Tetrahedron Letters 55 (2014) 6935–6938

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Scandium triflate catalyzed ester synthesis using primary amides

Benjamin N. Atkinson *, Jonathan M. J. Williams

Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK

ARTICLE INFO

Article history:
Received 17 September 2014
Revised 10 October 2014
Accepted 22 October 2014
Available online 28 October 2014

Keywords:
Amides
Alcohols
Scandium
Esters
Alcoholysis

ABSTRACT

A scandium triflate ($ScOTf)_3$ catalyzed methodology has been developed to synthesize esters from primary amides. Various primary and secondary aliphatic alcohols have been shown to react in *n*-heptane with a range of primary amides for 24 h.

Amide bonds are robust and thermodynamically stable chemical moieties due to resonance of nitrogen with the carbonyl.[1] However, despite their inherent chemical inertness amides have gained popularity as acyl donors by providing alternative synthetic routes toward acyl derivatives. Transamidation reactions, the direct substitution reaction of an amide with an amine, have received substantial interest from a number of groups,[2] including our own. This has led to the broadening of reactivity scope as well as an increase in the variety of catalysts used including metals,[3] nonmetals,[4] and organocatalysts,[5] as well as stoichiometric amounts of promoters.[6]

Direct alcoholysis of amides with alcohols has been carried out using three main methods. The first method is the direct activation of an amide using activating agents, early examples used silicon or boron fluorides.[7] More recent examples used stoichiometric amounts of activating agents such as amide acetals (dimethylformamide dimethyl acetal),[8] tellurium ethoxide,[9] phosphates,[10] or triflic anhydride based protocols.[11] Other methods used a titanium catalyst and required a stoichiometric amount of hydrochloric acid.[12] The second method uses twisted amides to increase the susceptibility of the amide to nucleophilic attack via disruption of the amide bond resonance.[13] The third method uses directing-group-assisted activation of the amide bond, this ligand-like binding of an intramolecular heteroatom increases the susceptibility of the carbonyl toward nucleophilic attack.[14] However, in all cases, stoichiometric activators or tailored substrates were necessary. Mashima recently described an excellent and simple cooperative catalytic system using scandium triflate in combination with a boronic ester for the alcoholysis of a non-activated amide, however, a large excess of alcohol was required.[15] As such, we chose to investigate a general, metal-catalyzed methodology for the alcoholysis of amides not requiring the alcohol substrate as the reaction solvent.

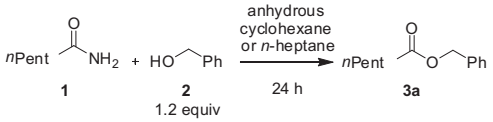
Identification of a suitable catalyst began by examining the alcoholysis, at 10 mol % loading, of *n*-hexanamide (**1**) with benzyl alcohol (**2**) (Table 1). Our choice of catalyst was influenced by previous work investigating the activation of amides using zirconocene dichloride (Cp_2ZrCl_2).[3h] Only $Sc(OTf)_3$ showed catalytic activity for the alcoholysis reaction (entry 3), with no activity seen with Cp_2ZrCl_2 or a titanium-based catalyst (entries 1 and 2). Increasing the temperature and reducing the catalyst loading gave 89% conversion into the ester **3a** (entry 4). Little or no catalytic activity was observed with other lanthanide triflates or with $Mg(OTf)_2$ (entry 5).[16] Only 23% conversion into ester **3a** was observed using triflic acid (15 mol %) (entry 6), highlighting the reaction dependence on $Sc(OTf)_3$. Increasing the concentration and equivalents of alcohol lowered the overall conversion, albeit marginally with regard to the equivalents of alcohol.[16]

$Sc(OTf)_3$ is known to be a water tolerant Lewis acid catalyst,[17] and we therefore investigated the tolerance of the reaction toward the presence of water. Interestingly, the use of anhydrous $Sc(OTf)_3$ in combination with anhydrous *n*-heptane resulted in reduction in the overall conversion to 80%.[16] Conversely, increasing the amount of water present did not increase conversion into the ester product, with 74% conversion seen with two equivalents of water present (entry 7).[16]

* Corresponding author.
E-mail address: b.n.atkinson@bath.ac.uk (B.N. Atkinson).

http://dx.doi.org/10.1016/j.tetlet.2014.10.124
0040-4039/

Table 1
Catalyst identification and reaction optimization



1 | 2 (1.2 equiv) | 3a

Entry	Catalyst (mol %)	Temp (°C)	Yield[a] of **3a** (%)
1	$Ti(Oi\text{-}Pr)_4$ (10)	80	0
2	Cp_2ZrCl_2 (10)	80	0
3	$Sc(OTf)_3$ (10)	80	53
4	$Sc(OTf)_3$ (5)	100	89
5	$Mg(OTf)_2$ (5)	100	0
6	TfOH (15)	100	23
7	$Sc(OTf)_3$ (5)	100	74[b]
8	$Sc(OTf)_3$ (5)	100	98[c]

[a] Conversions calculated by analysis of the crude ^{1}H NMR spectra.
[b] Carried out with two equivalents of H_2O.
[c] Carried out in reagent grade solvent and in an open reaction vessel.

Interestingly, throughout the optimization process, no symmetrical ether (dibenzyl ether) formation was observed.[18] Additionally, no benzylated amide products or *n*-hexanoic acid were observed. Using our optimized conditions (Table 1, entry 8) with $Sc(OTf)_3$ (5 mol %), we went on to explore the substrate scope of this reaction with respect to the alcohol (Table 2).

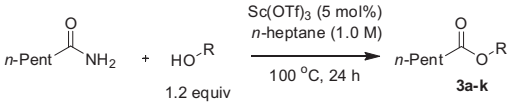
Alcoholysis of *n*-hexanamide with a variety of benzyl alcohols afforded the corresponding esters in moderate to excellent yields. Electron-withdrawing groups on the aryl ring gave reduced yields of products, likely due to the reduced nucleophilicity of the alcohol (entries 2 and 3). With electron-rich alcohols it was seen that a significant amount of the symmetrical ether was observed, notably with 4-methoxybenzyl alcohol only 55% conversion into product was observed and 13% conversion into symmetrical ether. However piperonyl alcohol gave a much cleaner reaction with only 2% of the symmetrical ether observed (entry 4). The straight chain alcohol *n*-octanol reacted cleanly to give 91% yield (entry 6). Other alcohols such as 3-phenylpropyn-1-ol and geraniol reacted cleanly, giving the corresponding esters in high yields without ether formation (entries 7 and 8).

Unfortunately, cyclohexanol only gave 34% conversion into the ester at 100 °C (entry 9). However, simply increasing the temperature to 125 °C for this substrate and for other secondary alcohols resulted in good yields of ester products (entries 9–11), for both acyclic and cyclic secondary alcohols. L-Menthol reacted cleanly giving the ester product (entry 10) whilst maintaining the enantiomeric purity (>99% ee by HPLC). When secondary benzylic alcohols were used, such as 1-phenylethanol, a significant amount of symmetrical ether was observed.[19] It was noted that even at 125 °C no reaction occurred under optimized reaction conditions (Table 2), between phenol and *n*-hexanamide.

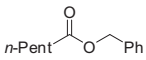
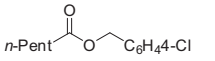
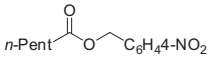
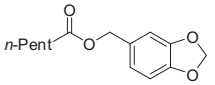
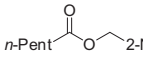
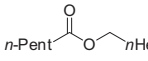
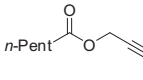
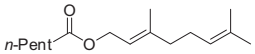
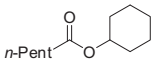
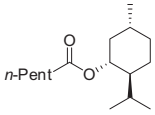
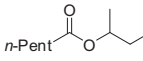
Alcoholysis of primary amides was also investigated using benzyl alcohol (Table 3). 2-Phenylacetamide reacted cleanly to give a 90% yield of ester product (entry 1). Alkyl halides were also tolerated; 2-chloropropionamide gave a modest yield of 55% of the corresponding benzyl ester (entry 2). Higher temperatures were required for less reactive amides, however good yields of 78% and 71% were obtained for both benzamide and thiophene-2-carboxamide (entries 3 and 4, respectively). Even at these higher temperatures, only a 39% yield of benzyl pivalate was obtained (entry 5). Secondary and tertiary amides, specifically *N*-methylacetamide and *N*,*N*-dimethylacetamide, showed no reaction with benzyl alcohol at 125 °C, highlighting the specificity of the reaction toward primary amides.

Competition reactions were carried out to determine the reactivity in comparison with carboxylic acids and esters (Scheme 1).

Table 2
Alcoholysis scope using *n*-hexanamide[a]



1.2 equiv | 3a-k

Entry	Product	Yield[b] (%)
1		**3a** 90 (98)
2		**3b** 83 (92)
3		**3c** 48 (53)
4		**3d** 74 (80)
5		**3e** 93 (99)
6		**3f** 91 (98)
7		**3g** 82 (87)
8		**3h** 85 (93)
9		**3i** –(34) 84 (90)[c]
10		**3j** 72 (80)[c]
11		**3k** 83 (88)[c]

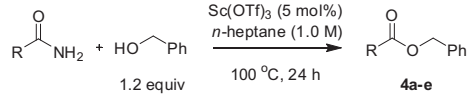
[a] Reactions performed on 2 mmol scale with 2.4 mmol of alcohol in 2 mL of solvent.
[b] Isolated yield; figures in parentheses are conversions determined by analysis of the ^{1}H NMR spectra.
[c] Reaction carried out at 125 °C in *n*-octane.

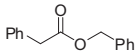
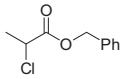
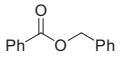
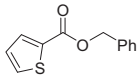
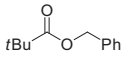
On reaction of ethyl hydrocinnamate and 2-phenylacetamide with one equivalent of benzyl alcohol an 89% total conversion into benzyl ester products was observed (Scheme 1). Of the converted starting materials, a 61:39 ratio of alcoholysis product (**4a**) to transesterified product (**4f**) was seen indicating the greater reactivity of the amide over the ester. Interestingly, although a lower total conversion of 67% was observed, esterification of the hydrocinnamic acid proceeded more quickly than the alcoholysis of the primary amide with an observed ratio of 24:76 (**4a**:**4f**).

The use of symmetrical aryl ether **5** in the reaction did not yield any ester product (Scheme 2). Even with 0.5 equiv of water present, no reaction was seen indicating that the reaction pathway did not proceed via ether formation and subsequent fragmentation.

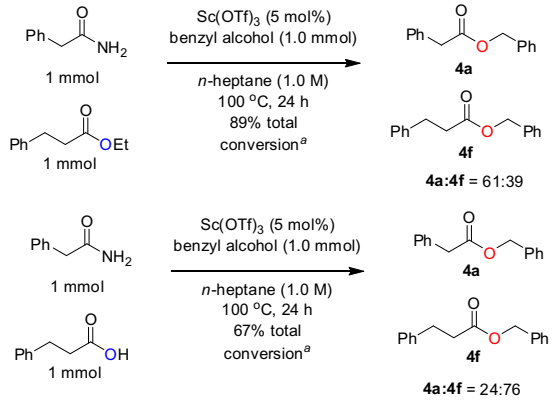
To a 1:1 mixture of *n*-hexanamide–*n*-octanol in $CDCl_3$ at 30 °C, increasing amounts of $Sc(OTf)_3$ were added. Analysis of both the ^{1}H and ^{13}C NMR spectra showed a downfield shift of both the NH amide signals, in the ^{1}H NMR, and the carbonyl signal in the ^{13}C NMR, clearly indicating coordination to the scandium atom (Table 4). As such, a mechanism analogous to that of the Fischer esterification of carboxylic acids is proposed, via activation of the amide to nucleophilic attack through carbonyl coordination. The significantly low solubility of ammonia in the reaction solvent, as

Table 3
Alcoholysis scope using benzyl alcohol[a]

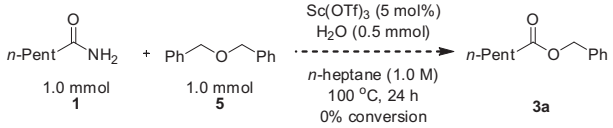


Entry	Product	Yield[b] (%)
1		**4a** 90 (99)
2		**4b** 55 (59)
3		**4c** –(23) 78 (82)[c]
4		**4d** 71 (78)[c]
5		**4e** 39 (46)[c]

[a] Reactions performed on 2 mmol scale with 2.4 mmol of alcohol in 2 mL of solvent.
[b] Isolated yield; figures in parentheses are conversions determined by analysis of the ^{1}H NMR spectra.
[c] Reaction carried out at 125 °C in *n*-octane.



Scheme 1. Competition reactions with carboxylic acids and esters. [a]Conversion determined by analysis of the crude ^{1}H NMR spectra.



Scheme 2. Reaction of *n*-hexanamide with a symmetrical benzyl ether. [a]Conversion determined by analysis of the crude ^{1}H NMR spectra.

well as the temperature at which the reactions are carried out, will also favor the product formation via loss of ammonia from the reaction system.

In conclusion, we have developed a $Sc(OTf)_3$-catalyzed methodology for the synthesis of esters using primary amides and alcohols. By proceeding in hydrocarbon solvents, only 1.2 equiv of alcohol were required for alcoholysis of primary amides. This method provides a complementary method to existing protocols where using the reacting alcohol as the reaction medium would not be feasible. Competition reactions highlight the greater reactivity, under these conditions, toward nucleophilic acylation reactions of primary amides rather than esters. Mechanistic studies revealed the activation of the primary amide by scandium, as demonstrated by analysis of both ^{1}H and ^{13}C NMR spectra.

Table 4
NMR data for $Sc(OTf)_3$ binding to *n*-hexanamide[a]

$Sc(OTf)_3$ (mol %)	^{1}H NMR		^{13}C NMR
	NH shifts (ppm)	α-CH_2 shift (ppm)	C=O shift (ppm)
0	6.22 (2H)	2.10	176.79
5	6.86, 6.49	2.15	177.79
10	7.37, 6.78	2.19	178.70

[a] Conditions: *n*-hexanamide (0.6 mmol), *n*-octanol (0.6 mmol), $CDCl_3$ (0.6 mL), 25 °C, 400 MHz.

Acknowledgements

We thank the EPSRC for funding and the University of Bath for further support.

Supplementary data

Supplementary data (experimental details, optimization reactions, characterizations and spectroscopic data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.124.

References and notes

1. (a) Robin, M. B.; Bovey, F. A.; Basch, H. Molecular and Electronic Structure of the Amide Group. In *The Chemistry of Amides—Patai Series*; Zabicky, J., Ed.; Interscience, 1970; pp 1–72; (b) Greenberg, A.; Berneman, C. M.; Liebman, J. F. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*; John Wiley & Sons: New York, 2003; (c) Glover, S. A.; Rosser, A. A. *J. Org. Chem.* **2012**, *77*, 5492.
2. For recent developments in transamidation, see: Lanigan, R. M.; Sheppard, T. D. *Eur. J. Org. Chem.* **2013**, 7453–7465.
3. (a) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 3422–3423; (b) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 5177–5183; (c) Kissounko, D. A.; Hoerter, J. M.; Guzei, I. A.; Cui, Q.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 1776–1783; (d) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Cui, Q.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 647–654; (e) Stephenson, N. A.; Zhu, J.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 10003–10008; (f) Zhang, M.; Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3905–3909; (g) Tamura, M.; Tonomura, T.; Shimizu, K.-I.; Satsuma, A. *Green Chem.* **2012**, *14*, 717–724; (h) Atkinson, B. N.; Chhatwal, A. R.; Lomax, H. V.; Walton, J. W.; Williams, J. M. J. *Chem. Commun.* **2012**, 11626–11628; (i) Becerra-Figueroa, L.; Ojeda-Porras, A.; Gamba-Sanchez, D. *J. Org. Chem.* **2014**, *79*, 4544–4552; (j) Singh, D. P.; Allam, B. K.; Singh, K. N.; Singh, V. P. *RSC Adv.* **2014**, *4*, 1155–1158.
4. (a) Allen, C. L.; Atkinson, B. N.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 1383–1386; (b) Nguyen, T. B.; Sorres, J.; Tran Minh, Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 3202–3205; (c) Stephenson, N. A.; Gellman, S. H.; Stahl, S. S. *RSC Adv.* **2014**, *4*, 46840–46843.
5. (a) Vanjari, R.; Kumar Allam, B.; Nand Singh, K. *RSC Adv.* **2013**, *3*, 1691–1694; (b) Nguyen, T. B.; Ermolenko, L.; Dau, M.-E. T. H.; Al-Mourabit, A. *Heterocycles* **2014**, *88*, 403–416; (c) Wu, J.-W.; Wu, Y.-D.; Dai, J.-J.; Xu, H.-J. *Adv. Synth. Catal.* **2014**, *356*, 2429–2436.
6. (a) Bon, E.; Bigg, D. C. H.; Bertrand, G. *J. Org. Chem.* **1994**, *59*, 4035–4036; (b) Dineen, T. A.; Zajac, M. A.; Myers, A. G. *J. Am. Chem. Soc.* **2006**, *128*, 16406–16409; (c) Starkov, P.; Sheppard, T. D. *Org. Biomol. Chem.* **2011**, *9*, 1320–1323; (d) Suchy, M.; Elmehriki, A. A. H.; Hudson, R. H. E. *Org. Lett.* **2011**, *13*, 3952–3955; (e) Lanigan, R. M.; Starkov, P.; Sheppard, T. D. *J. Org. Chem.* **2013**, *78*, 4512–4523.
7. (a) Sowa, F. J.; Nieuwland, J. A. *J. Am. Chem. Soc.* **1933**, *55*, 5052–5053; (b) Gierut, J. A.; Sowa, F. J.; Nieuwland, J. A. *J. Am. Chem. Soc.* **1936**, *58*, 786–787.
8. Anelli, P. L.; Brocchetta, M.; Palano, D.; Visigalli, M. *Tetrahedron Lett.* **1997**, *38*, 2367–2368.
9. Omote, K.; Aso, Y.; Otsubo, T.; Ogura, F. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1759–1761.
10. Spaggiari, A.; Blaszczak, L. C.; Prati, F. *Org. Lett.* **2004**, *6*, 3885.
11. (a) Charette, A. B.; Chua, P. *Synlett* **1998**, 163–165; (b) You, S.-L.; Razavi, H.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 83–85.
12. Fisher, L. E.; Caroon, J. M.; Stabler, S. R.; Lundberg, S.; Zaidi, S.; Sorensen, C. M.; Sparacino, M. L.; Muchowski, J. M. *Can. J. Chem.* **1994**, *72*, 142–145.

13. (a) Yamada, S. *J. Org. Chem.* **1992**, *57*, 1591; (b) Yamada, S. *J. Org. Chem.* **1996**, *61*, 941; (c) Yamada, S.; Sugaki, T.; Matsuzaki, K. *J. Org. Chem.* **1996**, *61*, 5932–5938; (d) Hutchby, M.; Houlden, C. E.; Haddow, M. F.; Tyler, S. N. G.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2012**, *51*, 548–551.
14. (a) Nanjappan, P.; Czarnik, A. W. *J. Am. Chem. Soc.* **1987**, *109*, 1826–1833; (b) Berreau, L. M.; Makowska-Grzyska, M. M.; Arif, A. M. *Inorg. Chem.* **2000**, *39*, 4390–4391; (c) Kawaguchi, S.; Araki, K. *Inorg. Chim. Acta* **2005**, *358*, 947–956; (d) Szajna-Fuller, E.; Ingle, G. K.; Watkins, R. W.; Arif, A. M.; Berreau, L. M. *Inorg. Chem.* **2007**, *46*, 2353; (e) Bröhmer, M. C.; Bannwarth, W. *Eur. J. Org. Chem.* **2008**, 4412; (f) Bröhmer, M. C.; Mundinger, S.; Bräse, S.; Bannwarth, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 6175; (g) Raycroft, M. A. R.; Maxwell, C. I.; Oldham, R. A. A.; Andrea, A. S.; Neverov, A. A.; Brown, R. S. *Inorg. Chem.* **2012**, *51*, 10325–10333.
15. Kita, Y.; Nishii, Y.; Onoue, A.; Mashima, K. *Adv. Synth. Catal.* **2013**, *355*, 3391–3395.
16. See the Supplementary material for full optimization details.
17. (a) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15–27; (b) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439–455.
18. For an example of $Sc(OTf)_3$-catalyzed substitution of benzyl alcohols, see: Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S.-I. *Synlett* **1996**, 557–559.
19. For an example of $Sc(OTf)_3$-catalyzed substitution of 1-arylethanols, see: Noji, M.; Ohno, T.; Fuji, K.; Futaba, N.; Tajima, H.; Ishii, K. *J. Org. Chem.* **2003**, *68*, 9340–9347.