A Route to 6-Functionalised 1,3-Diaza-azulenes and Aminotropones *via* Hydride Replacement from Cycloheptatrienones

By **Marino Cavazza, Renzo Cabrino, Francesco Del Cima,** and **Francesco Pietra,*** Department of Chemistry, Università di Pisa, 56100 Pisa, and Facoltà di Scienze, Libera Università di Trento, 38050 POVO (Trento), Italy

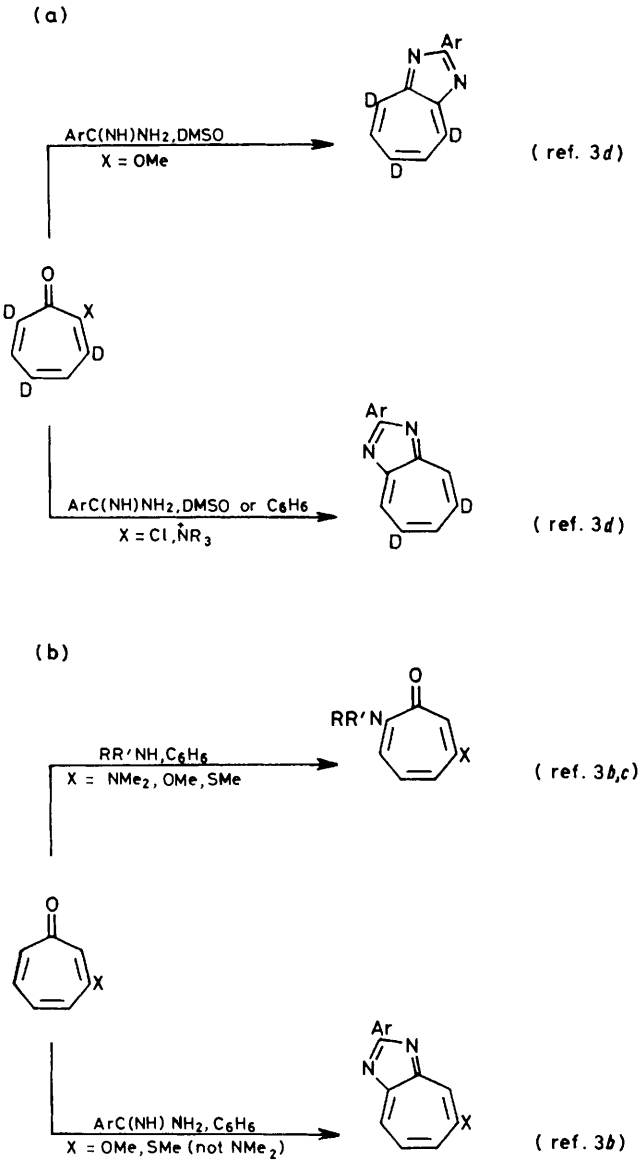
4-Methylthiotropone regiospecifically cyclises with toluamidine in benzene, but less readily in dimethyl sulphoxide, to give 6-methylthio-2-*p*-tolyl-1,3-diaza-azulene. With dimethylamine hydride replacement occurs in dimethyl sulphoxide (but not in benzene) at both C(7) and C(2) (*ca.* 1 : 1 ratio) to give the corresponding amino(methylthio)tropones which are slowly de(methylsulphenyl)ated in the reaction medium. This reaction is favoured by oxidising agents such as potassium ferricyanide. In contrast, 4-methoxy-, 4-dimethylamino-, and 2-dimethylamino-substituents inhibit reactions by both amidines and amines with the cycloheptatrienone nucleus. Further attempts directed at obtaining 4-functionalized 1,3-diaza-azulenes failed because both 2-ethylthiotropone and 2-dimethylsulphoniotropone tetrafluoroborate cyclise with benzamidine to give the corresponding 1,3-diaza-azulene with loss of sulphur.

RECENTLY, as a prelude to a total synthesis of zoanthoxanthins, marine metabolites incorporating the 1,3-diaza-azulene unit,[1]† we have studied additions and cyclisations with the cycloheptatrienone nucleus.[3] Methods have been devised to condense amidines regiospecifically with cycloheptatrienones carrying mobile groups at C-2 to give 1,3-diaza-azulenes. Thus, an electron-attracting group, such as Cl or R_3N^+, at C(2) induces clean cyclisation at C(7)–C(1), whereas a mesomerically electron-donating group, such as OMe, induces clean cyclisation (albeit much more slowly) at C(2)–C(1) [Scheme 1(a)].[3d]

The subsequent discovery that cycloheptatrienones carrying NMe_2,[3c] OMe,[3b] or SMe [3b] groups at C-3 undergo regiospecific nuclear hydride replacement at C-7 by primary or secondary amines [Scheme 1(b)] was combined with the above findings to give a novel synthesis of 1,3-diaza-azulenes functionalized at C-5 [Scheme 1(b)].[3b]

A logical extension of these studies was to attempt the synthesis of 1,3-diaza-azulenes functionalized at either C-6 or -4. We report here both on the success with the first proposal and the lack of success with the second, as well as on the complete non-regiospecificity in the corresponding aminations which were followed by unusual de(methylsulphenyl)ation.

We have found that a suitable substrate for 6-functionalized 1,3-diaza-azulenes is 4-methylthiotropone. In fact, whereas both the dimethylamino-group and the methoxy-group, which had previously proved suitable for functionalization at C(5) [Scheme 1(b)],[3b] rendered the cycloheptatrienone nucleus unreactive towards arylamidines in both benzene and dimethyl sulphoxide (DMSO), 4-methylthiotropone, with a two-fold molar excess of toluamidine in benzene at reflux for 24 h, gave 6-methylthio-2-*p*-tolyl-1,3-diaza-azulene in *ca.* 10% yield [Scheme 2(a)]. No trace of isomeric materials was detected.



SCHEME 1

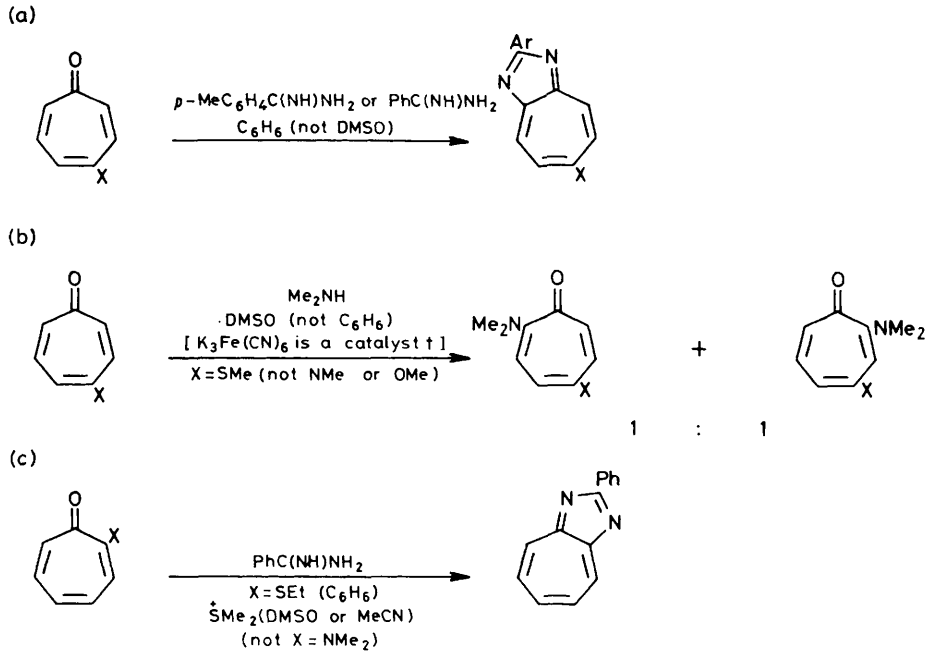
† An elegant synthesis based on a different strategy has been reported.[2]

[1] L. Cariello, S. Crescenzi, G. Prota, and L. Zanetti, *Tetrahedron*, 1974, **30**, 3611.
[2] M. Braun and G. Büchi, *J. Amer. Chem. Soc.*, 1976, **98**, 3049.
[3] (*a*) V. Farina, M. Cavazza, R. Cabrino, C. A. Veracini, and F. Pietra, *Tetrahedron Letters*, 1976, 1319; (*b*) F. del Cima, M. Cavazza, C. A. Veracini, and F. Pietra, *ibid.*, 1975, 4267; (*c*) B. Ricciarelli, R. Cabrino, F. del Cima, C. A. Veracini, and F. Pietra, *J.C.S. Chem. Comm.*, 1974, 723; (*d*) R. Cabrino, B. Ricciarelli, and F. Pietra, *Tetrahedron Letters*, 1974, 3069.

The structure was assigned by ^1H n.m.r. spectroscopy with the aid of $Eu(fod)_3$ as a chemical-shift reagent Thus, the n.m.r. spectrum (see Experimental section), from which the two methyl groups are clearly identified, showed splitting of the multiplet at 8.4 p.p.m. into two doublets ($J = 8.5$ Hz) on addition of the europium complex. Two AB quartet patterns are only compatible with the symmetrical diaza-azulene structure [see Scheme 2(a); Ar = 4-MeC_6H_4] and clearly incompatible with the isomeric 5-methylthio isomer, which could only display one AB quartet pattern with its benzenoid moiety.

The behaviour of benzamidine towards 4-methylthiotropone was similar, although the structure of the product [Scheme 2(a); Ar = Ph] was not investigated as closely as that for the toluamidino-analogue owing to the complexity of the n.m.r. spectrum. However, because of a single spot in chromatography and the analogy with the toluidino-case above, we can safely assume the structure shown in Scheme 2 (a; Ar = Ph).

Attempts directed to obtain 1,3-diaza-azulenes functionalized at C(4) failed. We thought that the best chance of obtaining such an annelation reaction was for two- and three-co-ordinated sulphur substituents at C-2, which were known both to activate the seven-membered ring and to resist replacement.[4] However, as shown at Scheme 2(c), with either the ethylthio or the dimethylsulphonio-group at C(2), cyclisation occurs with loss of the C(2) substituent. We have not investigated this to see whether it is a case of C(2)–C(1) condensation, as with 2-methoxytropone [Scheme 1(a)],[3d] or proton removal from C(7), as previously found for activating groups at C(2).[3d,5] In fact we had already established methods for both C(2)–C(1) and C(7)–C(1) condensation with loss of the C-2 substituent [Scheme 1(a)]. However, if condensation at C(2)–C(1) occurred, which could be checked by means of deuteriated substrates,[3d,5]



SCHEME 2

† The product isomeric ratio in the catalysed reaction has not been determined.

the alkylthio-group is superior to the alkoxy-group as indicated by the higher yields of products. With the sulphonium salt yields of the 1,3-diaza-azulene were very poor, perhaps because the most appropriate solvent for such reactions, benzene, could not be used because of insolubility of the sulphonium salt.

We have also tried aminations of 4-functionalized cycloheptatrienones. As with amidinations, 4-dimethylamino- and 4-methoxy-groups inhibit amination, even in the presence of potassium ferricyanide. In contrast amination occurs with the 4-methylthio substituent, being favoured, in accordance with our earlier proposals,[3c] by addition of oxidising agents [Scheme 2(b)]. However, it is interesting that, in contrast with the corresponding amidination, which occurs in benzene with complete regiospecificity [Scheme 2(a)], amination with dimethylamine does not proceed in benzene but requires DMSO as a medium, giving a mixture of both α- and α′-isomers in a *ca.* 1 : 1 ratio [Scheme 2(b)]; these could not be separated by t.l.c.

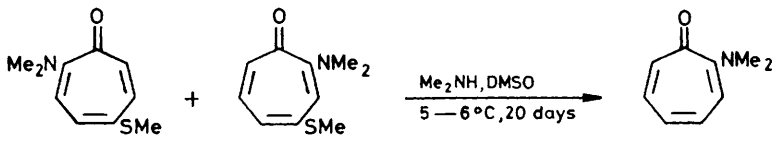
The basis of the structural assignment is the u.v.

[4] (*a*) C. A. Veracini and F. Pietra, *J.C.S. Chem. Comm.*, 1974, 623; (*b*) M. Cavazza, C. A. Veracini, and F. Pietra, *Tetrahedron Letters*, 1975, 2085.

[5] G. Biggi, F. del Cima, and F. Pietra, *J. Amer. Chem. Soc.*, 1973, **95**, 7101; 1972, **94**, 4700.

spectrum, characteristic of 2-aminotropones [6] the mass spectrum, which shows the expected molecular ion, and the ^{1}H n.m.r. spectrum, which is consistent with the presence of two different dimethylamino-groups (four singlets in the expected integration ratio). Further, the above mixture of isomers is de(methylsulphenyl)ated to the known 2-dimethylaminotropone,[7] the structure of which was confirmed by ^{1}H n.m.r. spectroscopy (Scheme 3).

We have also found that a 2-dimethylamino-group on the cycloheptatrienone nucleus inhibits amination and amidination, both in dimethyl sulphoxide and



1 : 1

SCHEME 3

benzene and with forcing conditions, such as high temperature or added potassium ferricyanide.

In general, it is clear that the above processes are favoured by two-co-ordinated sulphur as a ring substituent owing to either the great polarizability of sulphur or the participation of its 3*d* orbitals in accepting the extra negative charge brought into the seven-membered ring by the nucleophile.[8] It is also understandable that hydride removal requires an oxidising agent,[9] which may be the troponoid itself [3c] (a process reminiscent of hydride removal from Janovsky-type complexes by polynitroaromatics [9]), or an added oxidising agent, such as potassium ferricyanide, as in the present work.

Also, it is understandable that deactivating [5] groups such as dimethylamino or methoxy-groups at C(4), *i.e.* groups which mesomerically tend to give electrons to the ring, inhibit nucleophilic attack to the ring, thus added oxidising agents having no chance to affect the process.

EXPERIMENTAL

M.p.s were taken on a Kofler hot-stage apparatus and are uncorrected. U.v. spectra were obtained with a Unicam SP 800 spectrophotometer. Mass spectra were taken with a Varian MAT-CH7 spectrometer. ^{1}H N.m.r. spectra were obtained with either a Varian T-60 or a JEOL PS 100 spectrometer. Chemical shifts are given with respect to tetramethylsilane as an internal standard.

6-Methylthio-2-p-tolyl-1,3-diaza-azulene.—To a solution of 4-methylthiotropone [10] (0.080 g, 0.59 mmol) in benzene (2 ml) was added toluidine (0.130 g, 1.2 mmol) in benzene (10 ml). The mixture was refluxed for 24 h under nitrogen after which the solvent was evaporated *in vacuo*. The residue was chromatographed on a silica gel layer [eluant benzene–diethyl ether–ethanol (75 : 20 : 5)]. The yellow band at R_F 0.65 was extracted with chloroform, the solvent evaporated *in vacuo* and the residue chromatographed again as above [eluant benzene–diethyl ether (60 : 40)] to give yellow crystals, m.p. 165—169 °C (0.0152 g, 10%) (Found: C, 72.0; H, 5.4; N, 10.3; S, 11.9. $C_{16}H_{14}N_2S$ requires C, 72.1; H, 5.3; N, 10.5; S, 12.0%), $\lambda_{max.}$(EtOH) 323 and 370 nm; δ(CDCl$_4$) 2.42 (3 H, s), 2.70 (3 H, s), 7.20 (2 H, d, J = 8.5 Hz), 7.62 (2 H, d, J = 8.5 Hz), and 8.4 (4 H, m), see text for assignment.

6-Methylthio-2-phenyl-1,3-diaza-azulene.—The reaction of 4-methylthiotropone (0.080 g, 0.52 mmol) with benzamidine (0.16 g, 1.33 mmol) was run as in the above case of toluamidine to give 0.014 g (11%) of a yellow oil (Found: C, 71.2; H, 4.9. $C_{15}H_{12}N_2S$ requires C, 71.4; H, 4.8%), $\lambda_{max.}$(EtOH) 318 and 363 nm; δ 2.5 (3 H, s), 7.4 (3 H, m), 7.7 (2 H, m), and 8.5 (4 H, m).

Cyclisation of 2-Ethylthiotropone with Benzamidine.—To a solution of 2-ethylthiotropone (0.033 g, 0.2 mmol) in dried benzene (2 ml) was added under N_2 a solution of benzamidine (0.096 g, 0.8 mmol) in benzene (8 ml). The mixture was refluxed for 10 h, after which the solvent was evaporated and the residue was chromatographed on a silica gel layer [eluant benzene–ethanol (80 : 20)]. The yellow band at R_F 0.6 gave 0.03 g (60%) of 1,3-diaza-azulene.[3d]

Cyclisation of Benzamidine with 2-Dimethylsulphoniotropone Tetrafluoborate. To a solution of 2-dimethylsulphoniotropone tetrafluoborate [4b] (0.046 g, 0.18 mmol) in dried DMSO (1 ml) was added, under N_2 with stirring, benzamidine (0.056 g, 0.46 mmol) in DMSO (1 ml). After 1 h the mixture was chromatographed on a silica gel layer [eluant benzene–ethanol (80 : 20)], to give several coloured bands. That at R_F 0.6 gave 0.0014 g (3%) of 1,3-diaza-azulene.[3d]

Reaction of Dimethylamine with 4-Methylthiotropone.—(i) *With immediate isolation of the products.* To a solution of 4-methylthiotropone [12] (0.093 g, 0.69 mmol) in DMSO (9 ml) (carefully distilled under N_2 over calcium hydride at 100 mmHg through a Vigreux column and collected over molecular sieves) was added at room temperature, under N_2, dimethylamine (1.5 ml). After 6 h excess of amine and DMSO were evaporated off at 1 mmHg. The residue dissolved in a little chloroform was twice chromatographed on a silica gel layer [first eluant benzene–diethyl ether–ethanol (75 : 20 : 5) yellow band at R_F 0.3; second eluant benzene–acetonitrile (40 : 60)]. Extraction with chloroform followed by sublimation on a water-cooled finger at 0.2 mmHg and 60 °C gave 0.015 g (11%) of a *ca.* 1 : 1 oily mixture of 2-dimethylamino-5-methylthiotropone and

[6] F. Pietra, *Chem. Rev.*, 1973, **73**, 293.
[7] T. Nozoe, S. Seto, H. Tokeda, S. Morosoiva, and K. Matsumoto, *Sci. Reports Tohoku Univ. I*, 1952, **36**, 126.
[8] N. L. Allinger, M. P. Cava, D. C. de Jongh, C. R. Johnson, N. A. Lebel, and C. L. Stevens, 'Organic Chemistry,' 2nd edn., Worth Publishers, New York, 1976, p. 219.
[9] O. N. Chupaklin and I. Ya. Postowskii, *Russian Chem. Rev.*, 1976, **45**, 454.
[10] R. L. Shriner and F. W. Neumann, *Chem. Rev.*, 1944, **35**, 351.

2-dimethylamino-4-methylthiotropone (Found: C, 61.0; H, 6.5. $C_{10}H_{13}NOS$ requires C, 61.6; H, 6.7%), $\lambda_{max.}$(EtOH) 310 and 367 nm; δ($CDCl_3$, at 60 MHz) 2.35 (3 H, s), 2.38 (3 H, s), 2.95 (6 H, s), 2.98 (6 H, s), and 6—7 (4 H, m). In hexadeuteriobenzene the two groups of singlets are better separated (6 Hz between the two 3 H singlets and 2 Hz between the last two); *m/e* 195 (100%).

(ii) *After the reaction mixture had been set aside.* The reaction was carried out as above in (i), with 0.181 g (1.2 mmol) of 4-methylthiotropone, 7.5 ml of dimethylamine, and 30 ml of DMSO. However, before work-up the mixture was left at 5—6 °C (as a liquid) for 20 days. The mixture was evaporated under vacuum and the residue was twice chromatographed on a silica gel layer [eluant benzene–diethyl ether–n-hexane–methanol (70 : 15 : 8 : 7)]. The yellow band at R_F 0.45 gave 0.021 g (12%) of 2-dimethylaminotropone.[7] This de(methylsulphenyl)ation was also proved to occur on a specimen of a 1 : 1 mixture of 2-amino-4- and 2-amino-5-methylthiotropone in DMSO in the presence of an excess of dimethylamine.

[7/605 *Received, 5th April,* 1977]