Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9087–9090
Tetrahedron Letters

The samarium(II)-mediated intermolecular couplings of ketones and β-alkoxyacrylates: a short asymmetric synthesis of an antifungal γ-butyrolactone

Nessan J. Kerrigan, Tejas Upadhyay and David J. Procter*

Department of Chemistry, The Joseph Black Building, University of Glasgow, Scotland G12 8QQ, UK

Received 8 September 2004; revised 5 October 2004; accepted 5 October 2004

Abstract—The samarium(II) iodide-mediated coupling of ketones with β-alkoxyacrylates gives β-hydroxy-γ-butyrolactones in moderate yield. The process has been applied to the asymmetric synthesis of an antifungal, γ-butyrolactone natural product.

Samarium(II) iodide (SmI_2) continues to be used widely throughout organic synthesis.[1] This mild, single-electron reductant has been used to mediate a broad range of radical and anionic transformations ranging from functional group interconversions to complex carbon–carbon bond-forming sequences.[1] The reductive coupling of carbonyl compounds with olefins represents one of the most important classes of SmI_2 carbon–carbon bond forming reaction. In particular, the intermolecular coupling of aldehydes or ketones with α,β-unsaturated esters provides convenient access to substituted γ-butyrolactones (Fig. 1a).[2] In 1997, Fukuzawa reported an asymmetric approach to γ-butyrolactones in which aldehydes and ketones were coupled with ephedrinyl acrylates and crotonates.[3] The ephedrine auxiliary was found to be effective in controlling the asymmetry of the reaction producing γ-butyrolactones in moderate to high enantiomeric excess (Fig. 1b).[4–7]

We have recently adapted Fukuzawa's methodology in the development of a solid phase asymmetric catch–release approach to γ-butyrolactones using acrylates and crotonates linked to resin through an ephedrine chiral linker.[8] Our interest in this transformation has led us to investigate the use of β-oxygenated acrylates in the coupling, thus allowing access to more diverse γ-butyrolactone products. Although SmI_2-mediated intramolecular carbonyl–olefin couplings with β-alkoxyacrylates have been reported,[9] to the best of our knowledge, no intermolecular examples have been described.[10]

We began our studies by preparing four β-oxygenated acrylates for use in our studies. 3-Benzoyloxy methyl acrylate **1**, 3-benzyloxy methyl acrylate **2a**, 3-allyloxy methyl acrylate **2b**, and 3-(4-methoxybenzyloxy)methyl acrylate **2c** were prepared by the addition of benzoic acid, benzyl, allyl or 4-methoxybenzyl alcohol, respectively, to methylpropiolate (Scheme 1).

We next investigated the reaction of these substrates with carbonyl compounds in the presence of SmI_2. Interestingly, treatment of a mixture of **1** and 2-hexanone with SmI_2 and *t*-BuOH as a proton source, gave tertiary alcohol **5** in moderate yield with none of the desired γ-butyrolactone being formed (Scheme 2).

A possible mechanism for the formation of **5** is shown in Scheme 2. In an attempt to better intercept the samarium(III) enolate **4**, the use of more acidic proton sources (CF_3CH_2OH and $(CF_3)_2CHOH$)[11] was investigated but this failed to lead to the formation of any γ-butyrolactone product.

We turned our attention to 3-benzyloxy methyl acrylate **2a**, which although less electronically activated would be less prone to elimination. We were pleased to find that treatment of **2a** with 2-hexanone and SmI_2, with *t*-BuOH as a proton source, gave lactone **7** in moderate yield and as a 6:1 mixture of diastereoisomers, the

Keywords: Samarium(II) iodide; Intermolecular couplings; Antifungal; Natural product.
* Corresponding author at present address: The School of Chemistry, Oxford Road, The University of Manchester, Manchester M13 9PL, UK. Tel.: +44 161 275 1425; fax: +44 161 275 4939; e-mail: david.j.procter@man.ac.uk

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.027

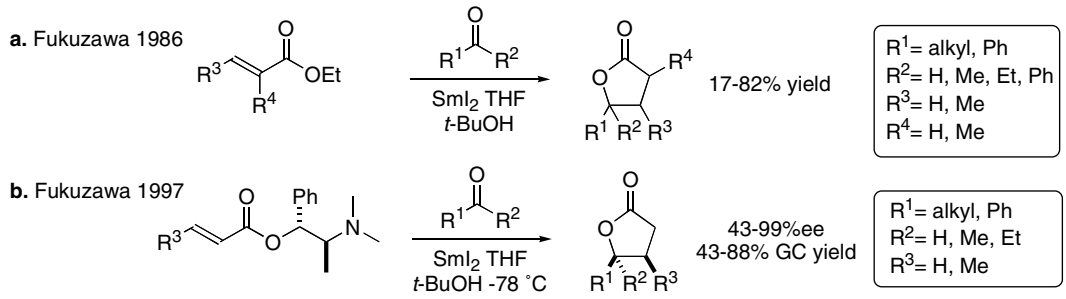
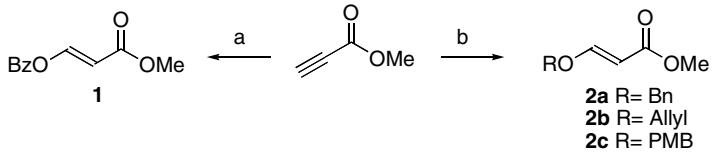
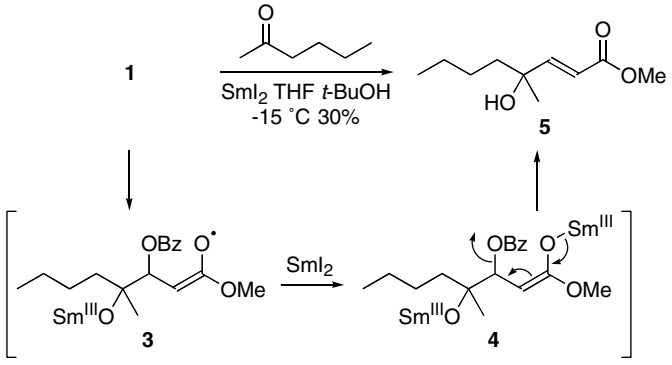


Figure 1. SmI_2-mediated reductive couplings to give γ-butyrolactones.



Scheme 1. Reagents and conditions: (a) $PhCO_2H$ (1 equiv), *N*-methylmorpholine (1 equiv), CH_2Cl_2, rt, 88%; (b) benzyl, allyl or *p*-methoxybenzyl alcohol (1 equiv), PBu_3 (0.15 equiv), CH_2Cl_2, 97% (**2a**), 95% (**2b**), and 98% (**2c**), respectively.



Scheme 2.

cis-isomer being the major product[12] (Table 1, entry 1). To assess the generality of the reaction, we carried out the ketone–olefin reductive coupling with a range of ketones and the acceptors **2a–c** (Table 1).[13]

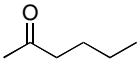
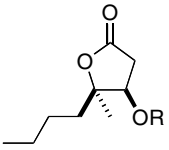
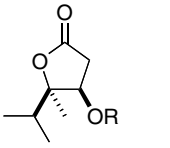
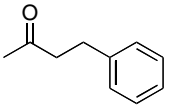
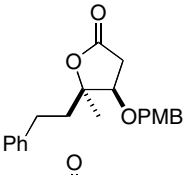
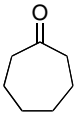
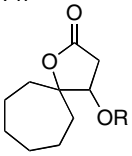
2-Hexanone was also found to undergo reductive coupling with the allyl-protected acceptor **2b**, to give **8** as a 4:1 mixture of diastereoisomers (entry 2). The more bulky 3-methylbutan-2-one underwent reductive coupling with **2a** and **2c** to give **9** and **10**, respectively, with complete selectivity for the *cis*-diastereoisomers (entries 3 and 4),[12] while benzylacetone underwent coupling with **2c** to give **11** as a mixture of diastereoisomers (entry 5). Finally, cycloheptanone reacted with acceptors **2a** and **2c** to give spirocyclic lactones **12** and **13**, respectively (entries 6 and 7). Although products were obtained in moderate isolated yields (40–52%), the coupling protocol represents a reliable, one-step, stereoselective protocol for the assembly of functionalised γ-butyrolactones. (By-products resulting from ketone reduction and pinacol coupling were sometimes observed in addition to some recovered starting materials. These could be separated from the desired products by chromatography.)

In order to illustrate the utility of this new coupling, we have carried out a short asymmetric synthesis of the antifungal furanone **14** isolated from *Mutisia friesiana*.[14] Our synthesis began with the preparation of ketone **16** by Swern oxidation of 1,4-pentanediol to give ketoaldehyde **15**, followed by Wittig reaction (Scheme 3).

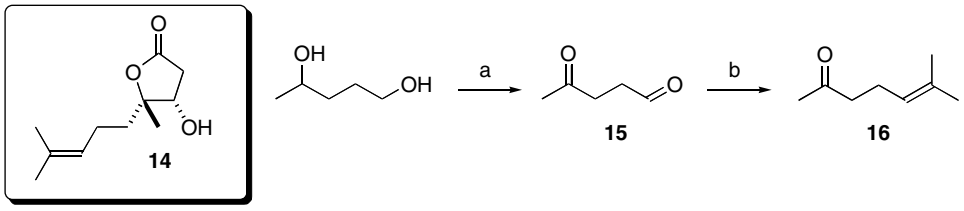
In order to carry out an asymmetric, Fukuzawa reductive coupling, 3-benzyloxy ephedrinyl acrylate **18** and 3-(4-methoxybenzyloxy) ephedrinyl acrylate **21** were prepared for reaction with ketone **16**. Hydrolysis of **2a** and **2c**, acid chloride formation and coupling with (1*R*,2*S*)-*N*-methyl ephedrine gave **18** and **21**, respectively. Satisfying, treatment of ketone **16** and benzyloxy substrate **18** gave the desired product **19** in moderate yield and as a 6:1 mixture of diastereoisomers[12] that were readily separated by chromatography (silica gel, 20% EtOAc/hexane as eluant). Attempts to remove the benzyl protecting group from **19** were unsuccessful.

Fortunately, coupling of PMB substrate **21** with ketone **16** also proceeded satisfactorily to give **22** as a separable

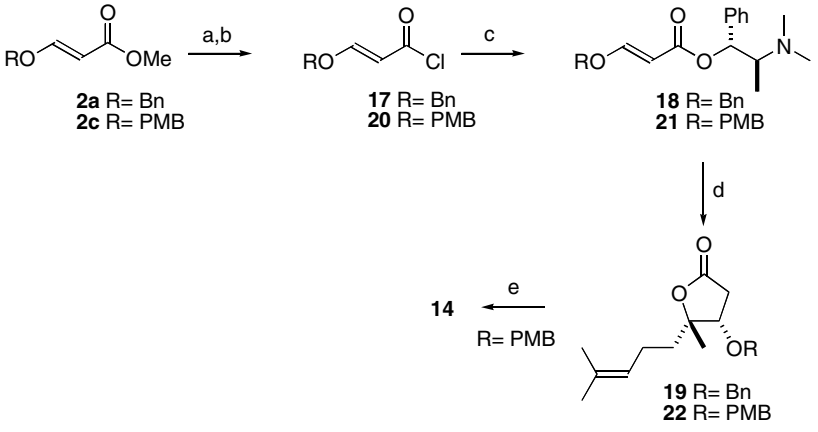
Table 1. SmI_2-mediated reductive couplings of ketones and β-alkoxy acrylates

Entry	Ketone substrate	Acceptor	Product (*racemic*)		*cis*/*trans* ratio[a]	Yield (%)
1		**2a**		**7** R=Bn	6:1	52
2		**2b**		**8** R=Allyl	4:1	42
3		**2a**		**9** R=Bn	1:0	52
4		**2c**		**10** R=PMB	1:0	42
5		**2c**		**11**	5:1	42
6		**2a**		**12** R=Bn		41
7		**2c**		**13** R=PMB		40

[a] Diastereoisomeric ratios determined from the crude ^1H NMR. The stereochemistry of the major product was confirmed by NOE studies for selected examples and inferred for the remainder (Ref. 12).



Scheme 3. Reagents and conditions: (a) DMSO, oxalyl chloride, NEt_3, CH_2Cl_2, −78 °C, 66%; (b) $(CH_3)_2CHPPh_3I$, *n*-BuLi, THF, −78 °C to rt, 40%.



Scheme 4. Reagents and conditions: (a) NaOH, dioxane, recrystallisation 43% R = Bn, 62% R = PMB; (b) $SOCl_2$, R = Bn = PMB, 100%; (c) (1*R*, 2*S*)-*N*-methylephedrine, NEt_3, CH_2Cl_2, rt, R = Bn 88%, R = PMB 89%; (d) SmI_2, *t*-BuOH, THF, rt, R = Bn 39%, R = PMB 37%; (e) DDQ, CH_2Cl_2, H_2O, 68%.

5:1 mixture of diastereoisomers. Removal of the PMB protection[15] then completed the synthesis and provided **14** in 97% ee (Scheme 4).[16]

In conclusion, we have described the reductive, intermolecular coupling of carbonyl compounds with β-alkoxyacrylates mediated by SmI_2. We have applied our

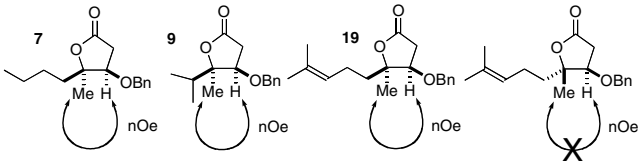
methodology in an asymmetric synthesis of the antifungal furanone **14**.

Acknowledgements

We thank the Engineering and Physical Research Council (EPSRC) (GR/R72242/01, N.J.K.), AstraZeneca for the award of a Strategic Research Grant (D.J.P.) and Pfizer for unrestricted funding (D.J.P.).

References and notes

1. For reviews on the use of samarium(II) iodide in organic synthesis: (a) Soderquist, J. A. *Aldrichim. Acta* **1991**, *24*, 15–23; (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68; (c) Molander, G. A. *Org. React.* **1994**, *46*, 211–367; (d) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338; (e) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321–3354; (f) Kagan, H.; Namy, J. L. In *Lanthanides Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer, 1999; pp 155–198; (g) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745–777; (h) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727–2751; (i) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351–10372; (j) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371–3403.
2. (a) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *Chem. Commun.* **1986**, 624–625; (b) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763–5764; (c) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669–1675.
3. Fukuzawa, S.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482–1483.
4. For diastereoselective couplings: (a) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900–6901; (b) Matsuda, F.; Kawatsura, M.; Dekura, F.; Shirahama, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2371–2375; (c) Matsuda, F.; Kawatsura, M.; Hosaka, K.; Shirahama, H. *Chem. Eur. J.* **1999**, *5*, 3252–3259; (d) Fukuzawa, S.; Miura, M.; Saitoh, T. *J. Org. Chem.* **2003**, *68*, 2042–2044; (e) Taniguchi, N.; Uemura, M. *Tetrahedron Lett.* **1997**, *38*, 7199–7202; (f) Merlic, C. A.; Walsh, J. C. *Tetrahedron Lett.* **1998**, *39*, 2083–2086; (g) Merlic, C. A.; Walsh, J. C. *J. Org. Chem.* **2001**, *66*, 2265–2274.
5. For other auxiliary-controlled couplings: (a) Xu, M.-H.; Wang, W.; Lin, G. *Org. Lett.* **2000**, *2*, 2229–2232; (b) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G. *J. Org. Chem.* **2001**, *66*, 3953–3962; (c) Wang, W.; Zhong, Y.; Lin, G. *Tetrahedron Lett.* **2003**, *44*, 4613–4616.
6. For a chiral ligand controlled coupling: Mikami, K.; Yamaoka, M. *Tetrahedron Lett.* **1998**, *39*, 4501–4504.
7. For sequential processes involving couplings: Molander, G. A.; Sono, M. *Tetrahedron* **1998**, *54*, 9289–9302.
8. (a) Kerrigan, N. J.; Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Chem. Commun.* **2003**, *23*, 1402–1403; (b) Kerrigan, N. J.; Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Org. Biomol. Chem.* **2004**, *2*, 2476–2482.
9. Matsuo, G.; Kadohama, H.; Nakata, T. *Chem. Lett.* **2002**, 148–149, and references cited therein.
10. Sibi has recently reported the enantioselective intermolecular addition of alkyl radicals to β-acyloxyenoates mediated by chiral Lewis acids: Sibi, M. P.; Zimmerman, J.; Rheault, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4521–4523.
11. Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, *68*, 3190–3198.
12. The *cis*-relative stereochemistry of lactones **7**,**9**,and **19** was determined by NOE studies (no corresponding NOE was observed for the minor diastereoisomer of **19**):



13. All new compounds were characterised by ^{1}H and ^{13}C NMR, IR and HRMS. *Typical procedure:* To a solution of SmI_2 (11.2 mL, 0.1 M in THF, 1.12 mmol, 5.5 equiv) at 0 °C was added a solution of 2-hexanone (77.0 μL, 0.61 mmol, 3 equiv), 3-benzyloxy methyl acrylate (39.2 mg, 0.21 mmol, 1 equiv) and *t*-BuOH (38.4 μL, 0.41 mmol, 2 equiv) in THF (1 mL). After 24 h, aqueous saturated NaCl was added and the aqueous layer extracted with ethyl acetate (3 × 5 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (silica gel, 30% ethyl acetate/petroleum ether (40–60)) gave *trans*-**7** (4 mg, 0.02 mmol, 8%) as a colourless oil. Further elution then gave *cis*-**7** (24 mg, 0.09 mmol, 44%) as a colourless oil. For *cis*-**7**: ν_{max} (thin film) 2863s, 1772s (C=O), 1458 m, 1090 m: δ_H (400 MHz, $CDCl_3$) 7.39–7.30 (5H m, ArH), 4.59 (1H, d, AB system, *J* 11.8 Hz, 1H from PhCH_2O), 4.45 (1H, d, AB system, *J* 11.8 Hz, 1H from PhCH_2O), 3.92 (1H, dd, *J* 6.4, 4.0 Hz, C*H*OBn), 2.81 (1H, dd, *J* 17.8, 6.4 Hz, 1H from CH_2CHOBn), 2.65 (1H, dd, *J* 17.8, 4.0 Hz, 1H from CH_2CHOBn), 1.84–1.79 (2H, m, CH_2), 1.42–1.33 (4H, m, $CH_2 \times 2$), 1.33 (3H, s, CH_3) and 1.03 (3H, t, *J* 8.2 Hz, CH_3CH$_2$): δ_C (100 MHz, $CDCl_3$) 175.1 (C=O), 138.0 (ArC), 129.3 (ArCH × 2), 128.8 (ArCH), 128.4 (ArCH × 2), 89.9 (C(O)), 81.1 (CHO), 72.6 (ArCH_2O), 36.1 (CH_2C(O)), 34.9 (CH_2), 26.5 (CH_2), 24.9 (CH_3), 24.0 (CH_2) and 14.8 (CH_2CH_3): *m/z* (CI mode, isobutane) 263.2 ((M + H)$^+$, 25%), 155 (100), 91 (10), 71 (12) (Found (M + H)$^+$ 263.1647. $C_{16}H_{23}O_3$ requires 263.1647).
14. Viturro, C. I.; Maier, M. S.; Stortz, C. A.; de la Fuente, J. R. *Tetrahedron: Asymmetry* **2001**, *12*, 991–998.
15. Kozikowski, A. P.; Wu, J.-P. *Tetrahedron Lett.* **1987**, *28*, 5125–5128.
16. The enantiomeric excess of **14** was determined by chiral GC (Supelco β-Dex 120 column) and by comparison with a racemic sample (prepared by the coupling of **16** with **2c**). The absolute stereochemistry of synthetic **14** was assigned based on the optical rotation and comparison with the literature value.[14]
Spectroscopic data was identical to that in the literature.[14] For example: δ_H (400 MHz, $CDCl_3$) 5.17 (1H, app. t, *J* 7.2 Hz), 4.20 (1H, br s, CHOH), 2.96 (1H, dd, *J* 18.0, 6.0 Hz, 1H from CH_2C(O)), 2.52 (1H, dd, *J* 18.0, 2.4 Hz, 1H from CH_2C(O)), 2.05–2.18 (2H, m, CH_2), 1.97 (1H, d, *J* 4.0 Hz, OH), 1.76–1.90 (2H, m, CH_2), 1.72 (3H, s, CH_3C=), 1.65 (3H, s, CH_3C=) and 1.36 (3H, s, CH_3).