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Organobase-Catalyzed Amidation of Esters with Amino Alcohols

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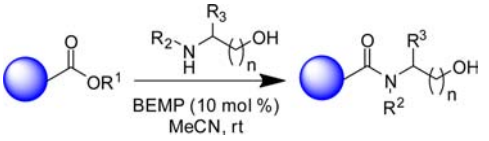
ABSTRACT



A base-mediated procedure for the amidation of unactivated esters with amino alcohols is reported. Optimization and exemplification of the catalytic process are described, furnishing products in 40−100% isolated yield.

The amide functional group is ubiquitous both in biology as the basic repeat unit in proteins and within small druglike molecules.[1,2] In this latter context, the formation of amide bonds has been identified as one of the most frequently deployed transformations within medicinal chemistry laboratories, accounting for a significant proportion of all reactions carried out in this setting.[3,4] Based on this, methods enabling the mild and efficient synthesis of amides are of considerable importance, and a raft of reagents which facilitate the condensation of carboxylic acids and amines have been reported.[5] In addition to stoichiometric reagents for amide condensations, catalytic approaches have also emerged which offer greater atom economy, thus minimizing environmental impact.[6]

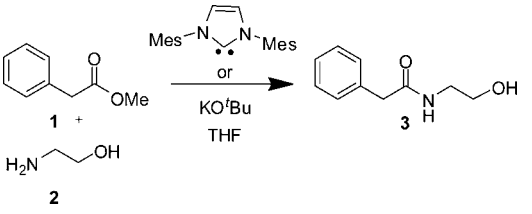


Figure 1. Amide bond formation from unactivated esters and amino alcohols.

As part of an ongoing program centered on sustainable synthesis, we were interested in developing catalytic methods for the transformation of ester derivatives into amide containing systems. In relation to this, a survey of the literature highlighted a study by Movassaghi[7] which demonstrated the use of *N*-heterocyclic carbene systems as catalysts which were capable of converting unactivated esters (e.g., **1**) into amido alcohol systems[8] such as **3** *via* transesterification and subsequent rearrangement to the amide (Figure 1).

In a corollary to this work, Movassaghi noted that potassium *tert*-butoxide was also competent at catalyzing the reaction, furnishing **3** in 74% isolated yield.[7] In this paper, we wish to report our efforts in developing this

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(1) *Peptides, Synthesis, Structures and Applications*; Gutte, B., Ed.; Academic Press: San Diego, 1995.
(2) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471.
(3) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.
(4) Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 2.
(5) For a review see: El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557.
(6) For representative examples, see: (a) Sabot, C.; Kumar, K. A.; Meunier, S.; Mioskowski, C. *Tetrahedron Lett.* **2007**, *48*, 3863. (b) Arnold, K.; Batsanov, A. S.; Davies, B.; Whiting, A. *Green Chem.* **2008**, *10*, 124. (c) Allen, C. L.; Chhatwal, C. R.; Williams, J. M. J. *Chem. Commun.* **2012**, *42*, 666. (d) Ghosh, S.; Bhaumik, A.; Mondal, J.; Mallik, A.; Sengupta, S.; Mukhopuahyay, C. *Green Chem.* **2012**, *14*, 3220. (e) Gernigon, N.; Al-Zoubi, R. M.; Hall, D. G. *J. Org. Chem.* **2012**, *77*, 8386. (f) Ohshima, T.l; Hayashi, Y.; Agura, K.; Fuji, Y.; Yoshiyama, A.; Mashima, K. *Chem. Commun.* **2012**, *48*, 5434.
(7) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453.

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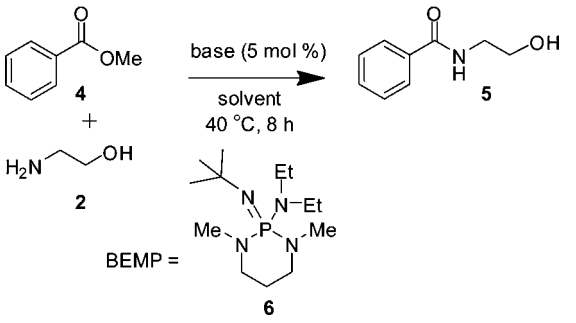
base-catalyzed manifold toward a process which is of broad utility in the preparation of synthetically useful compounds.

We commenced our campaign by screening a range of bases (potassium *tert*-butoxide, DBU, Cs_2CO_3, NaH, and BEMP, **6**[9]) and solvents (THF, dimethyl carbonate, MeCN, NMP, and toluene) for a model reaction examining the conversion of **4** to **5** (Table 1),[10] initially employing elevated temperatures to achieve the transformation and using 1 equiv each of **4** and **2**.[11] The most effective conditions identified are summarized in Table 1.

Table 1. Initial Base and Solvent Screening



solvent	base	conversion[a]
THF	*t*-BuOK	28
MeCN	Cs_2CO_3	37
NMP	Cs_2CO_3	50
MeCN	BEMP	61

[a] Determined by HPLC using an internal standard. See Supporting Information.

Based on the output from this initial screen, we selected the combination of **6** in MeCN for further optimization, again using the model reaction shown in Table 1. In order to expedite the optimization of the current process, and to simultaneously examine the effects of multiple parameters in a robust and high-throughput fashion, we employed the technique of Design of Experiments (DoE).[12] A half-fractional, two-level factorial design was utilized, employing Design Expert software[13] examining the following variables: temperature (20−60 °C), concentration (0.5−2 M), reaction time (8−22 h), and catalyst loading (5−20 mol %). We chose to retain a 1:1 stoichiometry of ester (**4**) to ethanolamine (**2**) in order to develop conditions where use of these reactants could be conserved if supplies were limited. Table 2 shows the specific reactions examined, including two center points to allow estimation of error (entries 2 and 8).

Table 2. Factorial Design for the Optimization of the Conversion of **4** to **5** Catalyzed by BEMP

entry	time (h)	temp (°C)	concn (M)	cat. loading (mol %)	conversion (%)[a]
1	22	20	2	5	60
2	15	40	1.25	12.5	98
3	8	20	0.5	5	32
4	22	20	0.5	20	92
5	22	60	2	20	97
6	8	60	2	5	55
7	22	60	0.5	5	67
8	15	40	1.25	12.5	100
9	8	20	2	20	100
10	8	60	0.5	20	96

[a] Determined by HPLC using an internal standard. See Supporting Information.

A cursory examination of the data generated from this initial design indicated that quantitative conversion of **4** to **5** could be achieved (e.g., Table 2, entry 9 using 20 mol % **6** as the catalyst). A more detailed examination of the results using a response surface (Figure 2) implied that the most important effects in determining conversion were catalyst loading and reaction concentration. Other effects such as reaction time were not found to influence the conversion over the range studied as part of the experimental design.

From consideration of the data generated by the design, we were able to identify reaction conditions that could

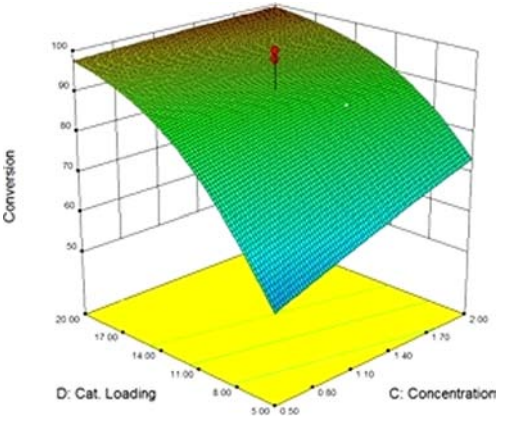


Figure 2. Response surface showing effects of catalyst loading and concentration on the conversion of **4** to **5**. Conversion assessed by HPLC. Red dots indicate center points of the design.

(8) For representative examples of amide formation with amino alcohols, see: (a) Guo, Z.; Schultz, A. G. *Tetrahedron Lett.* **2001**, *42*, 1603. (b) Blum, C. A.; Zheng, X.; De Lobaert, S. *J. Med. Chem.* **2004**, *47*, 2318. (c) Machetti, F.; Bucelli, I.; Indiani, G.; Kappe, C. O.; Guarna, A. *J. Comb. Chem.* **2007**, *9*, 454. (d) Montes D'Oca, C. D.; Coelho, T.; Marinho, T. G.; Hack, C. R. L.; Duarte, R. C.; Almeidada Silva, P.; Montes D'Oca, M. G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5255. (e) Chintareddy, V. R.; Ho, H. A.; Sadow, A. D.; Verkade, J. G. *Tetrahedron Lett.* **2011**, *52*, 6523. (f) Whitten, K. M.; Makriyannis, A.; Vadivel, S. K. *Tetrahedron Lett.* **2012**, *53*, 5753.

(9) 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine: Schwesinger, R. *Chimia* **1985**, *39*, 269.

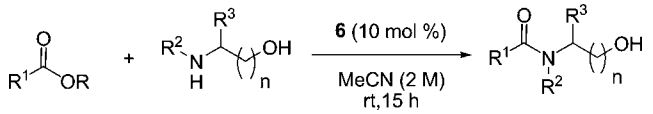
(10) Full details of the screen are provided in the Supporting Information.

(11) Control reactions conducted in the absence of base indicated that less than 7% conversion to **5** was observed in each case.

(12) Carlson, R. *Design and Optmization in Organic Synthesis*; Elsevier: Amsterdam, 1992; Chapter 2.

(13) Design Expert Software is available from Stat-Ease, Inc. Minneapolis, MN. http://www.statease.com.

Table 3. Assessment of Substrate Scope



entry	ester	amino alcohol	product	yield (%)[a]
1	**4**, R = H	**2**	**5** R = H	87
2	**7**, R = 4-CF_3	**2**	**8** R = 4-CF_3	95
3	**9**, R = 2-CH_3	**2**	**10** R = 2-CH_3	60 (94)[b]
4	**11**, R = 4-CH_3O	**2**	**12** R = 4-CH_3O	82
5	**13**, R = 2-Cl, 4-Br	**14**	**15**	93
6	**16**, R = 4-F	**17**	**18**	58 (69)[b]
7	**1**	**2**	**3**	99
8	**19**	**2**	**20**	94
9	**21**	**2**	**22**	99
10	**23**	**14**	**24**	86
11	**23**	**25**	**26**	89
12			**28**	100
13	**27**	**2**		40 (75)[b]
14	**30**, R = CH_3	**2**	**31**, R = CH_3	97
15	**32**, R = *i*-Pr	**2**	**33**, R = *i*-Pr	99
16	**34**, R = *t*-Bu	**2**	**35**, R = *t*-Bu	61 (91)[b]
17	**36**, R = *i*-Pr	**2**	**31**	100
18	**37**, R = *t*-Bu	**2**	**31**	9 (70)[b]
19	**38**	**17**	**39**	75
20	**40**	**17**	**41**	80

[a] Isolated yield following purification. [b] Reaction carried out at 40 °C.

maximize the conversion of **4** to **5** while making economical use of the catalyst and, where possible, minimizing heat input to the system. Accordingly, we subsequently screened the reaction of **4** and **2** using 10 mol % **6** at a reaction concentration of 2 M under ambient temperature for 15 h. Gratifyingly, this delivered amide **5** with 90% conversion (as assessed by HPLC) and in 87% isolated yield, representing a substantial overall improvement in the process.

Having established optimal conditions for the conversion, we next sought to determine the general utility of the method. To this end, a range of substrates were examined as outlined in Table 3.

The data indicated that the reaction conditions developed are highly general in nature, with a range of substrates shown to be compatible. Where lower isolated yields have been observed, conducting the reaction at 40 °C results in an improvement (Table 3, entries 3, 6, 13, 16, and 18). Aryl esters are converted to the corresponding amides in good to excellent yields (Table 3, entries 1−6), and heteroaromatic systems are more than competent substrates also (Table 3, entries 8−11). Aliphatic systems again are compatible (Table 3, entries 7 and 12−16), and variation of the ester leaving group is also tolerated (Table 3, entries 17 and 18). Lastly, amino acid derived building blocks are well tolerated substrates for the reaction conditions (Table 3, entries 19 and 20). Determination of the diastereomeric ratio for compound

(14) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167. *tert*-Butylimino-tris(dimethylamino)phosphorane, P_1-^{t}Bu: £54/5 mL from Sigma-Aldrich. *tert*-Butylimino-tri(pyrrolidino)phosphorane, BTPP: £52/5 mL from Sigma-Aldrich. *tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, BEMP: £150/5 mL from Sigma Aldrich.

41 indicated some erosion of chiral integrity had occurred (d.r. = 86:14 as determined by chiral HPLC). Efforts are ongoing in our laboratory to identify alternative base catalysts for use with this substrate class which minimize epimerization.

We also examined alternative phosphazene bases in the reaction (Figure 3).[14] The bases P_1-^{t}Bu (**42**) and BTPP (**43**) are around a third of the price of **6** and may offer a cost-effective alternative when conducting these reactions on a larger scale.[14] Using either P_1-^{t}Bu or BTPP for the conversion of **1** to **3** under the optimized conditions developed above furnished the desired product in 93 and 82% yields, respectively.

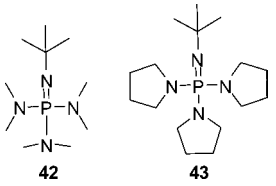


Figure 3. Alternative phosphazene bases examined.

In the last phase of our study, we sought to apply our methodology to the preparation of some medicinally relevant compounds. In the first instance, we targeted the synthesis of the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor potentiator Org 26576 (**46**, Figure 4),[15] a nootropic agent in clinical trials for Attention Deficit Hyperactivity Disorder. An unprotracted route starting from the commercially available nicotinic derived methyl ester **44** and (*S*)-prolinol (**14**) afforded the requisite intermediate amide **45** in 87% yield (which increases to 98% when carrying out the reaction at 40 °C).

In a previous synthesis,[16] nicotinamide derivative **45** was prepared using the corresponding nicotinic acid derivative with stoichiometric amounts of the coupling reagent *N*,*N*′-dicyclohexylcarbodiimide (DCC) combined with the additive 1-hydroxybenzotriazole (HOBt) in 86% yield, demonstrating the comparative utility of the current method. Following the base mediated amide formation subsequent S_NAr chemistry realized the target compound **46** in 97% yield.

In a second example, we targeted the synthesis of the α_1-receptor agonist midodrine **49** (Figure 5) which is utilized clinically for the treatment of orthostatic hypotension.[17] A concise synthetic route was implemented starting from the known amino alcohol **47**[18] and **38** which furnished the protected amide intermediate **48** in 70% isolated yield, illustrating an example of the process using a secondary alcohol moiety. Subsequent acidic cleavage of the Boc group delivered the active entity in 75% yield.

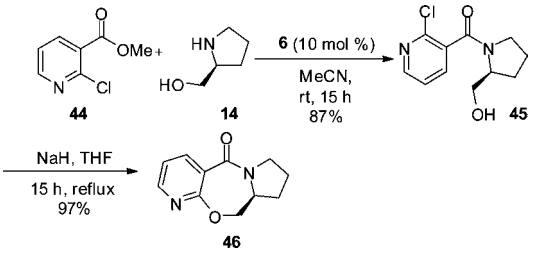


Figure 4. Preparation of an AMPA receptor potentiator.

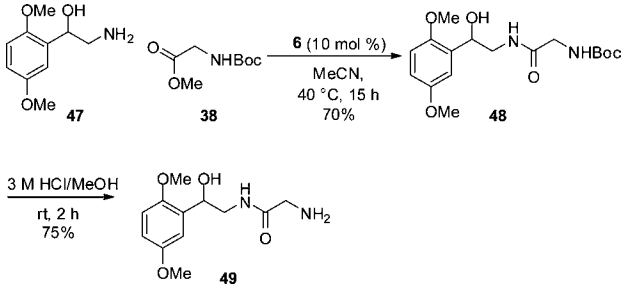


Figure 5. Synthesis of midodrine.

In summary, through reaction screening and statistically driven optimization we have developed a robust and highly general set of conditions for the base-mediated synthesis of amido alcohols. In addition, we have been able to exemplify the methodology in the preparation of bioactive compounds and anticipate it can be further utilized in this valuable context. Current work is focused on enhancing the substrate scope of the reaction, identification of additional base catalysts, and the mechanistic aspects of the process, and these will be reported in due course.

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

The authors declare no competing financial interest.

(15) Bursi, R.; Erdemli, G.; Campbell, R.; Hutmacher, M. M.; Kerbusch, T.; Spanswick, D.; Jeggo, R.; Nations, K. R.; Dogterom, P.; Schipper, J.; Shahid, M. *Psychopharmacology* **2011**, *218*, 713.

(16) Schultz, A. G.; Flood, L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 838.

(17) Oldenburg, O.; Kribben, A.; Baumgart, D.; Philipp, T.; Erbel, R.; Cohen, M. V. *Curr. Opin. Pharmacol.* **2002**, *2*, 740. Compound **49** is marketed as the racemate.

(18) Epifani, E.; Lapucci, A.; Macchia, B.; Macchia, F.; Tognetti, P.; Breschi, M. C.; Del Tacca, M.; Martinotti, E.; Giovannini, L. *J. Med. Chem.* **1983**, *26*, 254. Compound **47** is commercially available from Fluorochem UK, Ltd.