Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 5597–5599

Tetrahedron Letters

A convenient scalable one-pot conversion of esters and Weinreb amides to terminal alkynes ☆

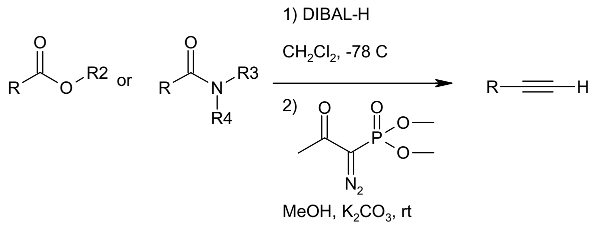
Hamilton D. Dickson, Stephon C. Smith and Kevin W. Hinkle*

Microbial, Musculoskeletal, and Proliferative Diseases Medicinal Chemistry, GlaxoSmithKline, RTP, NC 27709, USA

Received 18 May 2004; revised 24 May 2004; accepted 26 May 2004

Abstract—Esters and amides undergo reduction to the corresponding aldehydes using DIBAL-H followed by same pot conversion to terminal alkynes utilizing the Bestmann–Ohira reagent in good to excellent yields. Additionally chiral nonracemic substrates undergo this transformation with complete preservation of stereochemical integrity.

Recent advances in synthetic chemistry, like the Sonogashira cross-coupling reaction,[1] Grubbs olefin metathesis,[2] and the Ru catalyzed Alder-ene reaction[3] have greatly enhanced the synthetic utility of terminal alkynes. A variety of synthetic procedures have been developed to access terminal alkynes including the Corey–Fuchs,[4] Seyferth–Gilbert,[5] Colvin rearrangement,[6] and alkyne zipper reactions.[7] These procedures generally utilize strictly anhydrous conditions and can require multiple steps, often using strong base, making them of limited use with delicate substrates. The introduction of the Bestmann–Ohira[8] modification of the Seyferth–Gilbert reagent represents a significant advance in this technology, allowing for terminal alkynes to be synthesized directly from aldehydes at room temperature under mild conditions with a readily prepared reagent. Herein we report a convenient one-pot synthesis of terminal alkynes from esters and Weinreb amides that takes advantage of the mild nature of the Bestmann–Ohira reaction. In situ reduction of the starting esters and amides is accomplished by treatment with DIBAL-H at low temperature followed by a methanol quench. The resulting solution of aldehyde is further diluted with methanol and treated with K_2CO_3 and the Bestmann–Ohira reagent affording smooth conversion to the homologated alkynes (Eq. 1).



(1)

The reaction works with a variety of alkyl esters, entries a–c (Table 1). The scope of the reaction extends to cover a broad range of functional groups, such as nonconjugated double bonds (entry b), ethers and carbamates (entries d and e). Entry f is noteworthy as the reductive alkynylation takes place in the presence of an unprotected alcohol. The procedure requires an extra equivalent of DIBAL-H, presumably to first form an aluminum alkoxide of the free hydroxyl before reducing the ester. Additionally, entry f has been carried out on 1, 10, and 27 g of starting ester affording 74%, 75%, and 72% yield of the desired alkyne, respectively.[9] Importantly, the conversion of this substrate and other chiral substrates leads to terminal alkynes with complete preservation of stereochemical integrity. This transformation also works with Weinreb amides to afford the terminal alkynes in yields equivalent to the ester substrates (entries g–j).

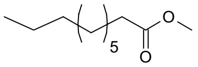
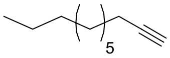
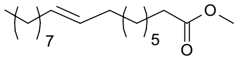
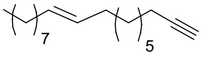
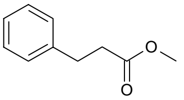
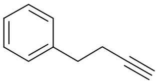
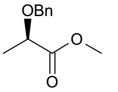
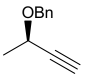
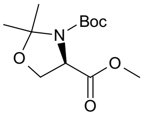
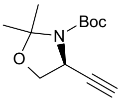
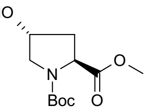
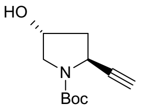
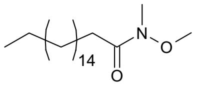
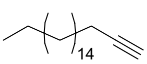
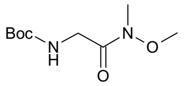
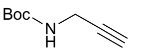
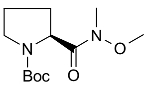
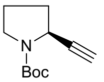
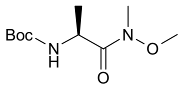
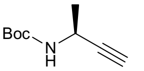
Keywords: Bestmann–Ohira; Seyferth–Gilbert; Alkynes; Weinreb amides.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.05.139

* Corresponding author. Tel.: +1-9194831453; fax: +1-9194836053; e-mail: kevin.w.hinkle@gsk.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.139

Table 1

Entry	Substrate	Product	% Yield[a,b]
a			88
b			76
c			84
d			72
e			71
f			75
g			85
h			78
i			83
j			77

[a] Satisfactory ^{1}H NMR, HRMS, and optical rotations were obtained.[10–14]

[b] Reaction yields have not been optimized.

Typical procedure: Ester a (1.0 g, 5.37 mmol) was dissolved in 10 mL anhydrous dichloromethane, and the solution cooled to −78 °C. DIBAL-H (6.44 mL, 6.44 mmol, 1 M solution in heptane) was added over 10 min, and the mixture stirred at −78 °C. The reaction was monitored by TLC and judged to be complete after the starting ester was consumed. The excess DIBAL-H was quenched with 5 mL anhydrous methanol, and the reaction mixture allowed to warm to 0 °C. Potassium carbonate (1.48 g, 10.7 mmol), the Bestmann–Ohira reagent (1.25 g, 6.44 mmol), and 5 mL anhydrous methanol were added and the reaction stirred overnight at rt. Rochelle's salt (20 mL) and diethyl ether (40 mL) was added and the mixture stirred vigorously for 1 h. The organic layer was separated, washed with brine, dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude mixture was purified via silica gel chromatography with 5% ethyl acetate/hexane, eluting the terminal alkyne as a colorless oil (720 mg, 88% yield).

In summary, we have developed a convenient scalable two step one-pot conversion of esters and Weinreb amides to the corresponding homologated alkynes that tolerates a wide range of functionality and is accomplished under mild conditions.

References and notes

1. Elangovan, A.; Wang, Y.; Ho, T. *Org. Lett.* **2003**, *5*, 1841–1844.
2. Kim, S.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073–1081.
3. Trost, B. M.; Indolese, A. F.; Mueller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615–623.
4. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769–3772.
5. Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. *J. Org. Chem.* **1996**, *61*, 2540–2541.
6. Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, *2*, 107–108.
7. Macaulay, S. R. *J. Org. Chem.* **1980**, *45*, 734–735.
8. Mueller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *6*, 521–522.

9. Typical large scale experimental procedure: ester f (27.0 g, 110 mmol) was dissolved in dichloromethane (100 mL), anhydrous toluene (300 mL) was added, and the solution cooled to −78 °C. DIBAL-H (242 mL, 242 mmol, 1 M solution in toluene) was added via syringe over 45 min, and the mixture stirred for 4 h at −78 °C. The reaction was monitored by TLC and judged to be complete after the starting ester was consumed. The mixture was quenched with anhydrous methanol (100 mL) at −78 °C and allowed to warm to 0 °C. The solvent volume was then reduced by approximately 50% under reduced pressure at 0 °C. More MeOH (300 mL) was added followed by potassium carbonate (61.0 g, 220 mmol) and dropwise addition of the Bestmann–Ohira reagent (27.7 g, 143 mmol). The reaction was stirred to completion overnight at room temperature. Most of the solvent was removed, then ethyl acetate (800 mL) and Rochelle's salt (800 mL) was added. The mixture was stirred for 2 h and the organic layer was separated from the aqueous, washed with brine, dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude was purified with 50% ethyl acetate/hexane eluting the alkyne as a white solid (16.9 g, 72% yield).
10. Optical rotation for d $[\alpha]_D^{20}$ +106.1 (*c* 0.015, $CHCl_3$), compared to $[\alpha]_D^{20}$ +110.5 (*c* 0.96, $CHCl_3$) Ortiz, J.; Ariza, X.; Garcia, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1127–1131.
11. Optical rotation for e $[\alpha]_D^{20}$ +93 (*c* 0.018, $CHCl_3$), compared to $[\alpha]_D^{20}$ +90 (*c* 0.007, $CHCl_3$)[13] Dondoni, A.; Mariotti, G.; Marra, A.; Massi, A. *Synthesis* **2001**, *14*, 2129–2137.
12. No diastereomers/epimerization observed for f $[\alpha]_D^{20}$ −121 (*c* 1.7, CH_2Cl_2).
13. Optical rotation for i $[\alpha]_D^{20}$ −99 (*c* 0.015, MeOH), compared to $[\alpha]_D^{20}$ −99 (*c* 0.010, MeOH) Cossy, J.; Cases, M.; Pardo, D. G. *Bull. Soc. Chim. Fr.* **1997**, *134*, 141–144.
14. Optical rotation for j $[\alpha]_D^{20}$ −59.4 (*c* 0.014, $CHCl_3$), compared to $[\alpha]_D^{20}$ −61.5 (*c* 0.010, $CHCl_3$) Reginato, G.; Mordini, A.; Messina, F.; Degl'Innocenti, A.; Poli Giovanni *Tetrahedron* **1996**, *5*, 10985–10996.