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Technical Note

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Demonstration on Pilot-Plant Scale of the Utility of 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) as a Catalyst in the Efficient Amidation of an Unactivated Methyl Ester

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ABSTRACT: The utility of 1,5,7-triazabicyclo[4.4.0]dec-5-ene as a reagent to facilitate efficient amide formation by reaction of an amine with an unactivated ester was demonstrated on pilot-plant scale as a key step in the synthesis of an H-PGDS inhibitor.

INTRODUCTION

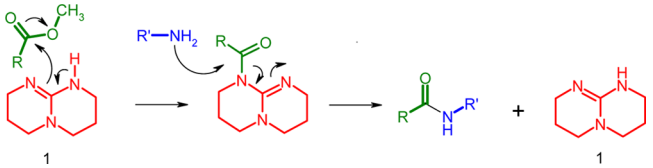
The formation of an amide bond is one of the more common and important reactions in organic chemistry. This transformation is especially important in a strategic sense in synthesis design because amide bonds are usually installed late in multistep syntheses and thus provide opportunities for convergency.

On large scale,[1] amides are often formed by functional group interconversion of an ester to its carboxylic acid, which is then activated, for example, as an acid halide, and then treated with an amine.[2]

A more direct amidation is coupling of an ester with an amine, but this approach normally requires an activated ester,[3] for example, the *p*-nitrophenol ester of a carboxylic acid. More convenient would be direct amidation of methyl and ether esters because they are usually more economical and commercially available. However, simple alkyl esters are relatively unreactive, even under forcing conditions, and they generally afford poor conversions to amides.[4]

In 2006, Hedrick et al.[5] reported on 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, **1**) as an organocatalyst useful for acyl transfer reactions. Waymouth et al.[6] proposed that TBD behaves not merely as a base but also as a participant in the acyl transfer as shown in Scheme 1. More recently,

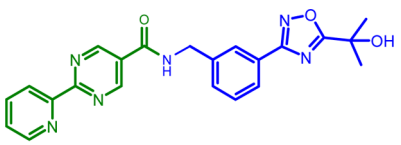
Scheme 1. Amidation Mechanism



Mioskowski et al.[7] demonstrated the utility of TBD as an effective catalyst for the facile amidation of alkyl esters. High yields of amides were obtained with simple esters in reactions with a selection of primary and some secondary amines under solvent-free conditions. Recently, an opportunity to evaluate this technology arose. Herein is described an application of TBD technology for amide bond formation on pilot-plant scale for the synthesis of a drug substance.

RESULTS AND DISCUSSION

Recently, multi-kilogram quantities of compound **2**, an H-PGDS inhibitor,[8] were needed to support preclinical studies. In the original Discovery routes to the molecule, the amide bond in **2** was formed by saponification of an ester substrate, activation of the resulting acid as its acid chloride or as its acylimidazole derivative, and then treatment with the requisite benzyl amine.



2

During efforts to improve the synthesis of this molecule and related analogs, attempts to directly form the amide bond from the methyl ester in the presence of tetramethylguanidine or DBU[9] gave poor conversions (<8%). In contrast, it was found that the use of TBD was effective in promoting the last-step amide bond forming reaction to give **2** (Scheme 2) directly from the corresponding methyl ester **3** and the benzyl amine **4**. For example, in the presence of TBD (0.2−0.5 equiv), >97 area % (A%) conversion (HPLC) was achieved after 3−5 h at 70−80 °C in 2-MeTHF or toluene. Toluene was selected early on as the preferred solvent for further optimization compared to MeTHF because it gave a slightly better isolated yield of **2**. The reaction was clean, with the only significant side reaction being 3−7 A% saponification of the ester together with small amounts (<0.5 A%) of a nitrile impurity formed by degradation of the oxadiazole ring in **2**. Accordingly, the ester was employed in 6% excess in order to compensate for saponification and to substantially consume the amine substrate. The carboxylate side product and water-soluble TBD[10] were removed during workup. The product was isolated extractively in ca. 95% yield. Alternatively, the reaction mixture was simply cooled, filtered, rinsed, and dried to give **2** in 77−87% yield and 96−99 A% purity.

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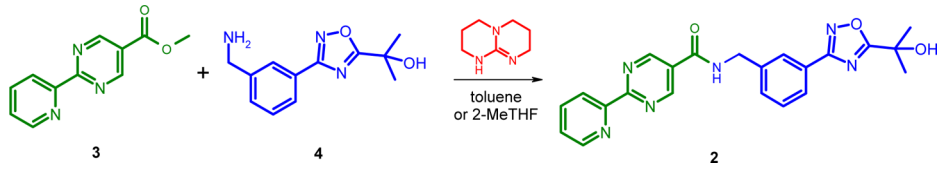
Scheme 2. Direct amidation of ester 3



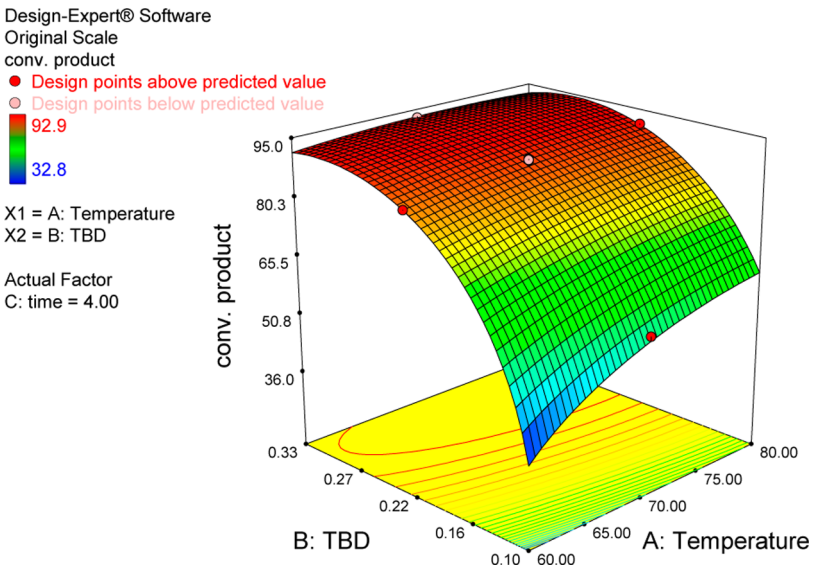


Figure 1. DoE optimization of the formation of **2**.

In anticipation of a pilot plant campaign of **2**, the TBD process was optimized using Design of Experiments (DoE) statistical methods. The reaction conditions employed a slight excess of the ester (1.06 equiv relative to the amine) in toluene as solvent. The three factors that were investigated in a second order central composite response surface design were amount of TBD catalyst (0.10−0.33 equiv), temperature (60−80 °C), and reaction time (3−5 h). The objective was to maximize conversion to product while using relatively low loadings of TBD and while maintaining conditions in a robust reaction zone. Data analysis indicated that the amount of TBD was the parameter having the greatest influence on reaction profile and robustness, followed by reaction temperature. Optimal and robust conditions, predicted to be 0.28 equiv TBD at 70−80 °C (Figure 1) for 4 h, were subsequently confirmed by separate lab-scale experiments.

The optimized process was then transferred to the pilot plant, and three batches were performed on about 9-kg scale. On scale up, the reaction profile closely paralleled lab experiences; namely, >90 A% product with less than 3 A% of **3** and **4** was achieved after ca. 4 h at 70 °C. After the amidation was completed, 1.6 parts of ethanol and an additional 5 parts of toluene were added. The suspension was then held at 70 °C for 30 min to facilitate solubilization of gummy impurities. After cooling and filtration, crude **2** was isolated in 82% yield as a nicely crystalline solid, with a purity of 99.2 A% and containing 3700 ppm toluene.[11] Recrystallization from EtOH of two combined batches yielded 19.5 kg (88.6% recovery) of **2** with a purity of 99.9 A% and containing no detectable levels of toluene.

In summary, the utility of TBD as a reagent for amide bond formation from a methyl ester was demonstrated on pilot-plant scale. The amidation process was optimized; best results were achieved using 0.28 equiv of TBD and 1.06 equiv of the ester to afford the amide in 82% isolated yield. The technology allowed elimination of two chemical steps[12] in the synthesis of **2**, namely, saponification of the ester and activation of the resulting carboxylic acid, and it enabled accelerated deliveries of multi-kilogram quantities of the desired drug substance.

EXPERIMENTAL SECTION

General. The following HPLC method was used to monitor reactions and analyze products: Zorbax Eclipse XDB-C8, 150 mm × 4.6 mm column, 5 μm particle size, mobile phase gradient program, water/ACN/TFA 95:5:0.1 (v:v:v) for 2 min, then linear ramp over 18 min to 10:90:0.1 (v:v:v), at a column temperature of 30 °C, flow rate 1.0 mL/min, detection wavelength 240 nm; retention times: **3**, 7.4 min; **4**, 8.3 min; **2**, 10.2 min.

*2-(Pyridin-2-yl)pyrimidine-5-carboxylic Acid 3-[5-(1-Hydroxy-1-methylethyl)-1,2,4]oxadiazol-3-yl]benzylamide (**2**).* A glass-lined reactor was charged with 86.9 kg of a solution obtained from the workup of the prior step[13] containing **4**[8] (8.7 kg, 37.3 mol) in 2-methyltetrahydrofuran (70.4 wt %) and toluene (18.9 wt %). The solution was partially concentrated (100−200 Torr, 50−70 °C) to a volume of ∼10 L. After cooling to 45 °C, the vacuum was released with nitrogen and the batch was diluted with toluene (37 kg). The solution was partially concentrated (100−200 Torr, 50−70 °C) to a volume of ∼50 L. After cooling to 20−25 °C and venting the reactor with nitrogen, analyses of in-process samples indicated that the solution contained 0.03 wt % water (target: ≤0.10%) and a solvent ratio of 12.5:1 toluene/2-MeTHF. The ester **3**[8] (8.5 kg, 39.5 mol, 1.06 equiv) and TBD (1.5 kg, 10.8 mol, 0.29 equiv) were charged. The suspension was stirred at 20−26 °C for 30 min, heated to 50−56 °C and held for 30 min, and then heated

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to 68−72 °C and held for 4 h.[14] In-process HPLC analysis of a sample of the suspension indicated 0.9 A% of unreacted **4** (target: ≤3.0 A%). The batch was cooled to 20−26 °C, diluted with abs. ethanol (11 kg), stirred for 30 min at 19−25 °C, and then further diluted with toluene (37 kg). The suspension was heated and held at 68−72 °C for 30 min, cooled to 25 °C over a period of about 3 h, stirred at 17−23 °C for 16 h, and then filtered. The cake was rinsed twice with solutions comprised of toluene (24.0 kg) and absolute ethanol (3.2 kg), and then it was rinsed with water (142 kg). After drying (<100 Torr, 55−60 °C), 12.50 kg (82.1%) of **2** was obtained as a white, crystalline solid, 99.2 A% pure by HPLC analysis and containing 3700 ppm toluene.

Recrystallization of ***2***. A suspension of **2** (22.0 kg) and 382 kg of abs. EtOH was heated and held at 67−73 °C for about 1 h. The resulting solution was cooled to 63−67 °C and then passed through a 0.8-μm cartridge filter (to remove extraneous matter) with a rinse using abs. EtOH (24 kg, ca. 65 °C). The solution was partially concentrated[15] (atmospherically, 78 °C) to a volume of ∼286 L.[16] The batch was cooled to 55 °C at a rate of 0.5 °C/min and then was held at 53−57 °C for 2 h, during which time the product crystallized. The batch was cooled to −5 °C at a rate of 0.2 °C/min, was held at −3 to −7 °C overnight, and was then filtered. The filter cake was rinsed with abs. EtOH (36 kg, −5 °C) and then dried (<100 Torr, 30 °C for 3 h, then 58 °C for 20 h) to give 19.5 kg (88.6% recovery) of **2** as a white, crystalline solid, 99.9 A% pure by HPLC analysis. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 1.61 (s, 6H), 4.65 (s, 2H), 6.10 (s, 1H), 7.53−7.63 (m, 3H), 7.91−8.04 (m, 3H), 8.44 (d, 1H), 8.78 (d, 1H), 9.37 (s, 2H), 9.58 (s, 1H); ^{13}C NMR (DMSO-d_6, δ): 28.8, 42.8, 68.1, 124.3, 125.8, 126.0, 126.4, 126.6, 129.7, 131.0, 137.5, 140.4, 150.1, 154.0, 157.0, 163.3, 164.7, 167.6, 184.6.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For a review of amide bond formation on industrial scale as applied to preparing peptides, see: Marder, O.; Albericio, F. *Chim. Oggi* **2003**, *21* (6), 6.

(2) For recent reviews of amide bond formation, see: (a) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827. (b) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405. (c) Joullié, M. M.; Lassen, K. M. *ARKIVOC* **2010**, *8*, 189. (d) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606. (e) Benz, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: New York, 1991; Vol. *6*, 381−417.

(3) See ref 2a, 2d, and 2e, and references cited therein.

(4) Smith, M. B.; March, J. In *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 2001; pp 510−511.

(5) Pratt, R. C.; Lohmeijer, B. G. G.; Long, D. A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 4556.

(6) Kiesewetter, M. K.; Scholten, M. D.; Kirn, N.; Weber, R. L.; Hedrick, J. L.; Waymouth, R. M. *J. Org. Chem.* **2009**, *74*, 9490.

(7) Sabot, C.; Kumar, K. A.; Meunier, S.; Mioskowski, C. *Tetrahedron Lett.* **2007**, *48*, 3863.

(8) VanDeusen, C. L.; Weiberth, F. J.; Gill, H. S.; Lee, G.; Hillegass, A. *PCT Int. Appl.* WO2011044307, 2011.

(9) Price, K. E.; Larrivée-Aboussafy, C.; Lillie, B. M.; McLaughlin, R. W.; Mustakis, J.; Hettenbach, K. W.; Hawkins, J. M.; Vaidyanathan, R. *Org. Lett.* **2009**, *11*, 2003.

(10) Recovery of TBD was not investigated.

(11) Attempts to substantially reduce toluene levels by modifying the crystallization or drying steps were unsuccessful. Subsequent development will evaluate employing an alternative solvent for the amidation.

(12) The elimination of processing steps more than compensated for the upfront cost of TBD (ca. 2,400 USD/kg in 10-kg lots, Aldrich). The cost contribution of TBD was further mitigated because it was employed in substoichiometric quantities. It is reasonable to anticipate more competitive pricing should this reagent become more commonly employed.

(13) Alternatively, **3** can be charged as a dry, isolated solid, and the partial concentration and azeotropic drying steps eliminated.

(14) A stepwise heating profile gave cleaner conversion to product compared to directly heating to 70 °C.

(15) High dilution was used for the initial dissolution to avoid the potential of premature crystallization during the polish filtration.

(16) A narrow ring of solid formed on the wall of the reactor at the liquid line during the distillation. Periodic increases in the agitation rate dislodged most of the solid off the wall. At the end of the partial concentration, the batch was held at 75 °C, just under reflux temperature, to allow the solvent vapor to condense and redissolve the small amount of solid on the wall.