ELSEVIER

Journal of Organometallic Chemistry 624 (2001) 380–382

Journal of Organometallic Chemistry

www.elsevier.nl/locate/jorganchem

Communication

1,4-Bis(arylsulfonyl)dihydropyridines in synthesis. Enantioselective synthesis of 2,3,6-trisubstituted piperidines

Santiago Carballares, Donald Craig *

Centre for Chemical Synthesis, Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW 7 2AY, UK

Received 18 October 2000; accepted 28 November 2000

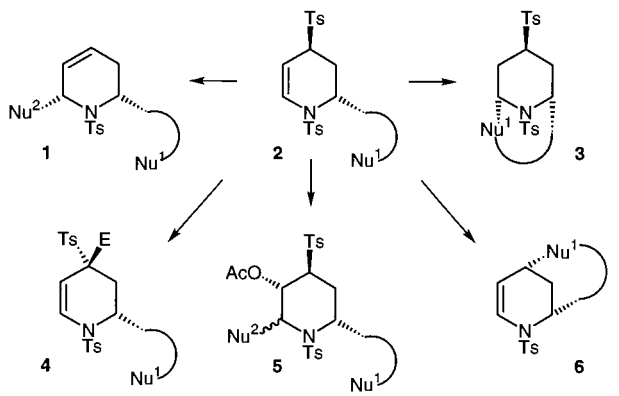
Dedicated with respect and admiration to Professor J.-F. Normant on the occasion of his 65th birthday

Abstract

A 2-substituted 1,4-bis(4-tolylsulfonyl)-1,2-dihydropyridine is readily accessed from an α-aminoester and 1,1-dimethoxy-3-(4-tolylsulfonyl)propane. This cyclic diene enters into highly selective addition reactions with carbon nucleophiles, and the product of one of these transformations is converted into a 2,3,6-trisubstituted piperidine via an S_N1' reaction. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: 2,3,6-Trisubstituted piperidines; Enantioselective synthesis; Organolithium

We have been investigating the preparation and use in nitrogen heterocycle synthesis of 1,4-bis(4-tolylsulfonyl)-1,2,3,4-tetrahydropyridines (**2**). These substances are readily assembled from 1,1-dimethoxy-3-(4-tolylsulfonyl)propane and N-(4-tolylsulfonyl)aziridines using a two-step sequence. Heterocycles **2** enter into a variety of carbon-carbon bond-forming reactions, including S_N1 [1], S_N1' (giving **1**) [2], alkylation (giving **4**) [2] and cyclisation reactions [3]. By varying the acidic reagents the latter processes could be tuned to give the products of 1,2- (as in **3**) or 1,4- attack (as in **6**) on the presumed iminium intermediates. We have also investigated oxidation reactions of **2**, and showed [4] that dihydroxylation of the enamide double bond took place with complete selectivity for the α,α-stereoisomer. The ester derivatives of these products underwent S_N1 reactions giving **5**, whose stereoselectivities varied according to the nature of the substituent at C-2 (Scheme 1).



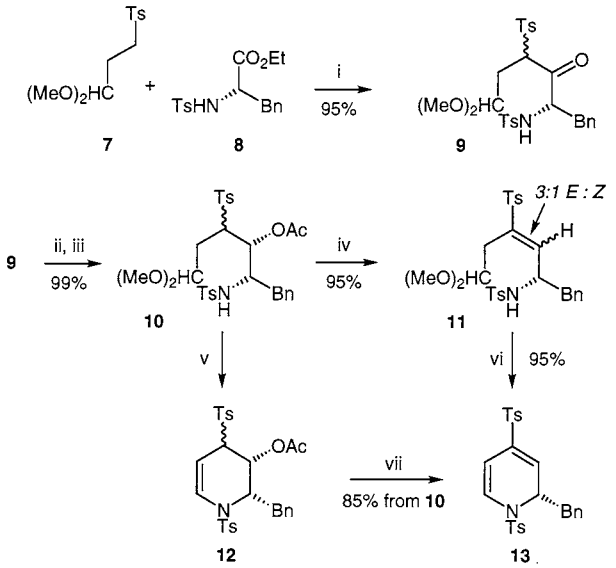
Scheme 1.

We rationalised the stereochemical outcomes of the reactions depicted in Scheme 1 in terms of either axial attack of the nucleophile on the positively-charged nitrogen template, or less hindered facial approach *anti*- with respect to the *N*-tosyl group, which might adopt conformations in which 1,2-interactions with the C-2 substituent are minimised. Subsequently we have become interested in exploiting similarly well-defined conformations anticipated for related, more highly unsaturated systems with a view to gaining access to more highly substituted piperidines by addition of

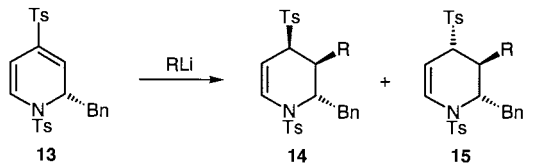
* Corresponding author: Tel.: +44-20-75945771; fax: +44-20-75945868.

E-mail address: d.craig@ic.ac.uk (D. Craig).

PII: S0022-328X(00)00918-9



Scheme 2. Reagents and conditions: (i) Add *n*-BuLi to **7**, THF, −78°C, then add **8** (0.3 equivalents), −78°C→−30°C, 1.5 h. (ii) DIBAL-H, CH_2Cl_2, −78°C, 2 h. (iii) Ac_2O, py, r.t., 15 h. (iv) *t*-BuOK (2 equivalents), *t*-BuOH, r.t., 10 min. (v) $BF_3{\cdot}OEt_2$ (15 equivalents), CH_2Cl_2, −78°C→0°C, 3 h. (vi) $BF_3{\cdot}OEt_2$ (15 equivalents) added to *E*-**11**, CH_2Cl_2, −78°C→0°C, 3 h. (vii) DBU (0.1 equivalents), PhMe, r.t., 70 min.



Scheme 3.

organometallic reagents to the electrophilic vinylic sulfone. This letter reports the results of these investigations.

Substrate **13** was prepared according to the simple sequence shown in Scheme 2. Thus, addition of an excess of lithiated 1,1-dimethoxy-3-(4-tolylsulfonyl)propane **7** [3,5] to *N*-(4-tolylsulfonyl)-L-phenylalanine ethyl ester **8** [6] gave the expected β-ketosulfone **9** as a diastereomeric mixture in good yield based on the aminoacid derivative. Reduction with DIBAL-H followed by acetylation gave a mixture of two diastereomeric β-acetoxysulfones **10** in good yield. The assignment of *R*,*S*- stereochemistry in **10** followed from the anticipated Felkin–Anh sense of reduction in a non-chelated reactive conformation [7]. Base-induced elimination of the mixture at this stage using *t*-BuOK–*t*-BuOH gave a 3:1 mixture of *E*- and *Z*- vinylic sulfones **11**; the major *E*-isomer underwent cyclisation on treatment with $BF_3{\cdot}OEt_2$ [8] to provide dihydropyridine **13**. It was subsequently found that higher overall yields of **13** could be obtained if cyclisation was carried out prior to the elimination step, because this obviated the loss of material through formation of *Z*-**11**, which was inert towards cyclisation. Thus, treatment of **10** with $BF_3{\cdot}OEt_2$ and exposure of the two-component mixture of diastereomeric tetrahydropyridines **12** to a *sub-stoichiometric amount* of DBU gave **13** in good overall yield. Material generated using the latter method was found using chiral HPLC analysis to have an enantiomeric excess of 91%; the use of increased quantities of DBU in the final step caused significant lowering of optical purity.

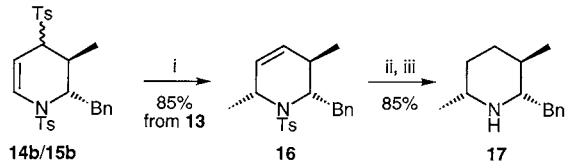
Attention was turned next to addition reactions of dihydropyridine **13**. A variety of reagents was screened, in order to define the scope of the reaction in terms of the degree of basicity and steric demand associated with the nucleophile. The results are depicted in Scheme 3 and are collected in Table 1.

For all of the organometallic reagents investigated, successful addition to dihydropyridine **13** was accompanied by the appearance of the deep red colour associated with the conjugate bases of tetrahydropyridines [2]. In all cases only 2,3-*anti*-tetrahydropyridines were formed, as mixtures of C-4 epimers **14** and **15**. We ascribe this high stereoselectivity to a propensity for nucleophilic attack to take place at the vinylic sulfone β-carbon atom on an axial trajectory, *anti*- with respect to the C-2 benzyl substituent. The major compound **14a** arising from vinyllithium addition was subjected to single-crystal X-ray diffraction analysis [9], which showed clearly the *trans*-diaxial relationship of the C-2 benzyl and C-3 vinyl groups, and the equatorial disposition of the C-4 tolylsulfonyl moiety.

Table 1
Addition of nucleophiles to **13**

Entry	R	Equivalent RLi	Scale (mmol)	T (°C)	Yield (%)	**14**:**15**
a	$H_2C{=}CH$	2	1	−78	95	77:23
b	CH_3	1.2	0.1	−78	95	24:76
c	C_6H_5	4	0.15	−78	95	30:70
d	$CH_3(CH_2)_5CC$	3	0.5	−78→−30	17 [a]	100:0
e	$C_6H_5SO_2CH_2$	2.5	0.4	−78	95	26:74
f	n-C_4H_9	2	0.07	−78	95	17:83
g	$NCCH_2$	2.5	0.24	−78	95	7:93

[a] 63% of unreacted **13** was recovered.



Scheme 4. Reagents and conditions: (i) Me_3Al (2 equivalents), CH_2Cl_2, r.t., 1 h. (ii) $(Ph_3P)_3RhCl$ (18 mol%), H_2 (1 atm), PhMe, r.t., 10 h. (iii) $Na^+C_{10}H_8^-$ (10 equivalents), DME, −60°C, 45 min.

The final part of this investigation was concerned with attempting to effect the previously reported S_N1 reactions on the more highly substituted tetrahydropyridine substrate **14b**/**15b**. We were particularly keen to assess whether the presence of the extra substituent would compromise any part of the sequence used previously for the generation of fully reduced, unprotected piperidines. In the event, treatment of a ca. 3:1 mixture of **14b**/**15b** with trimethylaluminium gave, in 85% overall yield from dihydropyridine **13**, the trisubstituted tetrahydropyridine **16** as a single diastereomer. High-yielding hydrogenation of the double bond was accomplished as before using Wilkinson's catalyst [10]. Finally, desulfonylation occurred efficiently to provide the piperidine **17** (Scheme 4). Crystallisation of its hydrochloride gave material which was subjected to X-ray crystallographic analysis [9]. This clearly demonstrated the *anti*- nature of the addition to the vinylic sulfone moiety in **13** and the *syn*- nature of the trimethylaluminium-mediated S_N1' reaction with respect to the C-2 substituent.

In summary, the results presented herein demonstrate that a 2-substituted 1,4-bis(4-tolylsulfonyl)-1,2-dihydropyridine enters into efficient and highly stereoselective addition reactions with carbon nucleophiles, and that diastereomerically pure trisubstituted piperidines may easily be accessed from the tetrahydropyridines produced. The ready availability of the dihydropyridine substrates is such that the method should prove to be a useful addition to existing methods for the preparation of polysubstituted piperidines [11].

Acknowledgements

We thank the European Commission (Marie Curie Fellowship to S.C.; contract number HPMF-CT-1999-00262) for financial support of this research.

References

[1] J.C. Adelbrecht, D. Craig, S.Thorimbert, unpublished observations.
[2] D. Craig, R. McCague, G.A. Potter, M.R.V. Williams, Synlett (1998) 55.
[3] D. Craig, R. McCague, G.A. Potter, M.R.V. Williams, Synlett (1998) 58.
[4] J.C. Adelbrecht, D. Craig, B.W. Dymock, S. Thorimbert, Synlett (2000) 467.
[5] P. Bonete, C. Najera, Tetrahedron 51 (1995) 2763.
[6] Compound **8** was prepared in 99% yield by *N*-tosylation of commercially available PheOEt·HCl (Aldrich Chemical Co.) using TsCl (1.1 equivalents), Et_3N (2.2 equivalents) and DMAP (0.2 equivalents) at 0°C in CH_2C1_2 (0.5M).
[7] Reduction may be considered to be in the Felkin–Anh sense if the benzyl and tosylamino groups are regarded as medium and large respectively. For related work on the stereoselectivity of reduction of α-aminoketones, see: F. Benedetti, S. Miertus, S. Norbedo, A. Tossi, P. Zlatoidzky, J. Org. Chem. 62 (1997) 9348 and references therein.
[8] After extensive experimentation we have found that $BF_3{\cdot}OEt_2$ is the reagent of choice for all of these cyclisation–condensation reactions, giving superior yields to those obtained both with iodotrimethylsilane and with strong Brönsted acids such as TFA and H_2SO_4.
[9] We thank Professor David J. Williams and Dr Andrew J.P. White of this Department for this determination.
[10] R. Noyori, H. Takaya, in: B.M. Trost (Ed.), Comprehensive Organic Synthesis, vol. 8, Pergamon, Oxford, 1991, p. 443.
[11] For a review of recent synthetic work on saturated nitrogen heterocycles including piperidines, and leading references, see: A. Mitchinson, A. Nadin, J. Chem. Soc. Perkin Trans. I (2000) 2862.