Ring Closure of *ortho*-Blocked 4-Aryl-1,2,4-triaza-1,3-dienes *via* 1,6-Electrocyclisation followed by Diels–Alder Dimerisation

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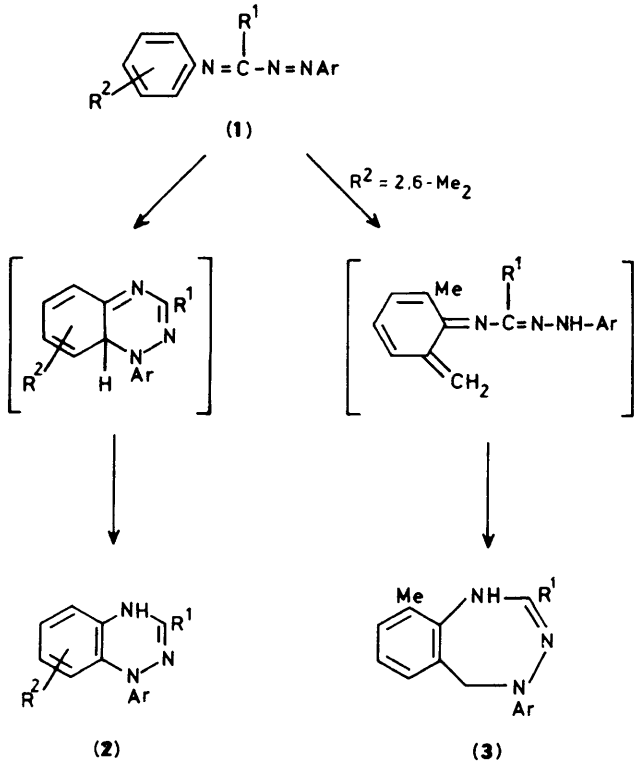
1-Acyl-4-(2,6-dimethylphenyl)-1,2,4-triaza-1,3-dienes (**7**), generated *in situ* upon manganese dioxide oxidation of the corresponding *N*-acyl-*N'*-(2,6-dimethylphenylaminomethylene)hydrazines (**6**), give the bridged heterocyclic compounds (**10**) *via* 1,6-electrocyclisation followed by Diels–Alder dimerisation. The isonitrile (**8**) is also obtained as a minor fragmentation product.

1,4-Diaryl-1,2,4-triaza-1,3-dienes (**1**) (*C*-arylazoanils) have been shown to afford upon heat treatment 1,4-dihydro-1,2,4-benzotriazines (**2**), the formation of which is explicable in terms of 1,6-electrocyclisation followed by hydrogen shift to restore the aromaticity of the system.[1–4] However, in cases where the *ortho* positions of the 4-aryl ring are both occupied by methyl (or ethyl) groups,[5,6] another pathway has been observed, *i.e.* formation of 1,3,4-benzotriazepines (**3**) through tautomerisation and subsequent 1,7-cyclisation (Scheme 1).



Scheme 1.

We now describe a new pattern of behaviour we have observed on studying the related *ortho*-blocked substrates (**7a**—**d**), which bear a different kind of substitution at the azo moiety (Scheme 2).

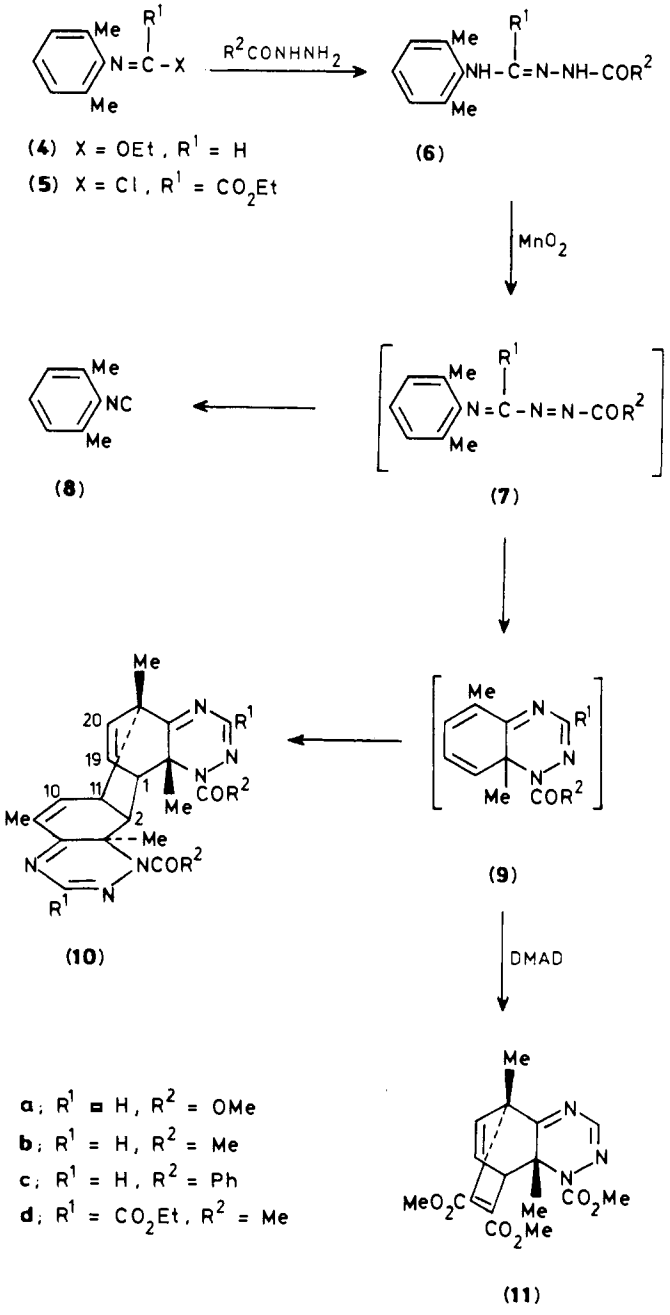
Results and Discussion

By analogy with previously reported substrates,[5,6] the species (**7a**—**d**) were thought to be accessible upon manganese dioxide oxidation of the corresponding amidrazones (**6a**—**d**), the syntheses of which were accomplished by treating the appropriate hydrazine derivatives with the imino ether (**4**) or the imino chloride (**5**). The amidrazones (**6a**—**d**) were found to react with manganese dioxide in dichloromethane or chloroform solution at room temperature; however, in line with the electron-withdrawing effect of the acyl substituents, their disappearance required much longer times than those reported for aryl-hydrazones. In all cases, work-up of the reaction mixture did not furnish the expected azo derivative (**7**), but gave the corresponding dimeric product (**10**) along with a minor amount of isonitrile (**8**).[7] The structures (**10a**—**d**) were based on analytical and spectral data and were confirmed on submitting one of them (**10b**) to an *X*-ray diffraction study.[8] The observed interproton couplings (see Table 1) are particularly worthy of noting since they reflect the peculiar values of the corresponding dihedral angles, as normally found for non-flexible bridged structures. Thus, no coupling was discernible between the nearly orthogonal hydrogens in positions 1 and 2.†

The formation of compounds (**10a**—**d**) can be rationalised by the following sequence: (i) oxidation of the starting amidrazones to the corresponding azo derivatives (**7a**—**d**), (ii) 1,6-electrocyclisation of the latter with concomitant loss of aromaticity of the benzene ring, and (iii) Diels–Alder dimerisation of the so-formed dienes (**9a**—**d**) as already observed for 6,6-disubstituted cyclohexa-2,4-dienones.[10] To gain evidence in favour of this mechanistic picture, the progress of the reactions between (**6a**—**d**) and manganese dioxide was monitored by t.l.c. In all cases, a primary product (giving a yellow spot on the thin layer) was shown, but its lability precluded isolation. However, when the reaction of (**6a**) was carried out in deuteriochloroform and submitted to periodic n.m.r. analysis, the spectra taken at intermediate times showed a set of signals which disappeared in the final mixture. These signals [δ 1.30(s), 2.10(s), 3.94(s), 6.13 (dd, *J* 10 and 7 Hz), 6.47 (d, *J* 7 Hz), 7.24 (d, *J* 10 Hz), and 7.72(s)] fit well to structure (**9a**). The intermediacy of this species was also proved by trapping it with dimethyl acetylenedicarboxylate to give the Diels–Alder adduct (**11**). It should be noted that the dimerisation of (**9**), which involves the less encumbered ethylenic bond as a dienophilic site, proceeds with regiospecificity and facial stereospecificity. As molecular models indicate, the observed products correspond to the topography of this approach, which leaves the bulky moieties as far as possible from each other.

When comparing the behaviour of the species (**7a**—**d**) with that of similar *ortho*-blocked substrates of formula (**1**),[5,6] a

† The reported n.m.r. spectra of dimers of cyclohexa-2,4-dienone derivatives may be used for comparison.[9]



Scheme 2.

striking difference is observed. In fact, the species (**7a**—**d**) are much more reactive and do not undergo any ring closure other than 1,6-electrocyclisation on the *ortho* position of the 4-aryl group, despite the absence of *ortho*-hydrogens precluding the restoration of the aromaticity. This dichotomy in behaviour must be related to the presence of acyl rather than aryl substituents in position **1**, but the actual factor responsible for it is not easy to recognise. The electron-withdrawing effect of the acyl groups is a plausible candidate on considering that the energy barrier for the 1,6-cyclisation could decrease as the polarisation of the heteropolyene system is enhanced.[11] Two facts are in accordance with this view: (i) the conversion of (**1**) into (**2**) was facilitated by preliminary protonation[1] and (ii) 1,6-cyclisation with concomitant destruction of the aromaticity has already been documented for *C*-nitrosoanils (4-aryl-1-oxa-2,4-diaza-1,3-dienes).[9] On the other hand, it is to be mentioned that electron-poor (*viz.* nitro substituted) aryl groups did not exhibit the same pattern of behaviour, but only accelerated the formation of benzotriazepines (**3**).[5,6] Owing to the spatial requirements for attaining the transition state leading to (**9**), it may be that steric factors intervene to play a significant role.

Finally, the formation of the isonitrile (**8**), which has no direct precedent in the literature, can be ascribed to a fragmentation reaction of (**7**), probably involving extrusion of nitrogen as frequently observed for azo compounds.[12] However, little can be said on the intimate mechanism of the concomitant loss of the ethoxycarbonyl group which occurs in the reaction of (**7d**).

Experimental

M.p.s were determined on a Büchi apparatus and are uncorrected. N.m.r. spectra were recorded on Varian EM-390 or Bruker WP80SY instruments; chemical shifts are given in p.p.m. from internal $SiMe_4$. I.r. spectra were recorded on a Perkin-Elmer 377 spectrophotometer.

Activated manganese dioxide was obtained commercially (Fluka).

N-(2,6-*Dimethylphenylaminomethylene*)-N′-*methoxycarbonylhydrazine* (**6a**).—A solution of compound (**4**)[13] (40 g) and methoxycarbonylhydrazine[14] (20 g) in chloroform (150 ml) was stirred at room temperature for 54 h. The solvent was removed under reduced pressure, and the residue was washed with light petroleum and recrystallised from aqueous ethanol to afford the amidrazone (**6a**) (17 g, 34%), m.p. 173—175 °C (Found: C, 59.5; H, 6.9; N, 18.8. $C_{11}H_{15}N_3O_2$ requires C, 59.7; H, 6.8; N, 19.0%); $\nu_{max.}$(Nujol) 3 200 and 1 700 cm^{-1}; δ[$(CD_3)_2SO$] 2.22 (6 H, s), 3.68 (3 H, s), 6.40 (1 H, m), 7.05 (3 H, H, br s); *m/z* 221 (M^+).

N-*Acetyl*-N′-(2,6-*dimethylphenylaminomethylene*)*hydrazine* (**6b**).—A solution of compound (**4**) (40 g) and acetylhydrazine[15] (16 g) in dichloromethane (225 ml) was stirred at room temperature for 54 h. The solvent was evaporated under reduced pressure and the residue was washed with light petroleum and then recrystallised from ethanol to give the amidrazone (**6b**) (23 g, 51%), m.p. 198—200 °C (Found: C, 64.6; H, 7.3; N, 20.4. $C_{11}H_{15}N_3O$ requires C, 64.4; H, 7.4; N, 20.5%); $\nu_{max.}$(Nujol) 3 190 and 1 670 cm^{-1}; δ[$(CD_3)_2SO$] 2.20 (3 H, s), 2.32 (6 H, s), 6.41 (1 H, m), 7.10 (3 H, m), 7.6 (1 H, br s), and 11.2 (1 H, br s); *m/z* 205 (M^+).

Evaporation of the light petroleum followed by recrystallisation from ethanol gave *N*,*N*′-bis(2,6-dimethylphenyl)formamidine[16] (1.2 g).

N-*Benzoyl*-N′-(2,6-*dimethylphenylaminomethylene*)*hydrazine* (**6c**).—A solution of (**4**) (10 g) and benzoylhydrazine[15] (9.0 g) in dichloromethane (160 ml) was stirred at room temperature for 30 h. The solid material was filtered off and recrystallised from methanol–chloroform to afford the amidrazone (**6c**) (12.5 g, 79%), m.p. 221—222 °C (Found: C, 71.7; H, 6.6; N, 15.7. $C_{16}H_{17}N_3O$ requires C, 71.9; H, 6.4; N, 15.7%); $\nu_{max.}$(Nujol) 3 190 and 1 660 cm^{-1}; δ[$(CD_3)_2SO$] 2.32 (6 H), 7.08 (3 H, s), 7.3—7.6 (3 H, m), 7.7—7.9 (3 H, m), and 10.5 (2 H, br s); *m/z* 267 (M^+).

Ethyl 2-*Chloro*-2-(2,6-*dimethylphenylimino*)*acetate* (**5**).—A mixture of ethyl *N*-(2,6-dimethylphenyl)oxamate[17] (16 g) and thionyl chloride (36 g) was gently refluxed for 45 h. The excess of thionyl chloride was removed under reduced pressure and the residue was distilled under reduced pressure to give the imino chloride (**5**) (63%), b.p. 115—120 °C/0.1 mmHg; $\nu_{max.}$(film) 1 740 cm^{-1}; δ($CDCl_3$) 1.43 (3 H, t), 2.10 (6 H, s), 4.48 (2 H, q), and 7.07 (3 H, s).

Table. ^{1}H N.m.r. data of 4,5,7,14,16,17-hexa-azapentacyclo[10.6.2.0^{2,11}. 0^{3,8}. 0^{13,18}]icosa-5,7,9,13,15,19-hexaenes (**10a—d**) (δ values in $CDCl_3$)

Compd.	CH_3C	CH_3C=[a]	11-H[b,c,d]	2-H	1-H[e]	20-H[f]	10-H[g]	19-H	R^1	R^2
	1.17s	1.96m	2.78m	3.85d	4.37d	5.75d	6.12m	6.32dd	7.15s (1 H)	4.00s (6 H)
(**10a**)	1.61s								7.59s (1 H)	
	1.76s									
	1.03s	1.81m	2.62m	3.90d	4.38d	5.67d	6.01m	6.24dd	7.00s (1 H)	2.23s (3 H)
(**10b**)[h]	1.50s								7.39s (1 H)	2.29s (3 H)
	1.61s									
	1.26s	1.95m	2.87m	4.33d	4.56d	5.80d	6.13m	6.36dd	7.03s (1 H)	
(**10c**)	1.64s								7.1—7.8m (11 H)	
	1.83s									
(**10d**)	1.13s	2.01m	2.80m	3.88d	*i*	5.76d	6.12m	6.27dd	1.44t (6 H)	2.47s (3 H)
	1.72s (6 H)								4.40q (4 H)	2.52s (3 H)

[a] (Homo)allylic couplings with H-10 and H-11 (*J* 1—2 Hz). [b] Double doublet on irradiation of the methyl group in position 9. [c] $J_{2,11}$ 8 Hz. [d] $J_{10,11}$ 4 Hz. [e] $J_{1,19}$ 7 Hz. [f] $J_{19,20}$ 7.5 Hz. [g] Doublet on irradiation of the methyl group in position 9. [h] ^{13}C N.m.r. ($CDCl_3$): δ 15.9q, 17.4q, 18.4q, 23.5q, 23.6q, 26.2q, 41.7d, 41.8d, 48.2d, 49.6s, 57.3s, 58.2s, 132.1d, 134.7d, 134.9s, 135.6d, 137.3d, 138.9d, 170.5s, 174.6s, 175.8s, and 178.9s. [i] Overlaid by the signal of the ethyl group.

Ethyl 2-Acetylhydrazono-2-(2,6-dimethylphenylamino)acetate (**6d**).—A solution of compound (**5**) (4.6 g) and acetylhydrazine (3.0 g) in dichloromethane (200 ml) was refluxed for 6 h. The reaction mixture was washed with water, dried (Na_2SO_4), and evaporated. The residue was treated with light petroleum and filtered to afford the amidrazone (**6d**) (0.70 g, 13%), m.p. 183—185 °C (from di-isopropyl ether) (Found: C, 60.8; H, 6.8; N, 15.0. $C_{14}H_{19}N_3O_3$ requires C, 60.6; H, 6.9; N, 15.2%); $\nu_{max.}$(Nujol) 3 180, 1 740, and 1 660 cm^{-1}; δ[$(CD_3)_2SO$] 0.90 (3 H, t), 2.20, 2.26 (9 H, two s), 3.97 (2 H, q), 7.08 (3 H, s), 7.9 (1 H, br s), and 9.9 (1 H, br s).

Reaction of the Amidrazone (**6a**) *with Manganese Dioxide.*—A solution of the amidrazone (**6a**) (3.3 g) in chloroform (330 ml) was treated with activated manganese dioxide (6.6 g) and stirred at room temperature for 48 h. The undissolved material was removed by filtration through Celite, the filtrate evaporated under reduced pressure, and the residue was heated at 30—35 °C *in vacuo* (0.1 mmHg) to give a white sublimate of the isonitrile (**8**) (0.18 g, 9%), m.p. 76 °C (lit.,[7] 73 °C); δ($CDCl_3$) 2.42 (6 H, s) and 7.10 (3 H, s). The remaining solid was washed with light petroleum and recrystallised from methanol to afford compound (**10a**) (1.7 g, 52%), m.p. 182 °C (Found: C, 60.4; H, 6.1; N, 19.3. $C_{22}H_{26}N_6O_4$ requires C, 60.3; H, 6.0; N, 19.2%); $\nu_{max.}$(Nujol) 1 725 and 1 705 cm^{-1}; *m/z* 438 (M^+); see Table.

Reaction of the Amidrazone (**6b**) *with Manganese Dioxide.*—A solution of the amidrazone (**6b**) (20 g) in dichloromethane (2 l) was treated with activated manganese dioxide (60 g) and stirred at room temperature for 48 h. The reaction mixture was worked up as described in the preceding preparation to afford the isonitrile (**8**) (1.4 g, 11%) and the dimer (**10b**) (13 g, 65%), m.p. 171 °C (from methanol) (Found: C, 65.2; H, 6.4; N, 20.7. $C_{22}H_{26}N_6O_2$ requires C, 65.0; H, 6.4; N, 20.7%); $\nu_{max.}$(Nujol) 1 690 and 1 675 cm^{-1}; see Table.

Reaction of the Amidrazone (**6c**) *with Manganese Dioxide.*—A solution of the amidrazone (**6c**) (2.0 g) in dichloromethane (400 ml) was treated with activated manganese dioxide (6.0 g) and stirred at room temperature for 30 h. The undissolved material was removed by filtration through Celite and the filtrate was evaporated under reduced pressure. Treatment of the residue with light petroleum–diethyl ether (1:1) gave the dimer (**10c**) (0.44 g, 22%), m.p. 184 °C (from methanol) (Found: C, 72.4; H, 5.9; N, 15.7. $C_{32}H_{30}N_6O_2$ requires C, 72.4; H, 5.7; N, 15.8%); $\nu_{max.}$(Nujol) 1 680 and 1 665 cm^{-1}; see Table. The residue from the mother liquor was chromatographed on a silica gel column with light petroleum–diethyl ether (1:1) as eluant to afford the isonitrile (**8**) (0.17 g, 17%) followed by a further amount of (**10c**) (0.22 g, 11%).

Reaction of the Amidrazone (**6d**) *with Manganese Dioxide.*—A solution of (**6d**) (0.60 g) in dichloromethane (60 ml) was treated with activated manganese dioxide (1.8 g) and stirred at room temperature for 24 h. After filtration through Celite, the filtrate was evaporated under reduced pressure and the residue was chromatographed on a silica gel column with dichloromethane–methanol (19:1) as eluant to give the isonitrile (**8**) (22 mg, 8%) and the dimer (**10d**) (0.25 g, 42%), m.p. 187 °C (from di-isopropyl ether) (Found: C, 59.5; H, 6.3; N, 16.1. $C_{26}H_{34}N_6O_6$ requires C, 59.3; H, 6.5; N, 16.0%); $\nu_{max.}$(Nujol) 1 730 and 1 690 cm^{-1}; see Table.

Trapping of the Diene (**9a**) *with Dimethyl Acetylenedicarboxylate.*—A solution of the amidrazone (**6a**) (1.5 g) in chloroform (150 ml) was treated with activated manganese dioxide (3.0 g) and stirred at room temperature for 5 h. After filtration through Celite, the solution was treated with dimethyl acetylenedicarboxylate (2.4 g) and left at room temperature for 48 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with benzene—ethyl acetate (1:1) as eluant. First fractions gave some dimethyl acetylenedicarboxylate followed by the isonitrile (**8**) (50 mg, 6%). Subsequent fractions contained 1,7-dimethyl-6,9,10-trimethoxycarbonyl-3,5,6-triazatricyclo[6.2.2.0^{2,7}]-dodeca-2,4,9,11-tetraene (**11**) (0.70 g, 29%), m.p. 142 °C (from di-isopropyl ether) (Found: C, 56.3; H, 5.4; N, 11.5. $C_{17}H_{19}N_3O_6$ requires C, 56.5; H, 5.3; N, 11.6%); $\nu_{max.}$(Nujol) 1 710 cm^{-1}; δ($CDCl_3$) 1.20 (3 H, s), 1.70 (3 H, s), 3.85, 3.94, 3.98 (9 H, three s), 5.65 (1 H, dd, *J* 7 and 1.5 Hz), 6.27 (1 H, dd, *J* 7.5 and 1.5 Hz), 6.78 (1 H, dd, *J* 7.5 and 7 Hz), and 7.51 (1 H, s); *m/z* 361 (M^+). Further elution provided the dimer (**10a**) (0.64 g, 42%).

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