Ring expansion of sulfur substituted *p*-quinamines: regiospecific synthesis of 4-aminotropones†

M. Carmen Carreño,* M. Jesús Sanz-Cuesta and María Ribagorda

Received (in Cambridge, UK) 23rd September 2004, Accepted 16th November 2004
First published as an Advance Article on the web 5th January 2005
DOI: 10.1039/b414666b

Synthesis of 4-aminotropones through a cyclization–ring expansion process occurs in a single step and with excellent yields from 4-amino-2,5-cyclohexadienones (*p*-quinamines) bearing a 4-sulfinyl or sulfonyl methyl group.

The tropone ring system is a recurring structural motif in a number of natural products,[1] ranging from structurally simple monocyclic systems[2] to more complex norditerpenoids[3] and alkaloids.[4] The wide range of biological properties that embrace these compounds have stimulated important synthetic efforts, with the regioselective construction of a seven-membered ring being one of the more prominent problems to be solved.[1c,5,6] Moreover, tropone seven-membered ring systems embody a variety of reactivities that continue to challenge the synthetic chemist.[7]

Among the strategies applied to the synthesis of the tropone ring,[8] different cycloaddition reactions have been reported.[9] Ring expansion of six-membered rings is also a recurring key step to synthesize the cycloheptatriene system.[10] However, appropriately substituted tropones are not easily synthesized, because the specific introduction of substituents at desired positions is difficult to achieve. In particular, an inspection of published work has unveiled the synthesis of 4-aminotropone from 4-aminotropolone sulfate[11] and 4-hydroxytropone[12] in stepwise sequences. Thus, development of general and flexible routes to aminotropones are welcome.

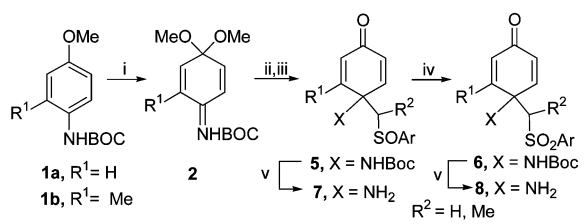
As a part of an ongoing program devoted to synthetic applications of sulfinyl substituted *p*-quinols[13] and nitrogen analogues,[14] we discovered that these systems behave like natural quinol metabolites giving rise to a trimerization process through a domino sequence of four conjugate additions when treated with NaH or LiCl.[14c] Herein, we report our findings on the ring expansion of the *p*-quinamine core promoted by a base and mediated by a pendant sulfinyl or sulfonyl methyl group. To our knowledge, this represents the first efficient synthesis of 4-aminotropones. The overall process opens easy and regiospecific access to C-3 or C-5 alkyl substituted 4-aminotropones.

The starting materials, *N*-(*tert*-butoxycarbonyl)-4-amino-4-[(*p*-tolyl or phenylsulfinyl)methyl]-2,5-cyclohexadienones[14b] **5a–c**, are accessible in three steps from *N*-Boc *p*-anisidine derivatives **1**, through anodic oxidation,[15] addition of the α-lithiocarbanion derived from methyl *p*-tolylsulfoxide **3** or ethyl phenyl sulfoxide **4** to the quinoneimine monoacetals **2**, and acid hydrolysis of the acetal group (Scheme 1). Sulfones **6a–c** resulted from MCPBA oxidation of the sulfoxides **5a–c**. Removal of the *N*-Boc protecting group afforded free NH_2 derivatives **7a–c** and **8a–c**.

Having in mind the known synthesis of tropones based on a radical cyclization and ring enlargement of 4-halomethyl-2,5-cyclohexadienones,[10c–e] and the lack of efficient methods to amino substituted tropones, we decided to explore whether sulfinyl substituted *p*-quinamines {4-amino-4-[(*p*-tolylsulfinyl)]methyl-2,5-cyclohexadienones} could be transformed into the cycloheptatrienone derivatives. To our delight, when we checked the behavior of the *N*-Boc protected *p*-quinamine **5a** in the presence of a base (K_2CO_3, NaOH, LDA, KHMDS, LiHMDS) we observed the exclusive formation of *N*-Boc-4-aminotropone **9a**. After several trials, we established that upon treatment of a THF solution of **5a** with NaH (4 equiv.), compound **9a** was rapidly formed in excellent yield (Table 1, entry 1).[16]

The formation of tropone **9a** is assumed to proceed from an initial α-sulfinyl carbanion resulting upon basic treatment of **5a**, which evolved to a norcaradiene-like intermediate **I**,[10c,17] by a favoured intramolecular 1,4-addition. Subsequent elimination of the *p*-toluene sulfenate anion from **I** occurred with simultaneous ring expansion leading to the tropone **9a** (Scheme 2). With the aim of trapping the intermediate enolate **I** and/or the sulfenate ion,[18] reaction of **5a** with NaH was run in the presence of MeI. Under these conditions, a clean mixture of **9a** and MeSOTol **3** (84% isolated yield), resulting from reaction of the nucleophilic sulfenate moiety, was formed. This result showed that the evolution of the cycloheptatrienone is strongly favoured and therefore recovery of the starting sulfoxide **3** for reutilization is possible.

The ring enlargement of sulfoxides was proved to occur also with *p*-quinamines bearing other substitution at the nitrogen. Thus, *N*,*N*-dimethyl **5d**, *N*-methyl **5e** and *N*-benzyl **5f** derivatives

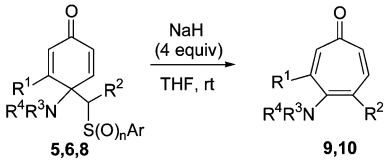


Scheme 1 *Synthesis of 4-sulfinyl (or sulfonyl) methyl substituted p-quinamines* **5–8**. *Conditions*: (i) Anodic oxidation, Pt/Cu, MeOH, $LiClO_4$, Py, 0 °C, (**2a**) 99%, (**2b**) 93%; (ii) MeSOTol (**3**) or EtSOPh (**4**), LDA, THF, −78 °C to rt; (iii) Oxalic acid, THF–H_2O, rt, (**5a**) 80% and (**5b**) 82% from **3** (R^2 = H), (**5c**) 40% from **4** (R^2 = Me) (yield of two steps); (iv) MCPBA, CH_2Cl_2, 0 °C, 99% (**6a–c**); (v) TFA, CH_2Cl_2, rt, (**7a**) 99%, (**7b**) 78%, (**7c**) 96%, (**8a**) 99%, (**8b**) 99%, (**8c**) 52%. See Table 1 for substrate details.

† Electronic supplementary information (ESI) available: Experimental procedures and compound characterization data of **9a–f**, **10a–c**, **11** (including NOESY experiments) and **12**. See http://www.rsc.org/suppdata/cc/b4/b414666b/

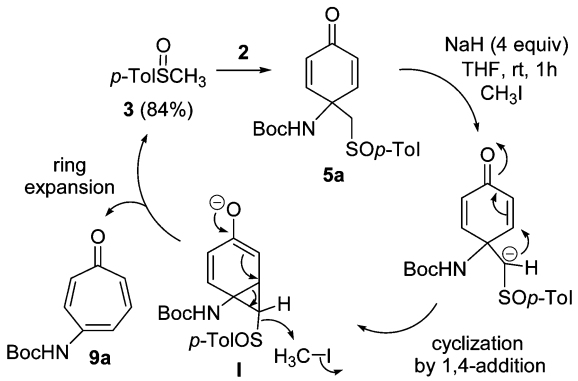
*carmen.carrenno@uam.es

Table 1 Regioselective synthesis of 4-amino substituted tropones



Entry	5,6,8	NR^3R^4	R^1	R^2	Ar	*n*	Time/h	9–10 (Yield)[a]
1	**5a**	NHBoc	H	H	*p*-Tol	1	3	**9a** (99)
2	**5d**	NMe_2	H	H	*p*-Tol	1	2	**9d** (99)
3	**5e**	NHMe	H	H	*p*-Tol	1	2	**9e** (70)
4	**5f**	NHBn	H	H	*p*-Tol	1	2	**9f** (99)
5	**5b**	NHBoc	Me	H	*p*-Tol	1	24	—[b]
6	**5c**	NHBoc	H	Me	*p*-Tol	1	24	—[b]
7	**6b**	NHBoc	Me	H	*p*-Tol	2	1	**9b** (77)
8	**6c**	NHBoc	H	Me	Ph	2	4	**9c** (94)
9	**6a**	NHBoc	H	H	*p*-Tol	2	2	**9a** (97)
10	**8a**	NH_2	H	H	*p*-Tol	2	6	**10a** (99)[c]
11	**8b**	NH_2	Me	H	*p*-Tol	2	24	**10b** (97)[c]
12	**8c**	NH_2	H	Me	Ph	2	2	**10c** (99)[c]

[a] Yield after purification by column chromatography. [b] Unaltered starting material was recovered despite the addition of 8 equiv. of NaH and heating at 50 °C. [c] Purified on a BondElut LRC-SCX, 500 mg column chromatography.

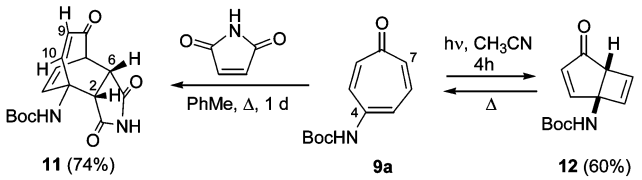


Scheme 2 Possible mechanism of 4-aminotropone formation and trapping of the sulfenate leaving group.

afforded the *N*-substituted 4-aminotropones **9d–f** in excellent yields (Table 1, entries 2–4). 3-Methyl *N*-Boc *p*-quinamine **5b** and the α-methyl sulfinyl *N*-Boc derivative **5c** remained unchanged upon treatment with NaH (Table 1, entries 5 and 6). Nevertheless, 3-methyl-*N*-Boc-4-aminotropone **9b** and the 5-methyl isomer **9c** were regioselectively obtained from the sulfonyl *p*-quinamines **6b** and **6c** (Table 1, entries 7 and 8). According to the proposed mechanism, the regioselective formation of **9b** must be a consequence of the initial conjugate addition of an intermediate α-sulfonyl anion derived from **6b** to the more electrophilic unsubstituted double bond of the cyclohexadienone moiety.

The ring expansion from the sulfone bearing *p*-quinamines was shown to be general. Tropone **9a** was also obtained from **6a** (Table 1, entry 9). The free amino sulfinyl derivatives **7a–c** under the basic conditions were inert to ring expansion, but fortunately the sulfone bearing analogues **8a–c** gave tropones **10a–c** in excellent yields (Table 1, entries 10–12).

Having found an efficient synthesis of 4-aminotropones, we initiated a preliminary study of their reactivity using **9a** as a model. Tropone **9a** behaves as a diene through the C-4–C-7 fragment in



Scheme 3 Diels–Alder reaction and 4π-electrocyclization of **9a**.

the Diels–Alder reaction with maleimide, yielding the single adduct **11**, resulting from the *endo*-approach, in 74% yield. The structure of **11** was secured by NOESY experiments, where interaction between the enone protons H-9 and H-10 with H-6 and H-2 respectively, was observed (Scheme 3). The photochemical behavior of **9a** was also studied.[19] Irradiating a MeCN solution of **9a**, a 4π-electrocyclization led to the *cis*-bicyclo[3.2.0]hepta-3,6-dien-2-one derivative **12** (60% yield). This bicyclic structure bears a protected bridged nitrogen function. Heating compound **12** (40 °C) promoted the cyclobutene opening to regenerate **9a** in 99% yield.

In summary, we have reported regioselective access to 4-aminotropones starting from *p*-sulfinylmethyl substituted *p*-quinamines, in turn accessible from *N*-Boc anilides in three steps. The position of alkyl substituents at C-3 or C-5 of the cycloheptatrienone can be directed by choosing the adequate substitution at both starting materials. The sulfonyl analogues behave similarly. To our knowledge, this is the first example of a ring expansion mediated by a simple alkyl aryl sulfoxide or sulfone.

This work was supported by the MCYT (Grant BQU2002-00371). M. J. S. C thanks MCYT for a fellowship. M. R. thanks the MEC for a Ramón y Cajal contract.

M. Carmen Carreño,* M. Jesús Sanz-Cuesta and María Ribagorda
Dpto. de Química Orgánica (C-I), Universidad Autónoma, Cantoblanco, 28049-Madrid, Spain. E-mail: carmen.carrenno@uam.es; Fax: +34 914973966; Tel: +34 914973924

Notes and references

‡ Crystal data for **9a**: $C_{12}H_{15}NO_3$, M = 221.25, monoclinic, a = 8.88460(10), b = 12.7624(2), c = 10.1950(2) Å, β = 100.7030(10)°, U = 1135.89(3) Å^3, T = 100(2) K, space group $P2_1/c$ (no. 14), Z = 4, μ(Mo–Kα) = 0.765 mm^{-1}, 4550 reflections measured, 2015 unique (R_{int} = 0.0247) which were used in all calculations. The final $R1$ and $wR2$ were 0.0348 and 0.0914 ($I > 2\sigma I$). CCDC 247411. See http://www.rsc.org/suppdata/cc/b4/b414666b/ for crystallographic data in .cif or other electronic format.

1 (*a*) T. Asao and M. Oda, *Methoden der Organischen Chemie, Houben–Weyl*, **vol. 5/2c**, pp. 710–768, Georg Thieme Verlag, Stuttgart, 1985; (*b*) M. G. Banwell, *Aust. J. Chem.*, 1991, **44**, 1–36; (*c*) F. Pietra, *Chem. Rev.*, 1973, **73**, 293–364; (*d*) T. Graening and H.-G. Schalmz, *Angew. Chem., Int. Ed.*, 2004, **43**, 3230–3256.
2 Y. Morita, E. Matsumura, T. Okabe, M. Shibata, M. Sugiura, T. Ohe, H. Tsujibo, N. Ishida and Y. Inamori, *Biol. Pharm. Bull.*, 2003, **26**, 1487–1490 and references cited therein.
3 J. Du, C. M.-H. Nie and R. L. Nie, *J. Nat. Prod.*, 1999, **62**, 1664–1665.
4 (*a*) H. G. Capraro and A. Brossi, *The Alkaloids*, 1984, **vol. 23**, pp. 1–70; (*b*) K. T. Buck, *The Alkaloids*, 1984, **vol. 23**, pp. 301–325; (*c*) W. Schuep, J. F. Blount, T. H. Williams and A. Stempel, *J. Antibiot.*, 1978, **31**, 1226–1236; (*d*) H. Morita, K. Takeya and H. Itokawa, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 597–598.
5 For general reviews, see: (*a*) T. Nozoe, *Pure Appl. Chem.*, 1971, **28**, 239–280; (*b*) P. L. Pauson, *Chem. Rev.*, 1955, **55**, 9–136.

6 (*a*) J. H. Rigby, *Tetrahedron*, 1999, **55**, 4521–4538; (*b*) H. Takeshita, H. Kawakami, Y. Ikeda and A. Mori, *J. Org. Chem.*, 1994, **59**, 6490–6492; (*c*) B. M. Trost and P. R. Seoane, *J. Am. Chem. Soc.*, 1987, **109**, 615–617.

7 (*a*) D. Mukherjee, C. R. Watts and K. N. Houk, *J. Org. Chem.*, 1978, **43**, 817–821; (*b*) J. H. Rigby, *Acc. Chem. Res.*, 1993, **26**, 579–585; (*c*) M. P. S. Ishar and R. P. Gandhi, *Tetrahedron*, 1993, **49**, 6729–6740; (*d*) J. H. Rigby, *Tetrahedron*, 1999, **55**, 4521–4538; (*e*) K. Saito, S. Ando and Y. Kondo, *Heterocycles*, 2000, **53**, 2601–2606; (*f*) K. Kumar, A. Kapur and M. P. S. Ishar, *Org. Lett.*, 2000, **2**, 787–789; (*g*) Y. Yoshitake, H. Nakagawa, M. Eto and K. Harano, *Tetrahedron Lett.*, 2000, **41**, 4395; (*h*) M. Rosenblum and J. C. Watkins, *J. Am. Chem. Soc.*, 1990, **112**, 6316–6322; (*i*) L. Isakovic, J. A. Ashenhurst and J. L. Gleason, *Org. Lett.*, 2001, **3**, 4189–4192.

8 D. Lloyd, *The Chemistry of Conjugated Cyclic Compounds*; Wiley, Chichester, 1989.

9 (*a*) V. Nair, D. Sethumadhavan, S. M. Nair, N. P. Rath and G. K. Eigendorf, *J. Org. Chem.*, 2002, **67**, 7533–7536; (*b*) J. C. Lee and J. K. Cha, *Tetrahedron*, 2000, **56**, 10175–10184; (*c*) D. L. Boger and C. E. Brotherton, *J. Am. Chem. Soc.*, 1986, **108**, 6713–6719; (*d*) H. M. L. Davis, T. J. Clark and G. F. Kimmer, *J. Org. Chem.*, 1991, **56**, 6440–6447; (*e*) C. Mak and G. Büchi, *J. Org. Chem.*, 1981, **46**, 1–3; (*f*) A. Dastan, N. Saracoglu and M. Balci, *Eur. J. Org. Chem.*, 2001, **18**, 3519–3522.

10 (*a*) J. Clayden, F. E. Knowles and C. J. Menet, *J. Am. Chem. Soc.*, 2003, **125**, 9278–9279; (*b*) K. S. Feldam and T. D. Cutarelli, *J. Am. Chem. Soc.*, 2002, **124**, 11600–11601; (*c*) M. Barbier, D. H. Barton, M. Devys and R. S. Topgi, *Tetrahedron*, 1987, **43**, 5031–5038; (*d*) D. P. Dygusch, W. P. Neumann and M. Peterseim, *Synlett.*, 1994, 363–5; (*e*) E. Hasegawa, Y. Tamura, K. Suzuki, A. Yonoeka and T. Suzuki, *J. Org. Chem.*, 1999, **64**, 8780–8785.

11 K. Doi, *Bull. Chem. Soc. Jpn.*, 1960, **33**, 887–888.

12 J. D. Hobson and J. R. Malpass, *J. Chem. Soc. C*, 1969, 1499–1503.

13 (*a*) M. C. Carreño, M. Ribagorda, A. Somoza and A. Urbano, *Angew. Chem., Int. Ed.*, 2002, **41**, 2755–2757; (*b*) M. C. Carreño, M. Pérez-González, M. Ribagorda, A. Somoza and A. Urbano, *Chem. Commun.*, 2002, 3052–3053.

14 (*a*) M. C. Carreño, G. H. Posner and M. Ribagorda, *Angw. Chem., Int. Ed.*, 2002, **41**, 2753–2755; (*b*) M. C. Carreño, M. C. García Luzón and M. Ribagorda, *Chem. Eur. J.*, 2002, **8**, 208–216; (*c*) M. C. Carreño and M. Ribagorda, *Org. Lett.*, 2003, **5**, 2425–2428.

15 M. C. Carreño and M. Ribagorda, *J. Org. Chem.*, 2000, **65**, 1231–1234.

16 Tropone **9a** was isolated as a pale yellow solid that was subjected to X-ray crystallographic analysis.‡ General Procedure for the reactions summarized in Table 1: To a THF solution (0.2 M) of the corresponding *p*-quinamine **5–8** (0.1 mmol), under an argon atmosphere, 4 equiv. of NaH were added at room temperature. After stirring for the time indicated in each case, the mixture was diluted with CH_3CN and filtered over Celite. The solvents were removed under reduced pressure and the crude purified by flash column chromatography on silicagel (hexane–EtOAC) or on BondElut LRC-SCX (see supporting information for spectrospcopic data).

17 D. A. Evans, D. J. Hart and P. M. Koelsch, *J. Am. Chem. Soc.*, 1978, **100**, 4593–4594.

18 Basic elimination of sulfenic acid has been observed from *N*-sulfinylaziridines: (*a*) F. A. Davies, H. Liu, C.-H. Liang, G. Venkat Reddy, Y. Zhang, T. Fang and D. D. Titus, *J. Org. Chem.*, 1999, **64**, 8929–8935; (*b*) E. Hecker and R. Lattrell, *Justus Liebigs Ann. Chem.*, 1963, **662**, 48–66.

19 (*a*) O. L. Chapman, *Adv. Photochem.*, 1963, **1**, 323–420; (*b*) L. Calucci, M. Cavazza, C. A. Veracini and M. Zandomeneghi, *J. Photochem. Photobiol., A*, 1998, **117**, 43–50.