Pergamon

Tetrahedron Letters 39 (1998) 147–150

TETRAHEDRON LETTERS

Heterocyclic Synthesis by C–C Bond Formation. Thionium Ion-mediated Preparation of Substituted Pyrrolidines and Piperidines

Donald Craig,*[a] James D. Meadows[b] and Muriel Pécheux[a]

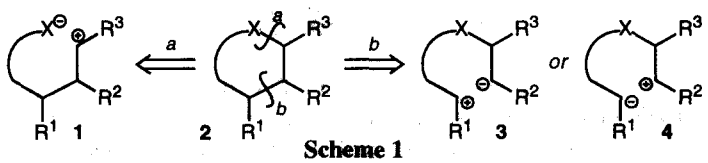
[a]Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, U.K.
e-mail: dcraig@ic.ac.uk

[b]Glaxo Wellcome Research and Development Ltd, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, U.K.

Received 22 September 1997; revised 20 October 1997; accepted 24 October 1997

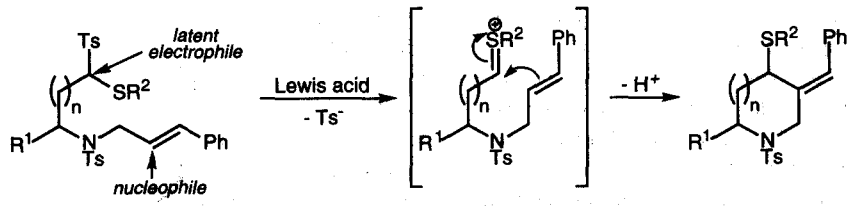
Abstract: Dithioacetal-*S,S*-dioxides **6** and **7** undergo cyclisation to give pyrrolidines and piperidines upon exposure to Lewis acid. An unexpected tandem cyclisation of **5** to give **10** is described.

Classical cyclisation-based strategies for the construction of heterocycles exploit the inherent nucleophilicity of the heteroatom in combination with electrophilic carbon functionality (Scheme 1; disconnection *a*). Alternatively, disconnection *b* of **2** leads retrosynthetically to a synthon **3** or **4** which possesses mutually reactive electrophilic and nucleophilic carbon functional groups. This approach has been deployed for the synthesis of a wide range of heterocycles, most notably by Overman.[1] In the context of our own interest in such cyclisation processes,[2] we showed that an oxygen-tethered 3-phenyl-2-propenyl group could intercept an anomeric cation,[3] and we have now looked at the Lewis acid-mediated cyclisations of substrates **5/6** and **7** as a route to nitrogen heterocycles (Scheme 2). This Letter reports the results of these investigations.



Scheme 1

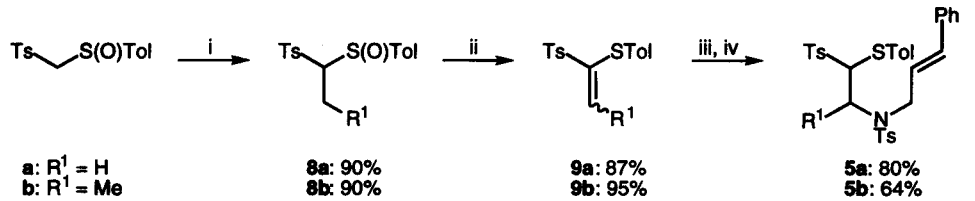
5 (n = 0, R^2 = Tol)
6 (n = 0, R^2 = Me)
7 (n = 1, R^2 = Me)



Scheme 2

Initial efforts were focused on cyclisation reactions of substrates **5**. These compounds were readily assembled by the nucleophilic addition of 3-phenyl-2-propenylamine[4] to α-(tolylsulfenyl) vinylic sulfones **9**, followed by *N*-tosylation under standard conditions.[5] Intermediates **9** were prepared by Pummerer-type reaction[6] of α-sulfinylsulfones **8** with TMSOTf–Hünig's base; **8** were obtained in good yields by simple alkylation of the known (4-tolylsulfinyl)(4-tolylsulfonyl)methane[7] (Scheme 3).

0040-4039/98/$19.00
PII: S0040-4039(97)10472-5



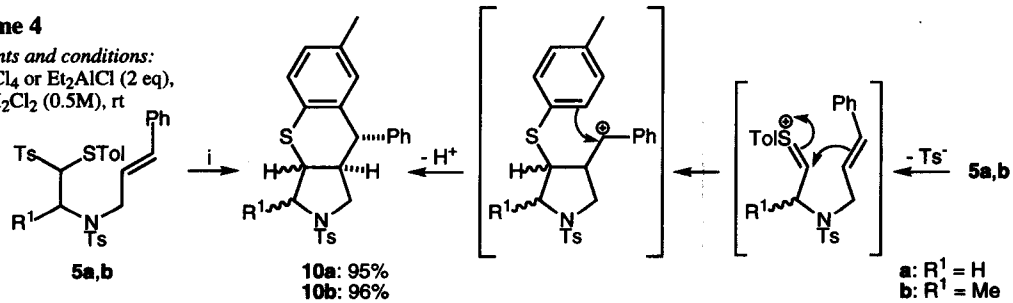
Reagents and conditions: (i) KH (1 equiv), R^1CH_2I, DMF (0.3M), rt; (ii) TMSOTf (2.1 equiv), *i*-Pr_2NEt (2.1 equiv), CH_2Cl_2 (0.5M), rt; (iii) $PhCH{:}CHCH_2NH_2$ (1 equiv), CH_2Cl_2 (1.5M), rt; (iv) TsCl (1.1 equiv), *i*-Pr_2NEt (1.1 equiv), DMAP (0.2 equiv), CH_2Cl_2 (0.5M), rt.

Scheme 3

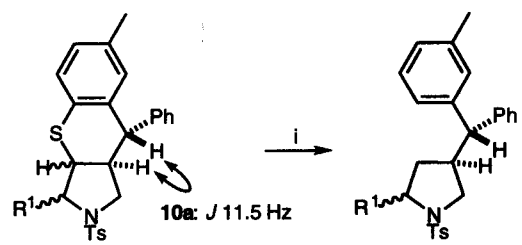
Treatment of **5** with $ZnCl_2$, $BF_3{\cdot}OEt_2$ or Me_3Al in dichloromethane resulted in high-yielding recovery of starting material. However, exposure to the more powerful Lewis acids diethylaluminium chloride or titanium tetrachloride unexpectedly gave the tricycles **10** in excellent yields. Where R^1 = H, **10a** was formed as a two-component diastereomeric mixture; in the case of the more substituted analogue **10b** (R^1 = Me) a mixture of four of the possible eight diastereomers was formed. Mechanistically, it seems likely that after Lewis acid-induced loss of tolylsulfinate ion, the sulfur-stabilised carbocation is intercepted non-stereoselectively by the nucleophilic styryl moiety to give a benzylic cation. This is subsequently attacked in a stereoselective fashion by the proximal tolyl group in an intramolecular electrophilic aromatic substitution process (Scheme 4).

Scheme 4

Reagents and conditions:
(i) $TiCl_4$ or Et_2AlCl (2 eq), CH_2Cl_2 (0.5M), rt



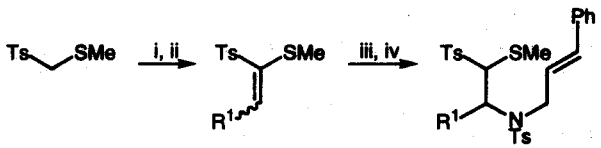
The structural assignments of **10** followed from their ^1H nmr spectra, and from subsequent chemical derivatisation experiments. Thus, in both isomers of **10a** the benzylic methine showed a large (11.5 Hz) *J* value due to coupling with its trans-diaxial vicinal neighbour. Most compellingly, treatment of **10a** and **10b** with Raney nickel in ethanol gave respectively a single isomer of **11** and a 1:1 mixture of **12**, demonstrating the fixed stereochemical relationship of the phenyl group and the vicinal hydrogen atom in **10** (Scheme 5). In view of this interesting but undesirable reactivity, analogues of **5** such as **6**, which possess the non-nucleophilic methylthio group were sought. The Pummerer-based route used previously for the synthesis of substrate precursors **9** failed when applied to the methylsulfinyl analogues of **8**. Instead, the requisite intermediates **13a** and **13b** were synthesised by the condensation of the thioacetal derivative (methylsulfenyl)(4-tolylsulfonyl)-methane[8] with formaldehyde and acetaldehyde respectively. Addition of *E*-3-phenyl-2-propenylamine and subsequent *N*-tosylation asbefore gave **6** in good overall yields (Scheme 6). In view of the successful cyclisation reactions of the *S*-phenyl analogues **5**, Et_2AlCl and $TiCl_4$ were selected as cyclisation initiators. Treatment of **6a,b** with two equivalents of Et_2AlCl in dichloromethane gave **14a,b** as diastereomeric mixtures in respective yields of 70 and 81%. Evidently the alumin-



Reagents and conditions: (i) Ni(R), EtOH (0.02M), reflux.

Scheme 5

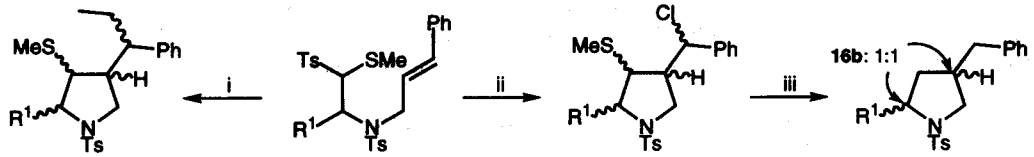
ium species formed by loss of phenylsulfinate during the ionisation step possesses an ethyl ligand which is sufficiently nucleophilic to trap the benzylic cation formed on pyrrolidine formation. Exposure of **6a,b** to $TiCl_4$ under near-identical conditions gave in almost quantitative yields the chlorinated products **15a,b** of non-stereoselective cyclisation. These were cleanly reduced using Raney nickel to give pyrrolidines **16**; **16a**[9] was obtained as a single isomer, whilst analogue **16b** was formed as an inseparable 1:1 mixture (Scheme 7).



a: R^1 = H **13a**: 50% **6a**: 68%
b: R^1 = Me **13b**: 90% **6b**: 89%

Reagents and conditions: (i) *n*-BuLi, R^1CHO; H^+; (ii) Ac_2O, DMAP, Et_3N; (iii) $PhCH{:}CHCH_2NH_2$ (2 equiv), CH_2Cl_2 (1-2M), rt; (iv) TsCl (1.2 equiv), *i*-Pr_2NEt (1.2 equiv), DMAP (0.2 equiv), CH_2Cl_2 (0.5M), rt.

Scheme 6

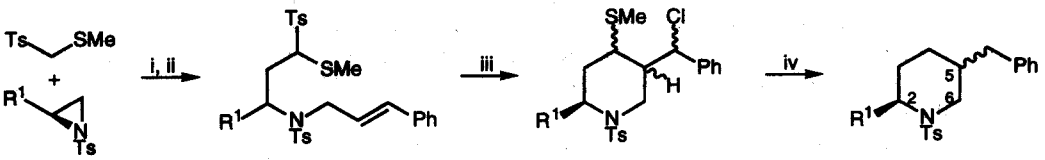


14a: 70% **a**: R^1 = H **6a,b** **15a**: 98% **16a**: 90%
14b: 81% **b**: R^1 = Me **15b**: 97% **16b**: 95%

Reagents and conditions: (i) Et_2AlCl (2 equiv), CH_2Cl_2 (0.5M), rt, 30 min; (ii) $TiCl_4$ (2 equiv), CH_2Cl_2 (0.5M), rt, 30 min; (iii) Ni(R), EtOH (0.02M), reflux, 2 h.

Scheme 7

Attention was next turned to the homologous substrates **7**, whose Lewis acid-initiated cyclisations were expected to give piperidines by direct analogy with the cation-mediated reactions of **6**. Compounds **7** were easily prepared in enantiomerically pure form from L-aminoacids, via the corresponding *N*-tosylaziridines **17**.[10] Thus, reaction of the lithio-anion of (methylsulfenyl)(4-tolylsulfonyl)methane with **17a-c** gave diastereomeric mixtures of adducts. These were alkylated by reaction of their sodium salts with *E*-1-bromo-3-phenyl-2-propene, giving **7a-c** in good overall yields for the two-step sequences from **17** and (methylsulfenyl)(4-tolylsulfonyl)methane. Treatment of **7** with $TiCl_4$ under identical conditions to those used for cyclisation of **6** gave piperidines **18a-c** as complex diastereomeric mixtures. These were subjected to reductive cleavage of the sulfur and chlorine substituents as before to give inseparable piperidine mixtures **19a-c**, which were formed predominantly as the 2,5-syn isomers. The synthesis and reactions of substrates **7** are depicted in Scheme 8.



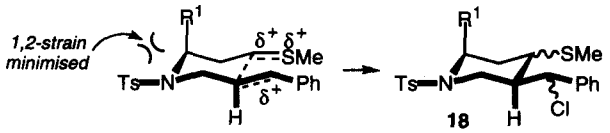
17a: R^1 = Bn **7a**: 58% **18a**: 97% **19a**: 96% 3:2 syn:anti
17b: R^1 = *i*-Pr **7b**: 63% **18b**: 97% **19b**: 97% 4:1 syn:anti
17c: R^1 = *i*-Bu **7c**: 56% **18c**: 97% **19c**: 95% 3:1 syn:anti

Reagents and conditions: (i) *n*-BuLi (1 equiv), THF (0.1M), -78°C, then add **17**; (ii) NaH (1 equiv), $PhCH{:}CHCH_2Br$ (1 equiv), DMF (0.3M), rt; (iii) $TiCl_4$ (2 equiv), CH_2Cl_2 (0.5M), rt, 30 min; (iv) Ni(R), EtOH (0.02M), reflux, 2 h.

Scheme 8

That the benzyl substituent was equatorially disposed was demonstrated by the two large *J* values (typically 13 and 12 Hz) due respectively to geminal and trans-diaxial coupling exhibited by the axial C-6 hydrogen in the ^1H nmr spectra of the three major isomers of **19a-c**. The anti, axial orientation of R^1 with respect to the 5-benzyl substituent was inferred from the absence of any large *J* values in the H-2 nmr signals indicative of trans-diaxial vicinal relationships, and from ample literature precedent describing the preferred axial disposition of C-2 alkyl substituents in *N*-protected piperidine systems. This has been reported both for *N*-tosyl[11] and *N*-acyl analogues,[12] and it has been postulated that the effect stems from minimisation of

unfavourable gauche interactions of R^1 with the protecting group. Thus, 2,5-syn-**18** would arise via the transition-states depicted in Scheme 9. The mixture of diastereomers of **19b** was readily desulfonylated using HBr–phenol–acetic acid[13] to give the parent 2,5-disubstituted piperidines in 77% yield.



Scheme 9

In summary, we have demonstrated that *N*-3-phenyl-2-propenyl-substituted tosamides bearing thioacetal dioxide side-chains are readily available substrates for high-yielding, and in some cases stereoselective heterocycle-forming reactions. The piperidine-forming transformations compare favourably with published approaches involving C–N bond-formation,[14] in that the stereochemical information contained within the substrate is efficiently relayed to the new stereocentre in the product. Further studies are aimed towards extending this work to larger nitrogen-containing rings, and we are actively exploring the ramifications of the unexpected conversion of **5** into **10** for the development of cation-mediated cascade reactions in a number of diverse applications. The results of these studies will be reported in due course.

ACKNOWLEDGEMENTS

We thank Glaxo Research and Development Ltd (Studentship to M. P.) for financial support of this research.

REFERENCES AND NOTES

1. For an excellent account, see: Overman, L. E. *Aldrichimica Acta* **1995**, *28*, 107-120.
2. Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1992**, *48*, 7803-7816, and refernces cited therein.
3. Craig, D.; Pennington, M. W.; Warner, P. *Tetrahedron Lett.* **1995**, *36*, 5815-5818.
4. Prepared using the Gabriel synthesis. See: Moody, C. J.; Rahimtoola, K. F.; Porter, B.; Ross, B. C. *J. Org. Chem.* **1992**, *57*, 2105-2114.
5. All yields cited herein are of isolated, purified materials which gave satisfactory ^1H, ^{13}C nmr and ir spectra, and which showed low-resolution ms and either elemental combustion analysis or high-resolution ms characteristics in accord with the assigned structures.
6. For a review of the Pummerer reaction, see: Kennedy, M.; McKervey, M. A. in *Comprehensive Organic Synthesis*, eds. Trost, B. M.; Fleming, I.; Pergamon Press: New York, 1991, vol. 7 pp 193-216.
7. (4-Tolylsulfinyl)(4-tolylsulfonyl)methane was prepared by addition of isopropyl 4-tolylsulfinate to a mixture of lithiated (4-tolylsulfonyl)methane and *t*-BuOK followed by protonation.
8. (Methylsulfenyl)(4-tolylsulfonyl)methane was prepared from dimethylsulfoxide according to a published procedure: Ogura, K.; Yahata, N.; Watanabe, J.-I.; Takahashi, K.; Iida, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3543-3544.
9. Compound **16a** has previously been synthesised (i) by intramolecular S_N2-like reaction: Kataoka, T.; Tsutsumi, K.; Kano, K.; Mori, K.; Miyake, M.; Yokota, M.; Shimizu, H.; Hori, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3017-3025, and (ii) by radical cyclisation: Ueno, Y.; Tanaka, C.; Okawara, M. *Chem. Lett.* **1983**, 795-796.
10. Berry, M. B.; Craig, D. *Synlett* **1992**, 41-44.
11. For studies on *N*-tosyl 2,6-dialkyl-2,6-dihydro-1*H*-pyridin-3-ones, see: Hopman, J. C. P.; van den Berg, E.; Ollero Ollero, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1995**, *36*, 4315-4318. For earlier work on the corresponding 3-hydroxy compounds, see: Lu, Z.-H.; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 593-596.
12. Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445-7447.
13. Poduska, K.; Rudinger, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1955**, *20*, 1174.
14. Rubiralta, M.; Giralt, E.; Diez, A., *Piperidine: Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its Derivatives,* Elsevier: New York, NY, 1991.