ORGANIC LETTERS

2009
Vol. 11, No. 9
2003−2006

Mild and Efficient DBU-Catalyzed Amidation of Cyanoacetates†

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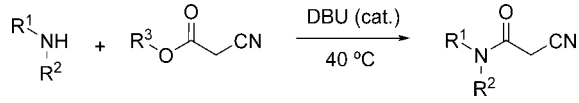
Received March 2, 2009

ABSTRACT



A mild, high-yielding, and practical protocol for the direct amidation of alkyl cyanoacetates using DBU is presented. This method eliminates the need for activation of cyanoacetic acid and/or high temperatures. It has been applied to the large-scale synthesis of CP-690,550-10 (1), a compound under development for the treatment of autoimmune diseases.

The formation of amide bonds is one of the most common reactions in organic synthesis.[1] Generally, amides are formed either by direct coupling of an amine with a carboxylic acid that is activated in situ[2,3] or in a two-step process involving activation of the carboxylic acid followed by reaction of the activated intermediate with an amine.[4−6] Although many amidation strategies have been developed, none of these are universally applicable across substrate classes. While investigating the synthesis of cyanoacetamides, we found that most of the known amidation methods were not ideal for our purposes (vide infra). Our subsequent studies have resulted in an effective protocol for the direct formation of cyanoacetamides from commercially available alkyl cyanoacetates. This method is mild and provides high yields with minimal waste.

The cyanoacetamide of particular interest to us, CP-690,550-10 (**1**), is a potent immunosuppressant currently under development for the treatment of autoimmune diseases, such as rheumatoid arthritis and psoriasis, as well as the prevention of transplant rejection.[7] The final bond-forming step in the synthesis of **1** is the installation of the cyanoacetyl moiety to afford free base **2** (Figure 1). The amidation had previously been executed in two steps via activation of cyanoacetic acid with pivaloyl chloride and subsequent reaction with piperidine **3** in CH_2Cl_2 (Scheme 1). This

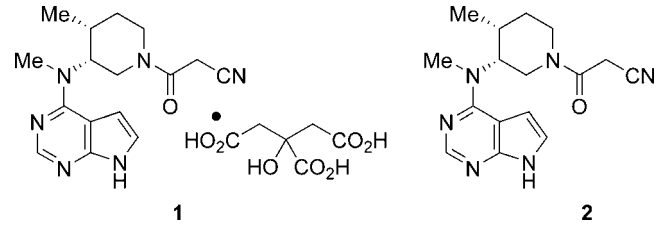


Figure 1. Structures of CP-690,550-10 (**1**) and the corresponding free base (**2**).

† This paper is dedicated to Prof. K. K. Balasubramanian (formerly of IIT, Madras) on the occasion of his 70th birthday.

(1) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852.

(2) Ormerod, D.; Willemsens, B.; Mermans, R.; Langens, J.; Winderickx, G.; Kalindjian, S. B.; Buck, I. M.; McDonald, I. M. *Org. Process Res. Dev.* **2005**, *9*, 499–507.

(3) Tang, P. *Org. Synth.* **2005**, *81*, 262–272.

(4) Ager, D. J.; Babler, S.; Erickson, R. A.; Froen, D. E.; Kittleson, J.; Pantaleone, D. P.; Prakash, I.; Zhi, B. *Org. Process Res. Dev.* **2004**, *8*, 72–85.

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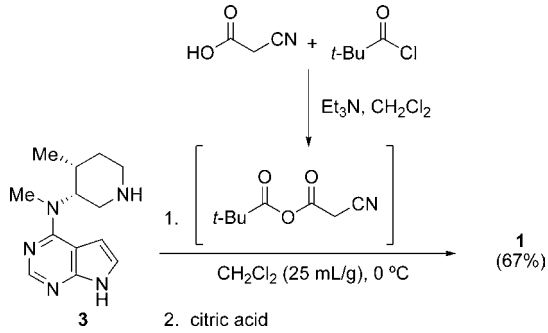
10.1021/ol900435t CCC: $40.75
Published on Web 04/02/2009

Scheme 1. Synthesis of **1** via Activation of Cyanoacetic Acid



method provided **1** in 67% yield, which was adequate to meet early clinical demands.[8]

As we moved toward a long-term synthetic solution for the manufacture of **1**, several factors were considered. (1) A single-step process would be preferred over a two-step activation−amidation sequence, both for process efficiency and to avoid decomposition of the activated cyanoacetic acid.[9] (2) Halogenated solvents should be avoided to reduce environmental impact.[10] (3) This is the final step in the synthesis of an active pharmaceutical ingredient, so mild conditions are needed to limit the formation of byproducts.

One of the most efficient and atom-economical options for the formation of an amide is the reaction of an amine with a simple ester. Alkyl cyanoacetates have been converted to simple cyanoacetamides in moderate to high yield under solvent-free conditions,[11,12] with microwave irradiation,[13] or at high temperatures.[14,15] Amidation has also been accomplished using lithium amides derived from primary and secondary amines at low temperatures.[16] However, none of these protocols seemed attractive for the large-scale manufacture of **1**.

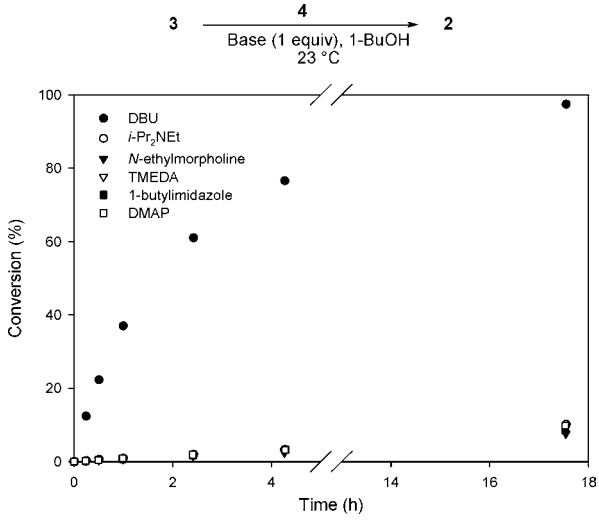
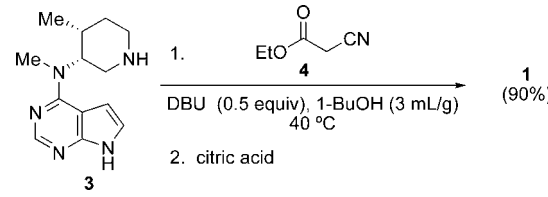


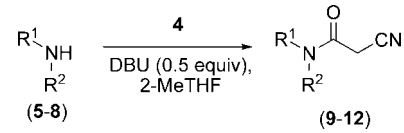
Figure 2. Profiles of the reaction between amine **3** and ethyl cyanoacetate (**4**) in 5 mL of 1-BuOH per gram of **3** with 1.0 equiv of various tertiary amines.

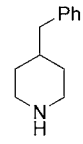
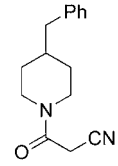
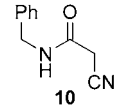
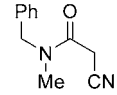
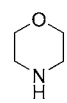
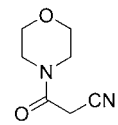
Scheme 2. Synthesis of **1** via Direct Amidation



We envisioned that amine **3** could be converted to cyanoacetamide **2**by direct treatment with an alkyl cyanoacetate in the presence of added base. The reaction of **3** with ethyl cyanoacetate (**4**) was examined at 55 °C with various bases in 1-butanol.[17] In this screen, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) afforded 26% conversion after 30 min while other bases provided only 1−6% conversion.[18,19] After 18 h at 55 °C, all reactions showed some decomposition. When the base screen was repeated at room temperature to minimize decomposition, the DBU-promoted reaction was

Table 1. Reaction of Amines with Ethyl Cyanoacetate in the Presence and Absence of DBU[a]



entry	amine	product	$t_{1/2}$ (min)[a] with DBU	$t_{1/2}$ (min)[a] without DBU	yield (%)[b]
1[c]	 **5**	 **9**	<15[d]	520	95
2	 **6**	 **10**	<10[e]	>360[f]	95
3	 **7**	 **11**	180	>>960[g]	89
4	 **8**	 **12**	10	>>360[g]	87

All reactions were run at 20 °C unless otherwise specified. [a] $t_{1/2}$ is the time required for the amidation to reach 50% conversion by HPLC or GC. [b] Isolated, purified yield. See the Supporting Information for full procedures. [c] Reaction run at 40 °C. [d] 64% conversion at 15 min. [e] 62% conversion at 10 min. [f] 36% conversion at 360 min. [g] No product visible on GC traces.

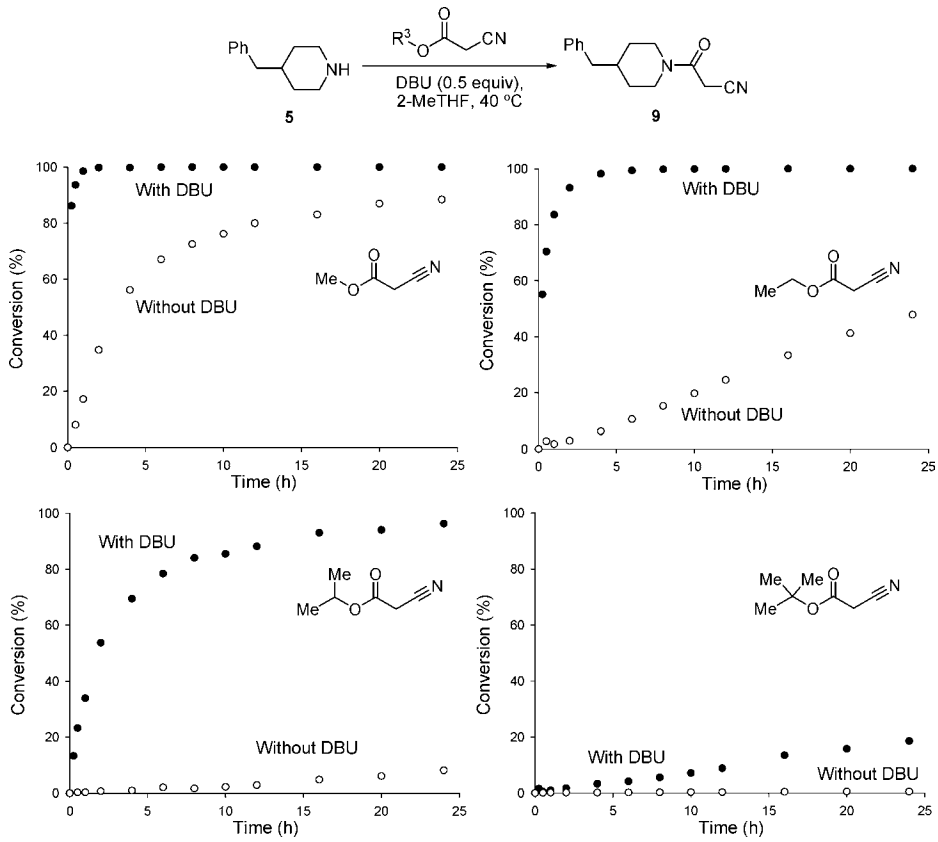


Figure 3. Comparison of reaction between **5** and various alkyl cyanoacetates (R = Me, Et, *i*-Pr, *t*-Bu) with and without DBU.

still much faster than those using other bases[20] and led to high conversion (Figure 2).

After further refinement, this step was streamlined to effect clean conversion of **3** to **2** within 12 h using only 0.5 equiv of DBU at 40 °C.[21] The new process was used to successfully synthesize multikilogram quantities of **1** in 90% yield after salt formation (Scheme 2).

In an effort to explore the generality of this method, several primary and secondary amines were treated with **4** under the above conditions (0.5 equiv of DBU, 2.0 equiv of ester) on a 2−10 g scale (Table 1). For these reactions, 2-methyltetrahydrofuran[22] was used as the solvent in order to simplify workup and product isolation.[23] The addition of DBU led to dramatic rate enhancement as evidenced by $t_{1/2}$ values and furnished the amides in high yield.

A series of alkyl cyanoacetates was treated with 4-benzylpiperidine (**5**) in order to understand the effect of the alkyl group on the reaction rate (Figure 3). In all cases, DBU was found to accelerate the amide formation. The relative rates of the reactions were dependent on the steric bulk of the ester. As the size of the alkyl group was increased, the difference in rates between the catalyzed and uncatalyzed reactions became more pronounced. In the extreme case of the *tert*-butyl ester, the background reaction was almost

(8) Ruggeri, S. G.; Hawkins, J. M.; Makowski, T. M.; Rutherford, J. L.; Urban, F. J. WO 2007/012953 A2, 2007.

(9) In our experience, some activated forms of cyanoacetic acid, such as the acyl imidazole, decomposed readily to unidentifiable products.

(10) Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M. *Green Chem.* **2008**, *10*, 31–36.

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(16) Bhawal, B. M.; Khanapure, S. P.; Biehl, E. R. *Synth. Commun.* **1990**, *20*, 3235–3243.

(17) 1-Butanol was chosen because **1** could be directly crystallized and isolated from this solvent.

(18) This screen was run in the Conjure Flow System, Accendo Corporation, Tucson, AZ.

(19) 1,5-Diazabicyclo[4.3.0]nonane (DBN) was subsequently compared to DBU in the reaction of **5** with **4** and gave virtually identical rate enhancement.

(20) The use of potassium *tert*-butoxide (*t*-BuOK) for the synthesis of cyanoacetamides under microwave conditions is known (see ref 13); however, it led to low conversions in our case at 23 °C in 1-BuOH.

(21) DBU accelerates the reaction of amine **5** and ethyl cyanoacetate (**4**) at lower loadings as well. The profiles for reactions run at 0.1−0.5 equiv of DBU are compared in the Supporting Information.

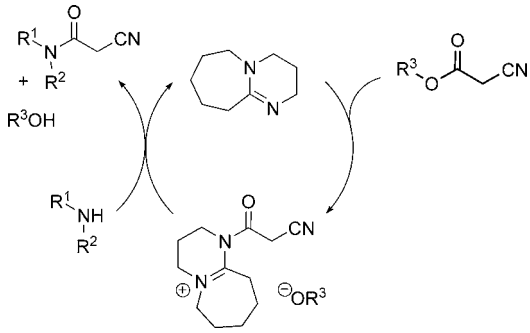
(22) Ripin, D. H. B.; Vetelino, M. *Synlett* **2003**, 2353.

(23) A solvent screen on the conversion of **3** to **2** indicated that the DBU-promoted reaction worked well in most solvents slowing down only in polar aprotic solvents (NMP, DMSO). See the Supporting Information for further details.

nonexistent and even the DBU reaction was too slow at 40 °C to be synthetically useful.

The fact that catalytic DBU provides significant acceleration compared to other amine bases (Figure 2) and *t*-BuOK[20] suggests that DBU is not simply acting as a base. While a number of pathways may be postulated to explain the effect of DBU, one of the most plausible is a nucleophilic (Lewis base) catalysis mechanism, wherein DBU displaces the alkoxy moiety and activates the carbonyl for attack by the amine (Scheme 3).

Scheme 3. Proposed Catalytic Cycle



While DBU has traditionally been considered a nonnucleophilic base, there have been a few reports on its use as a nucleophilic catalyst in recent literature.[24] For instance, DBU was found to catalyze reactions of dimethyl carbonate with carboxylic acids to form esters, and a nucleophilic catalysis pathway was proposed to explain the results.[25] In this case, 4-dimethylaminopyridine (DMAP), a more commonly employed nucleophilic catalyst, was less effective at accelerating the reaction than DBU. Aggarwal et al. have shown that DBU accelerates the Baylis−Hillman reaction relative to 1,4-diazabicyclo[2.2.2]octane (DABCO) and DMAP.[26] This behavior has been attributed to the higher carbon basicity[27] of DBU.[28] Thus, the nucleophilic catalysis pathway seems consistent with literature precedent and our own observations.[29]

In conclusion, we have developed a mild, high-yielding protocol for the direct amidation of alkyl cyanoacetates using DBU. These conditions obviate the need for preactivation of cyanoacetic acid prior to the amidation, thereby eliminating the associated waste. The byproduct from this reaction is a simple alcohol. Further work aimed at exploring the scope and elucidating the mechanistic aspects of this reaction is ongoing in our laboratory,[30] and the results will be communicated in due course.

Acknowledgment. We thank the following Pfizer colleagues: Nathan Ide, Stéphane Caron, and Sally Gut Ruggeri for helpful suggestions and discussions, Kevin Doyle for prompt analytical support, and Brian Marquez for NMR support.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) (a) Shieh, W. C.; Dell, S.; Repic, O. *J. Org. Chem.* **2002**, *67*, 2188–2191. (b) Shieh, W. C.; Dell, S. J. US 6515167, 2003.

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(27) Hine, J.; Weimar, R. D. *J. Am. Chem. Soc.* **1965**, *87*, 3387–3396.

(28) Baidya, M.; Mayr, H. *Chem. Commun.* **2008**, 1792–1794.

(29) It is conceivable that the rate enhancement is due to the direct formation of a ketene from ethyl cyanoacetate and DBU. However, in the reaction of ethyl cyanoacetate with hydroxide, pre-equilibrium formation of the enolate is unproductive due to the poor leaving ability of ethoxide, and hydrolysis proceeds by a BAc2 mechanism rather than an E1cB (ketene) mechanism:Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 3003–3009. Further work aimed at clarifying the mechanism is ongoing.

(30) Although the amidation of diethyl malonate with **5** was slow, the addition of DBU led to a 12-fold increase in reaction rate ($t_{1/2} = 16$ h with 0.5 equiv of DBU in 2-MeTHF at 40 °C). Significant rate enhancements have been observed in the amidation of acyl imidazoles as well. Larrivée-Aboussafy, C.; Price, K. E.; Hawkins, J. M.; Vaidyanathan, R. Manuscript in preparation.