Ab initio minimized conformations were then generated within Jaguar (version 7.6, Schrodinger, LLC, New York, NY, 2009) at the B3LYP/6-31G** level of theory in vacuum. Final energies were calculated using the SM8 solvation model with the M06-2X/6-31** basis set as implemented within Jaguar.
2. (a) Maki, T.; Ishihara, K.; Yamamoto, H. *Synlett* **2004**, *8*, 1355–1358; (b) Seiller, B.; Heins, D.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*(40), 10901–10912; (c) Maynert, E. W.; Washburn, E. *J. Org. Chem.* **1950**, *15*, 259–261; For the synthesis of second and tertiary acylureas see: (d) Wodka, D.; Robbins, M.; Lan, P.; Martinez, R. L.; Athanasopoulos, J.; Makara, G. M. *Tetrahedron Lett.* **2006**, *47*, 1899.
3. For a related study on hydrolysis of *N*-acylcyanamide see: Perronnet, J.; Jacques, P.; Taliani, L. *J. Heterocycl. Chem.* **1981**, *18*, 433–435.
4. Typical reaction procedure: A mixture of the acid **3** (1 mmol, 1 equiv), BOP (1.2 equiv), cyanamide (1.5 equiv), and DIEA (3 equiv) in DMF (1.2 mL) was stirred at rt for 16 h. To the reaction mixture, 12 N HCl (1 mL) was added and then stirred at 50 °C or rt for additional 16 h. After cooling, the precipitate was collected by filtration, washed with water, and vacuum dried to yield the desired compounds. The purities of the final compounds ranged from 98% to 100% by HPLC analysis. Representative example of **4K** $^{1}$H NMR (400 MHz, DMSO-*d*6) $\delta$ ppm: 8.25 (1H, s), 7.72 (1H, s), 7.23–7.49 (6H, m), 1.43–1.55 (2H, m), 1.08–1.25 (2 H, m). $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm: 15.61, 31.37, 127.86, 128.86, 130.01, 138.56, 152.97, 174. 22.