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A convenient aminolysis of esters catalyzed by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) under solvent-free conditions

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Abstract—Aminolysis of esters by using the organocatalyst 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) is reported. Secondary and tertiary amides were synthesized from alkyl or aryl esters with a variety of primary and secondary amines in good to excellent yields (60–94%) under solvent-free conditions (SFC).

The amide bond is among the most common chemical function present in natural or synthetic organic molecules.[1] Few protocols are reported for the direct aminolysis of alkyl and aryl esters. Most of them involve harsh conditions such as the use of strong basic reagents (sodium/potassium hydrides, alkoxides and alkyllithium),[2–4] or metallic reagents.[5–7] More recently, Woodward and Joullié reported the amide bond formation from esters using $AlMe_3$·DABCO complex[8] and bislithium amides,[9] respectively.

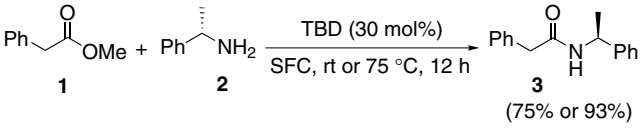
Guanidines are widely used in organic synthesis as acid scavengers and homogeneous base catalysts.[10,11] Bicyclic guanidines such as the commercially available TBD and its *N*-methyl derivative MTBD were shown to catalyze a variety of reactions such as Michael additions,[12] Henry reactions[13] and transesterifications.[14]

In the course of our studies on the applications of guanidine based catalysts, we decided to explore the use of TBD for aminolysis. Initially, the aminolysis of methyl phenylacetate **1** (1 equiv) by (*S*)-1-phenylethylamine **2** (1.2 equiv) was investigated. In toluene at 80 °C no product formation was observed, whereas the use of TBD (30 mol %) led to the expected amide **3** in 80% yield. A larger quantity of TBD did not improve the yield. The transformation was less efficient when more polar solvents were used (CH_2Cl_2, $CHCl_3$, CH_3OH, DMF), only THF afforded a similar TBD reactivity. The recent and successful use of solvent-free conditions (SFC) for ester aminolysis encouraged us to consider our optimized protocol under such conditions.[4] Indeed the solvent-free aminolysis in the presence of 30 mol % of TBD afforded amide **3** after 12 h at room temperature (75%) as well as at 75 °C (93%) (Scheme 1). Stereochemistry was conserved during the reaction (ee > 99%, determined by chiral HPLC).

The screening of a collection of oxygen and nitrogen containing bases indicated that only TBD was efficient under the solvent-free conditions at room temperature for the synthesis of **3** (Table 1). Potassium *tert*-butoxide and the bifunctional organocatalyst 2-hydroxypyridine gave the amide product in low yield (entries 1–2).[15] Nitrogen-containing bases other than TBD did not afford the expected amide product (entries 3–8) after 12 h at room temperature.

The optimized protocol was applied to various esters and amines (Scheme 2).[16]

In the presence of a catalytic amount of TBD (0.3 equiv) at 75 °C benzylamine reacted efficiently with methyl



Scheme 1. Aminolysis of **1** catalyzed by TBD under solvent-free conditions.

Keywords: Aminolysis; TBD; Organocatalyst; Solvent-free conditions.
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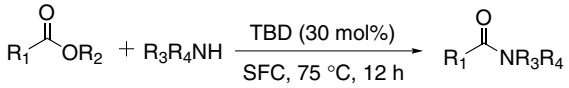
Table 1. Bases screening for the synthesis of **3** from ester **1**[a]

Entry	Catalyst	Yield[b] (%)
1	*t*-BuOK	21
2	2-Hydroxypyridine	<2
3	TEA	0[c]
4	DMAP	0[c]
5	DBN	0[c]
6	Imidazole	0[c]
7	TMG	0[c]
8	MTBD	0[c]
9	TBD	75

[a] 1.0 equiv of ester, 30 mol % of catalyst and 1.2 equiv of amine, rt, 12 h.
[b] Crude yield on the basis of ^{1}H NMR.
[c] Starting material was recovered.



Scheme 2. Aminolysis reactions catalyzed by 30 mol % of TBD under solvent-free conditions.

phenylacetate, methyl benzoate as well as with methyl pentanoate affording the corresponding amides in very good yields (Table 2, entries 1–3). The use of a more hindered ester did not reduce the yield for the synthesis of *N*-benzyl phenylacetamide (entry 4). Aniline as well as bulky primary amines reacted with methyl phenylacetate or benzyl benzoate in the presence of TBD leading to the corresponding amides in yields above 75% (entries 5–8). Secondary amines are well tolerated as shown by entries 9–11. Although primary amines are more reactive under the studied procedure. Indeed the reaction of *N*-methylethylenediamine on methyl phenylacetate affords exclusively the primary amide (entry 12). Ethanolamine under our conditions led to the aminolysis reaction affording *N*-(2-hydroxyethyl) phenylacetamide in 66% yield (entry 13). Finally reaction of benzylamine with γ-butyrolactone led to the expected opening of the lactone and amide formation in a good yield (entry 14).[17]

A mechanism for the reaction can be proposed by analogy with the work of Waymouth and Hedrick, who studied the TBD catalyzed polymerization of cyclic

Table 2. Amides syntheses catalyzed by 30 mol % of TBD under solvent-free conditions[a]

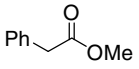
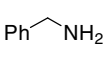
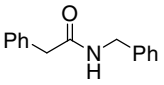
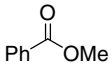
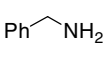
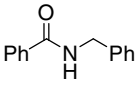
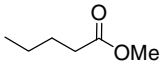
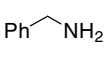
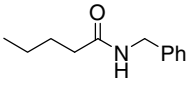
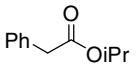
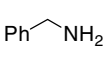
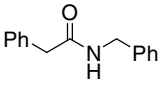
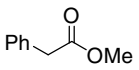
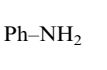
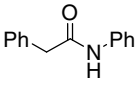
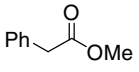
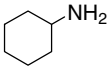
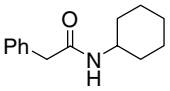
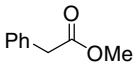
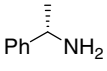
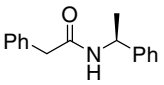
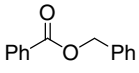
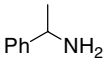
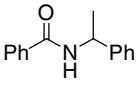
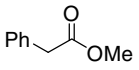
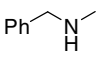
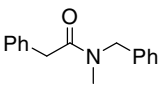
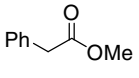
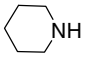
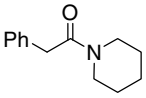
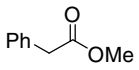
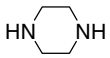
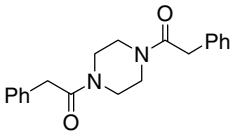
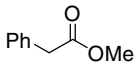
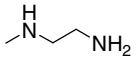
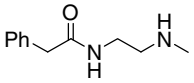
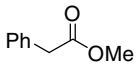
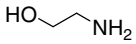
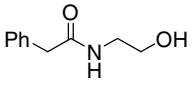
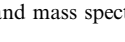
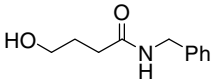
Entry	Ester	Amine	Product[b]	Yield[c] (%)
1				94
2				83
3				93
4				92
5				75
6				94
7				93 (ee > 99[d])
8				94
9				89
10				94

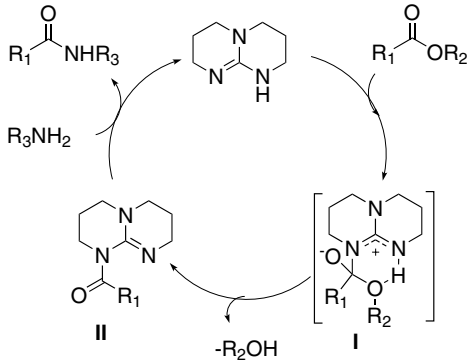
Table 2 (*continued*)

Entry	Ester	Amine	Product[b]	Yield[c] (%)
11				92[e]
12				78
13				66
14				60

[a] All reactions were carried out with 1.0 equiv of ester (except entry 11), 30 mol % of catalyst and 1.2 equiv of amine, at 75 °C for 12 h.
[b] All the products were characterized by ^{1}H, ^{13}C NMR and mass spectroscopy.
[c] The yield refers to isolated products.
[d] Enantiomeric excess (ee) determined by chiral HPLC analysis using a chiral phase column (Chiralcel OD-H, *n*-hexane/EtOH (97:3), 1 mL/min ($tr_1 = 21.83$ min and $tr_2 = 28.51$ min)).
[e] Reaction carried out with 2.0 equiv of ester, 30 mol % of catalyst and 1.0 equiv of diamine.

esters.[18] This analogy is supported by the observation of the inefficiency of MTBD for the catalysis of aminolysis despite a similar basicity than TBD (pK_a values of conjugate acid are 25.7 and 26.2, respectively). The proposed mechanism is based on TBD acting as a bifunctional nucleophilic organocatalyst. In a first step, TBD reacts on the ester leading to intermediate I (Scheme 3) where the protonated nitrogen allows an easy proton transfer affording the TBD amide II and liberating the alcohol. Finally hydrogen bond activation of the amine facilitates the amide formation and the regeneration of TBD.

In summary, we have established that TBD, an inexpensive and non toxic commercially available compound, is an efficient organocatalyst for the aminolysis of a range of esters in the presence of various amines under solvent-free conditions. The superior activity of TBD compared to other bases could be ascribed to its nucleophilicity and to a bifunctional nucleophilic mechanism.



Scheme 3. Mechanism proposed for the aminolysis of esters catalyzed by TBD.

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16. *Representative procedure for the aminolysis reaction* (Table 2, entry 1): To a stirred solution of methyl phenylacetate (100 μL, 0.71 mmol) was added TBD (29.6 mg, 30 mol %) followed by benzylamine (93 μL, 0.85 mmol) under nitrogen atmosphere. The reaction mixture was slowly warmed to 75 °C and stirred for 12 h, allowed to cool to ambient temperature and concentrated in vacuo. The residue obtained was chromatographed on silica gel using 20% ethyl acetate/cyclohexane as eluent to afford *N*-benzyl phenylacetamide as a solid (453 mg, 94%), mp 119 °C. IR (transmission, film KRS-5): 3291, 3084, 3032, 1643, 1552, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.20–7.30 (m, 10H), 6.27 (s, 1H), 4.38 (d, $J = 4.5$ Hz, 2H), 3.57 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 138.7, 135.4, 129.8, 129.4, 129.0, 127.9, 127.8, 127.7, 44.1, 43.9. MS (m/z) = 226.12 ($M^{+\cdot}$).
17. All new compounds were characterized by ^1H, ^{13}C NMR and mass spectroscopy. *N*-(2-Hydroxyethyl)-2-phenylacetamide (Table 2, entry 13): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.23–7.33 (m, 5H), 6.27 (bs, 1H), 3.54–3.62 (m, 5H), 3.30–3.35 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.8, 135.0, 129.6, 129.2, 127.6, 62.0, 43.7, 42.8. MS (m/z) = 180.10 ($M^{+\cdot}$). *N*-Benzyl-4-hydroxybutanamide (entry 14, Table 2): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.19–7.28 (m, 5H), 6.89 (b, 1H), 4.32 (d, $J = 5.6$ Hz, 2H), 4.02 (bs, 1H), 3.54–3.58 (m, 2H), 2.27–2.31 (m, 2H), 1.77–1.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.0, 138.5, 128.9, 127.9, 127.6, 62.0, 43.8, 33.7, 28.5. MS (m/z) = 194.10 ($M^{+\cdot}$).
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