Pergamon

Tetrahedron Letters 42 (2001) 8369–8372

TETRAHEDRON LETTERS

1,4-Bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines in synthesis. Regio- and stereoselective S_N1 reactions

Jean-Claude Adelbrecht, Donald Craig* and Serge Thorimbert[†]

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

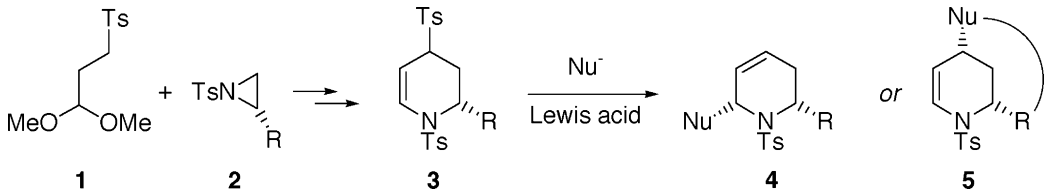
Received 8 August 2001; revised 11 September 2001; accepted 19 September 2001

Abstract—1,4-Bis(4-tolylsulfonyl)-1,2,3,4-tetrahydropyridines undergo stereoselective S_N1 reactions with soft carbon nucleophiles in the presence of Lewis acids. Subsequent dihydroxylation of the double bond followed by esterification enables the stereoselective preparation of substituted piperidines.

Previous studies from this laboratory[1] have demonstrated that 1,4-bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines **3**, readily made from sulfonyl acetal **1** and *N*-tosylaziridines **2**, undergo loss of the tolylsulfonyl group in the presence of nucleophiles on treatment with Lewis acid; depending on the nucleophile–Lewis acid combination 1,2- or 1,4-substitution products were isolated. Strikingly, intermolecular nucleophiles invariably intercepted the putative conjugated iminium species in a 1,2-sense to give **4**, arising from overall S_N1' reaction, whereas substrates with appended nucleophilic functionality gave the S_N1-type products **5** of intramolecular 1,4-attack (Scheme 1). We ascribed this change in reactivity to the greater accessibility for the internal nucleophiles of the required trajectory for interception of the cations in the 1,4-sense.

We became interested in identifying ways of modifying the reactivity of tetrahydropyridines **3** such that intermolecular transformations would deliver the products of 1,4-attack. Such compounds would retain the enamide functional group, which we had already shown to be amenable to selective oxidation reactions, thereby extending the utility of the methodology. The studies of Husson[2] and Lounasmaa[3,4] nearly 20 years ago independently established that soft nucleophiles such as metal enolates or silyl enol ethers derived from β-dicarbonyl compounds react at the 4-position of 5,6-dihydropyridinium ions generated in situ from *N*-alkyl-2-cyanotetrahydropyridines. In view of these precedents we anticipated that treatment of **3** with such nucleophiles in the presence of a Lewis acid would trigger S_N1 reactions leading to the formation of 4-substituted-*N*-tosyl-1,2,3,4-tetrahydropyridines. This letter reports the results of investigations, and describes further cation-mediated transformations of the products which take place with modified stereoselectivity compared with the parent 1,4-bis(arylsulfonyl) compounds.

After initial experiments, in which use of the silyl ketene acetal or sodium enolate derived from dimethyl malonate as the nucleophilic coupling partner gave no



1 **2** **3** **4** **5**

Scheme 1.

Keywords: alkylation; diastereoselectivity; Lewis acid; piperidines; S_N1.

* Corresponding author. Fax: +44 20 7594 5868; e-mail: d.craig@ic.ac.uk

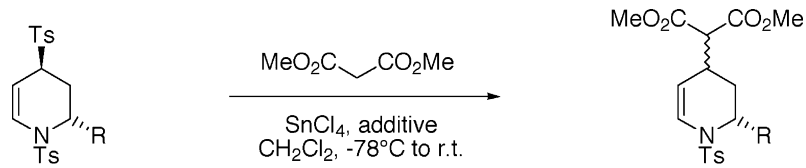
[†] Present address: Université Pierre et Marie Curie, Laboratoire de Chimie Organique de Synthèse, Tour 44-54, Place Jussieu, F-75252 Paris Cedex 05, France.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01771-3

substitution product and the corresponding lithio-species gave only moderate yields, we elected to generate the nucleophilic species under non-basic conditions. Titanium(IV) and tin(IV) enolates of mono- or diesters have been employed extensively in C–C bond forming transformations,[5] and we envisaged that Lewis acidic reagents such as $SnCl_4$ or $TiCl_4$ might simultaneously activate the C-4 tosyl leaving group and effect formation of the nucleophilic enolate in situ. In practice, treatment of a dichloromethane solution of tetrahydropyridine **3a** (1 equiv.) with tin tetrachloride (3 equiv.) and dimethyl malonate (3 equiv.) was ineffective. However, inclusion of *N*,*O*-bis(trimethylsilyl)acetamide (BSA)[6] in the reaction mixture caused complete consumption of the starting material to take place during 4 h at ambient temperature; the product **6a** was isolated in excellent yield as a mixture of C-4 epimers. This reaction procedure was extended to other tetrahydropyridine substrates **3** (Scheme 2); the results are collected in Table 1.[7]

These high-yielding substitution reactions were completely regioselective for the S_N1 rather than the S_N1' products, in marked contrast to our earlier findings.[1a] Replacing BSA with Hünig's base as the additive (entry 3) did not have a significant effect on the efficiency of the reaction, provided an additional equivalent of $SnCl_4$ was employed. It may be seen from the data in Table 1 that the stereoselectivity of the S_N1 reactions is variable. For tetrahydropyridines **3a**, **3c** and **3d** bearing sterically less demanding 2-substituents the reactions showed almost no selectivity (entries 1, 4 and 5). For substrates **3b** and **3e** possessing bulkier R groups (*i*-Pr, $CH_2OTBDPS$) the *anti* product was the only stereoisomer detectable by ^1H NMR analysis of the crude products (entries 2 and 6).[8] It would appear from these results that the β-face is sterically more accessible, and that α-attack is significantly hindered. This explanation is consistent with the likely axial disposition of the 2-substituent on the six-membered ring, and might also indicate that the distal nature of the electrophilic 4-position renders it less susceptible to steric hindrance arising from the *N*-tosyl group. Mechanistically, it seems plausible that initial tin(IV) chloride-mediated heterolysis of the C4–Ts bond occurs with concomitant generation of chloride ion, which then attacks BSA to yield TMSCl and the conjugate base of *N*-(trimethylsilyl)acetamide. Subsequent proton exchange with dimethyl malonate generates the nucleophilic tin(IV) enolate which intercepts the iminium species in a 1,4-sense.

The next phase of our study sought to evaluate alternative active methylene compounds as nucleophilic partners in the S_N1 reactions. In the event, reaction of methyl acetoacetate with **3e** under identical conditions to those developed for dimethyl malonate gave **7**, whilst **3e** combined with ethyl nitroacetate to give **8**; both reactions were high-yielding. Again, the reactions showed complete 2,4-*trans*-selectivity, with low stereo-

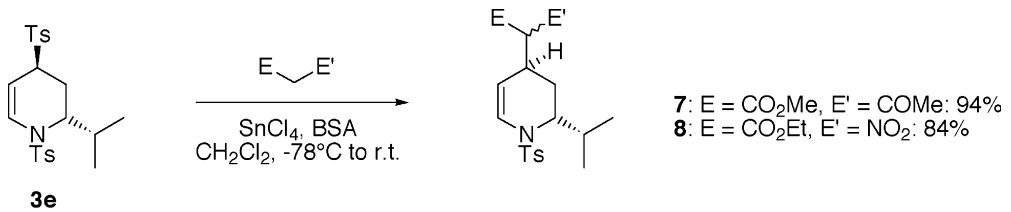


Scheme 2.

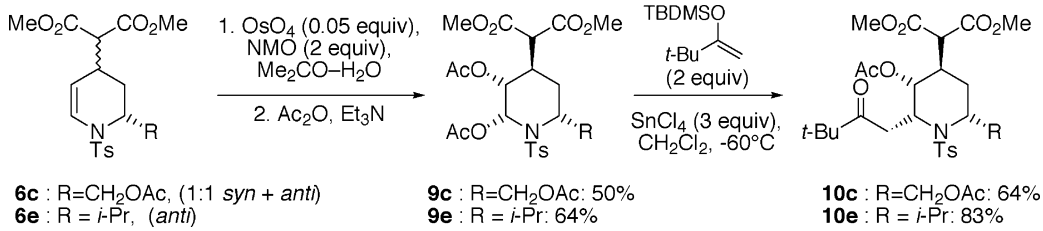
Table 1.

Entry	Substrate	R	Additive	Yield of **6**	*syn*-**6**:*anti*-**6**
1	**3a**	Me	BSA	100	45:55
2	**3b**	$CH_2OTBDPS$	BSA	100	>98:2
3	**3b**	$CH_2OTBDPS$	*i*-Pr_2NEt	90	>98:2
4	**3c**	CH_2OAc	BSA	80	50:50
5[a]	**3d**	CH_2*i*-Pr	BSA	65 (80)[b]	45:55
6	**3e**	*i*-Pr	BSA	88	>98:2

[a] Reaction performed over 4 h at rt.
[b] Yield in parentheses based on recovered starting material.



Scheme 3.



6c : R=CH_2OAc, (1:1 *syn* + *anti*)
6e : R = *i*-Pr, (*anti*)

9c : R=CH_2OAc: 50%
9e : R = *i*-Pr: 64%

10c : R=CH_2OAc: 64%
10e : R = *i*-Pr: 83%

Scheme 4.

control at the newly-formed exocyclic stereocentre (Scheme 3). Other nucleophiles which were evaluated either suffered degradation (α-cyanoesters, α-iminoesters) under the reaction conditions or were recovered unchanged (α-sulfonylesters and -ketones).

The final part of this investigation focused on the effect of the malonate substituent in **6** on the stereochemistry of oxidation of the tetrahydropyridine double bond, and on transformations of the dioxygenated products. Dihydroxylation of **6c** and **6e** using OsO_4–*N*-methylmorpholine-*N*-oxide (NMO)[9] was carried out as previously described for tetrahydropyridines **3**.[10] Direct diacetylation of the crude diol mixtures gave derivatives **9c** and **9e** as single diastereomers in, respectively, 50 and 64% yields over two steps. X-Ray diffraction analysis of a single-crystal of **9e** provided unequivocal proof of its stereochemistry.[11] Next, compounds **9c** and **9e** were separately subjected to the S_N1 reaction conditions used previously by us[10] for the analogous 4-(tolylsulfonyl) substrates.[12,13] Thus, $SnCl_4$ was added to the diacetates in cold (−60°C) dichloromethane solutions containing the TBDMS enol ether of pinacolone. The acetoxymethyl-substituted compound **10c** was obtained in 64% yield, in addition to a significant amount (36%) of the product of selective hydrolysis of the C-2 ester. Reaction of the analogous isopropyl-substituted substrate **9e** gave **10e** in 83% isolated yield, without detectable formation of the corresponding hydroxy derivative. Both reactions were completely selective for the products corresponding to nucleophilic attack on the α-face of the iminium intermediate, *syn* with respect to the 2-substituent; for isopropyl-substituted compound **9e** this is in marked contrast to the selectivity observed for the analogous 4-(tolylsulfonyl) substrate (Scheme 4).[10]

These results may be rationalised in terms of stabilisation of the iminium cation by a carbonyl oxygen atom within the malonate function. Such internal coordination would render the β-face sterically more encumbered, forcing the nucleophile to attack the α-face. Stable, isolable bicyclic products resulting from this type of interaction have indeed been isolated from reactions of 2-cyano-1,2,5,6-tetrahydropyridines, which have been postulated to proceed via cationic intermediates closely related to those proposed here.[2,3]

In summary, we have demonstrated that soft nucleophiles derived from malonate and other active methylene species enter into completely regioselective and in some cases stereoselective S_N1 reactions with bis(arylsulfonyl)tetrahydropyridines under Lewis acidic conditions. Dihydroxylation–esterification of two of the malonate-containing products gives substrates for further S_N1 reactions, which proceed with complete stereoselectivity and in a complementary sense to that observed for the sulfonyl-substituted analogues.

Acknowledgements

We thank the Department of Chemistry, Imperial College and Roche Discovery Welwyn (Teaching Assistantship to J.-C.A.), and the Université Pierre et Marie Curie, the CNRS and NATO (Fellowship to S.T.) for financial support of this research.

References

1. (a) Craig, D.; McCague, R.; Potter, G. A.; Williams, M. R. V. *Synlett* **1998**, 55–57; (b) Craig, D.; McCague, R.; Potter, G. A.; Williams, M. R. V. *Synlett* **1998**, 58–60.
2. Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064–1082.
3. Koskinen, A.; Lounasmaa, M. *Tetrahedron Lett.* **1983**, *24*, 1951–1952.
4. Lounasmaa, M.; Miettinen, J.; Hanhinen, P.; Jokela, R. *Tetrahedron Lett.* **1997**, *38*, 1455–1458.
5. (a) Kitagawa, O.; Suzuki, T.; Fujiwara, H.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 2549–2552; (b) Poli, G.; Giambastiani, G.; Mordini, A. *J. Org. Chem.* **1999**, *64*, 2962–2965.
6. Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143–1145.
7. For the preparation of related structures by S_N1' reactions, see: Matsumura, Y.; Yoshimoto, Y.; Horikawa, C.; Maki, T.; Watanabe, M. *Tetrahedron Lett.* **1996**, *37*, 5715–5718.
8. All yields reported herein refer to isolated, pure materials which had ^1H and ^{13}C NMR, IR and high-resolution MS characteristics in accord with the proposed structures.
*Preparation of **6e***. To a solution of tetrahydropyridine **3e** (43 mg, 0.1 mmol), BSA (74 μl, 3 equiv.), and dimethyl malonate (34 μl, 3 equiv.) in CH_2Cl_2 was added at −78°C $SnCl_4$ (300 μl of a 1 M solution in CH_2Cl_2, 0.3 mmol, 3 equiv.). The yellow mixture was stirred for 1 h at −78°C then overnight at rt. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with ether (2×10 ml). The combined organic layers were washed with brine (2×20 ml) and dried (Na_2SO_4). Concentration under reduced pressure followed by flash chromatography of the residue (5% ether–petrol) gave

tetrahydropyridine **6e** (36 mg, 88%); $[\alpha]_D^{20}$ +191.7 (*c* 0.96, CH_2Cl_2); ν_{max} (film) 2958, 2926, 1737, 1641, 1438, 1345, 1286, 1252, 1167 cm^{-1}; δ_H ($CDCl_3$, 270 MHz) 7.50 (2H, d, *J* 8 Hz), 7.24 (2H, m), 6.57 (1H, dd, *J* 8, 1.5 Hz), 4.88 (1H, dt, *J* 8, 1.5 Hz), 3.65 (3H, s), 3.60 (3H, s), 3.47 (1H, dt, *J* 10, 4 Hz), 2.93 (1H, d, *J* 9 Hz), 2.78 (1H, m), 2.40 (3H, s), 1.78 (2H, m), 1.07 (3H, d, *J* 7 Hz), 0.88 (3H, d, *J* 7 Hz), 0.45 (1H, td, *J* 13, 4 Hz); δ_C ($CDCl_3$, 67 MHz) 168.2, 168.1, 143.6, 135.6, 129.7, 125.5, 111.1, 59.4, 55.5, 52.6, 52.5, 28.9, 28.3, 25.5, 21.6, 20.6, 18.7; *m*/*z* (CI) 427 $[M+NH_4]^+$, 410 $[M+H]^+$ (found: $[M+NH_4]^+$, 427.1903. $C_{20}H_{27}NO_6S$ requires $[M+NH_4]^+$, 427.1894).

9. Schröder, M. *Chem. Rev.* **1980**, *80*, 187–213.
10. Adelbrecht, J.-C.; Craig, D.; Thorimbert, S. *Synlett* **2000**, 467–470.
11. We thank Professor D. J. Williams and Dr. Andrew J. P. White of this department for this determination. Crystallographic data (excluding structure factors) for **9e** have been deposited with the Cambridge Crystallographic Data Centre as supplementary data numbers CCDC 170601. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
12. (a) Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131–184; (b) Reider, P. J.; Rayford, R.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 379–382.
13. *Preparation of **10e***. To a solution of diacetate **9e** (10 mg, 1 equiv.) in CH_2Cl_2 (3 ml) at −60°C was added the TBDMS enol ether of pinacolone (16 μl, 3 equiv.) followed by $SnCl_4$ (60 μl of a 1 M solution in CH_2Cl_2, 0.06 mmol, 3 equiv.) causing the colourless solution to become yellow. The reaction was quenched after 3 h by the addition of saturated aqueous $NaHCO_3$ (10 ml) and the mixture was extracted with EtOAc (3×10 ml). The combined organic layers were washed with brine (10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue (40% EtOAc–petrol) gave **10e** (9 mg, 83%) as a colourless oil; $[\alpha]_D^{20}$ −35.0 (*c* 0.8, CH_2Cl_2); ν_{max} (film) 2959, 2922, 1742, 1440, 1340, 1221, 1161 cm^{-1}; δ_H (270 MHz) 7.80 (2H, d, *J* 8 Hz), 7.33 (2H, d, *J* 8 Hz), 5.06 (1H, dd, *J* 9, 6.5 Hz), 4.15 (1H, dd, *J* 12, 6 Hz), 3.66 (1H, m), 3.65 (3H, s), 3.48 (3H, s), 3.30 (1H, d, *J* 5.5 Hz), 3.15 (1H, dd, *J* 18, 9.5 Hz), 2.67 (1H, dd, *J* 18, 1.5 Hz), 2.52, (1H, tdd, *J* 12, 6, 2 Hz), 2.41 (3H, s), 2.00 (1H, m), 1.80 (3H, s), 1.62 (1H, m), 1.18 (3H, d, *J* 6.5 Hz), 1.13 (9H, s), 1.10 (1H, m), 1.01 (3H, d, *J* 6.5 Hz); δ_C ($CDCl_3$, 67 MHz) 211.3, 168.9, 168.4, 167.6, 143.2, 137.9, 129.9, 127.0, 70.0, 59.3, 52.5, 52.2, 51.3, 48.4, 43.9, 38.1, 30.5, 29.7, 27.9, 26.5, 21.5, 21.0, 20.6, 20.4; *m*/*z* (CI) 585 $[M+NH_4]^+$, 568 $[M+H]^+$, 414 (found: $[M+H]^+$, 568.2580. $C_{28}H_{41}NO_9S$ requires $[M+H]^+$, 568.2583).