Synthesis of 3,4-Dihydroisocoumarins from α-Lithiated *o*-Toluates

L. Ollero, L. Castedo, D. Domínguez*

Departamento de Química Orgánica, Facultade de Química, Universidade de Santiago y Unidad Asociada al C.S.I.C., 15706 Santiago de Compostela, Spain

Received 19 May 1997

Abstract: Tellurides **2** prepared from α-bromo-*o*-toluesters **1** undergo lithium-tellurium exchange to give benzylic anions that can be condensed with aldehydes or ketones to afford 3,4-dihydroisocoumarins **3**.

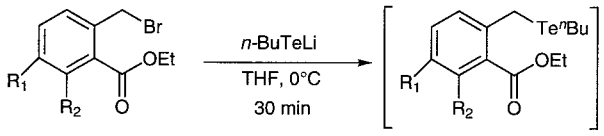
In connection with the synthesis of a natural product, we required a 7,8-methylenedioxy-3,4-dihydroisocoumarin intermediate. The 3,4-dihydroisocoumarins are an important class of naturally occurring, biologically active lactones with uses ranging from sweetening agents to bactericides.[1] They are commonly synthesized by condensation of an appropriately *ortho*-substituted benzylic-type anion with an aldehyde or ketone, followed by intramolecular cyclization; an appropriate substituent being one that promotes formation of the carbanion and is also susceptible to the desired cyclization. Suitable benzylic compounds used previously include α-lithiated *o*-tolualdehydes,[2] *o*-toluic acids,[3] *o*-toluamides[4] and *o*-tolyl oxazolines.[5] A problem common to these approaches is that, even if the deprotonation step is efficient,[6] the condensation product may be degraded or undergo elimination under the conditions required to bring about annulation, which range from heating at high temperature (160-170°C)[7] to hydrolysis under strongly alkaline[4a] or acidic[4b] conditions. One way to overcome this problem would be to use a highly electrophilic *ortho*-substituent to guarantee spontaneous cyclization to the lactone; necessarily, this substituent would also have to withstand the metallation conditions used to generate the benzylic anion.

Previous attempts at the direct generation of benzylic anions from *o*-toluic esters by reaction with LDA have failed due to self condensation,[8] except in cases where there was an alkoxy substituent *ortho* to the ester.[9] In accordance with these precedents, we treated ethyl 3,4-methylenedioxy *o*-toluate (**1b**, Br = H) with LDA in THF at low temperature; however, only decomposition products were detected after quenching the reaction with MeOD.[10]

Our search for a milder method for generation of the required α-lithiated benzylic anions led us to the method recently introduced by Kambe and Sonoda,[11a] which is based on lithium-tellurium exchange of tellurides. The required tellurides, which are conveniently generated *in situ* from the corresponding benzylic halide and lithium *n*-butanetellurolate, can undergo the Li-Te exchange reaction at very low temperatures, thus avoiding self-condensation of reactive intermediates. Note that, although α-lithiated unsubstituted *o*-toluonitriles generated in this way can be trapped with carbonyl compounds to give, after hydrolysis of the nitrile, 3,4-dihydroisocoumarins,[11b] this approach was not suitable for preparation of the desired substituted 3,4-dihydroisocoumarin intermediate.[12]

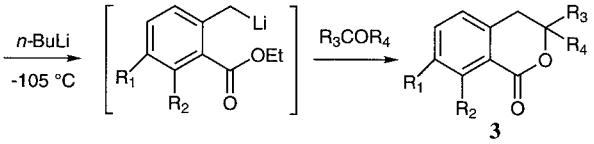
In this paper we report that lactones **3** can be readily prepared in a one-pot reaction starting from α-bromo *o*-toluates **1**. Our approach uses the lithium-tellurium exchange method for preparation of the α-lithiated toluates; this method was compatible with the presence of an *o*-ester functionality and, unlike the direct deprotonation of *o*-toluates, successful α-lithiation was not dependent on the presence of an alkoxy substituent on the benzene ring.

The unsubstituted α-bromo-*o*-toluate **1a**[13] was transformed into telluride **2a** by treatment with lithium *n*-butanetellurolate at 0°C for 30



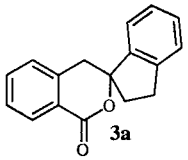
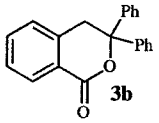
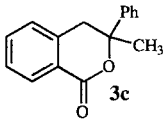
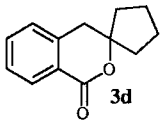
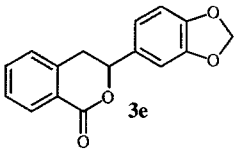
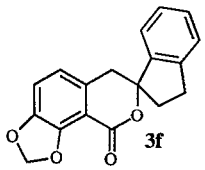
1a, R_1=R_2=H
1b, R_1+R_2=OCH_2O

2a, R_1=R_2=H
2b, R_1+R_2=OCH_2O



3

Table 1. Synthesis of 3,4-dihydroisocoumarins

Entry	Bromide	R_3	R_4	Product	Method[a]	Yield (%)[b]
1	**1a**	-$C_6H_4CH_2CH_2$-		 **3a**	A	66
2					B	85
3	**1a**	Ph	Ph	 **3b**	B	92
4	**1a**	Ph	CH_3	 **3c**	B	90
5	**1a**	-$(CH_2)_4$-		 **3d**	B	79
6	**1a**	Ar	H	 **3e**	A	70
7	**1b**	-$C_6H_4CH_2CH_2$-		 **3f**	B	88

[a] Reaction conditions:
A: (i) **1** (0.42 mmol), *n*-BuTeLi (0.42 mmol), THF (3 ml), 0°C, 30 min.
(ii) *n*-BuLi (0.42 mmol), -105°C, 5 min.
(iii) R_3COR_4 (0.35 mmol), -105°C, 30 min.
B: (i) **1** (0.42 mmol), *n*-BuTeLi (0.42 mmol), THF (3 ml), 0°C, 15 min.
(ii) R_3COR_4 (0.35 mmol), -105°C
(iii) *n*-BuLi (0.42 mmol), -105°C, 15 min.

[b] Yields refer to isolated, chromatographically pure materials.

Downloaded by: University of Queensland. Copyrighted material.

min.[11b] Addition of 1 equivalent of *n*-BuLi to the cooled (-105°C) reaction mixture and stirring for 20 min gave a solution with the red colour characteristic of stabilized benzylic anions. However, addition of 1-indanone and stirring for 15 min. gave product **3a** in only 30% yield, probably due to self-condensation of the α-lithiated toluate. An improved yield of **3a** (66%) could be obtained by earlier addition of the carbonyl compound after the lithium-tellurium exchange step (Method A; entry 1 in Table). Interestingly, this yield could be increased to 85% by adding the 1-indanone before the *n*-BuLi (Method B; entry 2), which is attributable to lithium-tellurium exchange being faster than addition of *n*-BuLi to ketones at -105°C. Following Method B products **3b-d** were obtained in 79-92% yields.

When the reaction was carried out using 3,4-methylenedioxy-benzaldehyde following Method B, addition of *n*-BuLi to the aldehyde was the major reaction. In this case, carrying out the Li-Te exchange reaction before addition of the aldehyde (Method A) gave **3e** in 70% yield (Entry 6).

Similar results were obtained for the 3,4-disubstituted starting compound **1b**,[14] which gave product **3f** in 88% yield when subjected to Method B (Entry 7).

In summary we have developed a direct method for the preparation of 3,4-dihydroisocoumarins by condensation of α-anions of *o*-toluates (obtained by lithium-tellurium exchange) with carbonyl compounds. Particularly excellent yields are obtained with enolizable ketones, mainly due to the very mild conditions needed for the Li-Te exchange reaction.

Typical experimental procedure. [15]

Method A: To a suspension of metallic tellurium (0.42 mmol) in THF (3 mL) at 20 °C was added dropwise *n*-butyllithium (1.6M; 0.26 mL, 0.42 mmol). After stirring for 20 min, the dark purple solution was cooled to 0 °C and a solution of α-bromo-*o*-toluate **1** (0.42 mmol) in THF (2 mL) was added. The mixture was stirred for 30 min, and then the orange solution formed was cooled to -105 °C and *n*-butylithium (1.6M; 0.26 mL, 0.42 mmol) was added dropwise. This dark red solution was stirred for 5 min, whereupon the carbonyl compound (0.42 mmol) in THF (3 mL) was added. After stirring for 15 min, the mixture was allowed to warm to rt and water was added. Extractive work-up with Et_2O afforded a yellow oil, which was chromatographed on silica gel, with ethyl acetate/hexane as eluant, to give the desired dihydroisocoumarin **3a** or **3e**.

Method B: To a suspension of metallic tellurium (0.42 mmol) in THF (3 mL) at 20 °C was added dropwise *n*-butyllithium (1.6M; 0.26 mL, 0.42 mmol). After stirring for 20 min, the dark purple solution was cooled to 0 °C and a solution of α-bromo-*o*-toluate **1** (0.42 mmol) in THF (2 mL) was added. The mixture was stirred for 30 min, the orange solution formed was cooled to -105 °C, and then the ketone (0.42 mmol) in THF (3 mL) was added, followed by *n*-butyllithium (1.6M; 0.26 mL, 0.42 mmol), dropwise at the same temperature. After stirring for 15 min, the mixture was allowed to warm to rt and water was added. Extractive work-up as in Method A afforded dihydroisocoumarins **3a-d** or **3f**.

Dihydroisocoumarin **3a**: Colourless crystals. Mp 133-134°C. IR (film): ν= 1718 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$, 250MHz): δ= 2.24 (ddd, *J*=13.7, 8.2, 6.1 Hz, C*H*H), 2.45 (ddd, *J*=13.7, 8.1, 5.0 Hz, CH*H*), 2.89 (ddd, *J*=13.5, 8.2, 5.0 Hz, C*H*H), 3.16 (ddd, *J*=13.5, 8.1, 6.1 Hz, CH*H*), 3.20 (d, *J*=16.2, C*H*H), 3.54 (d, *J*=16.2, CH*H*), 7.13-7.35 (m, 5H), 7.44 (t, *J*=7.5, 1H), 7.59 (t, *J*=7.5, 1H), 8.15 (d, *J*=7.5, 1H). ^{13}C-NMR ($CDCl_3$, 62.5 MHz): δ=29.2 (CH_2), 37.3 (CH_2), 38.5 (CH_2), 91.4 (*C*), 123.4 (*C*H), 125.2 (*C*H), 125.5 (*C*), 126.8 (*C*H), 127.8 (*C*H), 127.9 (*C*H), 129.5 (*C*H), 130.1 (*C*H), 133.8 (*C*H), 138.2 (*C*), 142.7 (*C*), 143.8 (*C*), 165.1 (*C*O).

Acknowledgements

We thank the Dirección General de Enseñanza Superior (Project PB95-0824) and the Xunta de Galicia (Project XUGA20907-B96) for financial support. Lourdes Ollero thanks the Xunta de Galicia for a predoctoral fellowship.

References and Notes:

(1) (a) Thomson, R. H. in *The Chemistry of Natural Products*; Chapman and Hall: New York, **1985**, p 113. (b) Hill, R. A.; Krebs, H. C.; Verpoorte, R.; Wijnsma, R. *Prog. Chem. Org. Nat. Prod.* **1986**, *49*, 1.

(2) Fitzgerald, J. F.; Pagano, A. R.; Sakoda, V. M.; Olofson, R. A. *J. Org. Chem.* **1994**, *59*, 4117.

(3) (a) Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396. (b) Hildebran, K. C.; Cordray, T. L.; Chan, K. W.; Beam, C. F. *Synth. Commun.* **1994**, *24*, 779.

(4) (a) Watanabe, M.; Sahara, M.; Kubo, M.; Furukawa, S.; Billedeau, R. J.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 742. (b) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1986**, *51*, 3566. (c) McNicholas, C.; Simpson, T. J.; Willett, N. J. *Tetrahedron Lett.* **1996**, *37*, 8053.

(5) Fu, P. P.; Unruh, L. E.; Miller, D. W.; Huang, L. W.; Yang, D. T. C. *J. Org. Chem.* **1985**, *50*, 1259.

(6) For a recent general review of the chemistry of benzylic anions see: Clark, R. D.; Jahangir, A. *Organic Reactions* **1995**, *47*, 1.

(7) Vaulx, R. L.; Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3514.

(8) (a) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. (b) Hauser, F. M.; Rhee, R. P.; Prasanna, S.; Weinreb, S. M.; Dodd, J. H. *Synthesis* **1980**, 72.

(9) (a) Kraus, G. A. *J. Org. Chem.* **1981**, *46*, 201. (b) Carpenter, T. A.; Evans, G. E.; Leeper, F. J.; Staunton, J.; Wilkinson, M. R. *J. Chem. Soc. Perkin Trans. I* **1984**, 1043. (c) Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shiori, T. *Tetrahedron* **1991**, *47*, 8635. (d) Dillon, M. P.; Simpson, T. J.; Sweeney, J. B. *Tetrahedron Lett.* **1992**, *33*, 7569.

(10) Paleo, M.R., Doctoral thesis, University of Santiago de Compostela, **1992**. Similar results have been obtained in attempts at generating the dianion of 3,4-methylenedioxy-*o*-toluic acid (see ref. 14), and the benzylic anion of methyl 3,4,5-trimethoxy-*o*-toluate (ref. 9d).

(11) (a) Kanda,T.; Kato, S.; Sugino, T.; Kambe, N.; Sonoda, N. *J. Organomet. Chem* **1994**, *473*, 71. (b) Kanda,T.; Kato, S.; Sugino, T.; Kambe, N.; Ogawa, A.; Sonoda, N. *Synthesis* **1995**, 1102.

(12) The 3,4-methylenedioxy-α-lithio-*o*-toluonitrile gave the hydroxy nitrile in good yield, but failed to undergo lactonization under both acidic and basic conditions. Instead, the elimination product was obtained exclusively.

(13) **1a** was obtained by bromination of commercial ethyl *o*-toluate with NBS in CCl_4.

(14) **1b** was obtained by bromination (NBS in CCl_4) of ethyl 3,4-methylenedioxy *o*-toluate, which was prepared as per: Cushman, M.; Choong, T.-C.; Valko, J.T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067.

(15) All new compounds were fully characterized by ^{1}H and ^{13}C-NMR and IR and HRMS.

Downloaded by: University of Queensland. Copyrighted material.