Formation of isomeric pyrrolones by flash vacuum pyrolysis of bisaminomethylene derivatives of Meldrum's Acid

Hamish McNab* and Mark Morrow

Department of Chemistry, The University of Edinburgh,
West Mains Road Edinburgh EH9 3JJ.
E-mail: H.McNab@ed.ac.uk

For Al Padwa, on the occasion of his 65th birthday

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Abstract

The bisaminomethylene derivatives, 7a–7c, of Meldrum's acid were made by reaction of appropriate N-methylaniline derivatives with the chloro-compound 15. Under flash vacuum pyrolysis (FVP) conditions (600 °C, 0.005 Torr), 7a–7c were transformed into mixtures of the pyrrolones 10a–10c and 12a–12c. The ratio of 10:12 is essentially independent of the nature of a *para*-substituent on the aryl ring; the implications of this result on the mechanism of the process are discussed

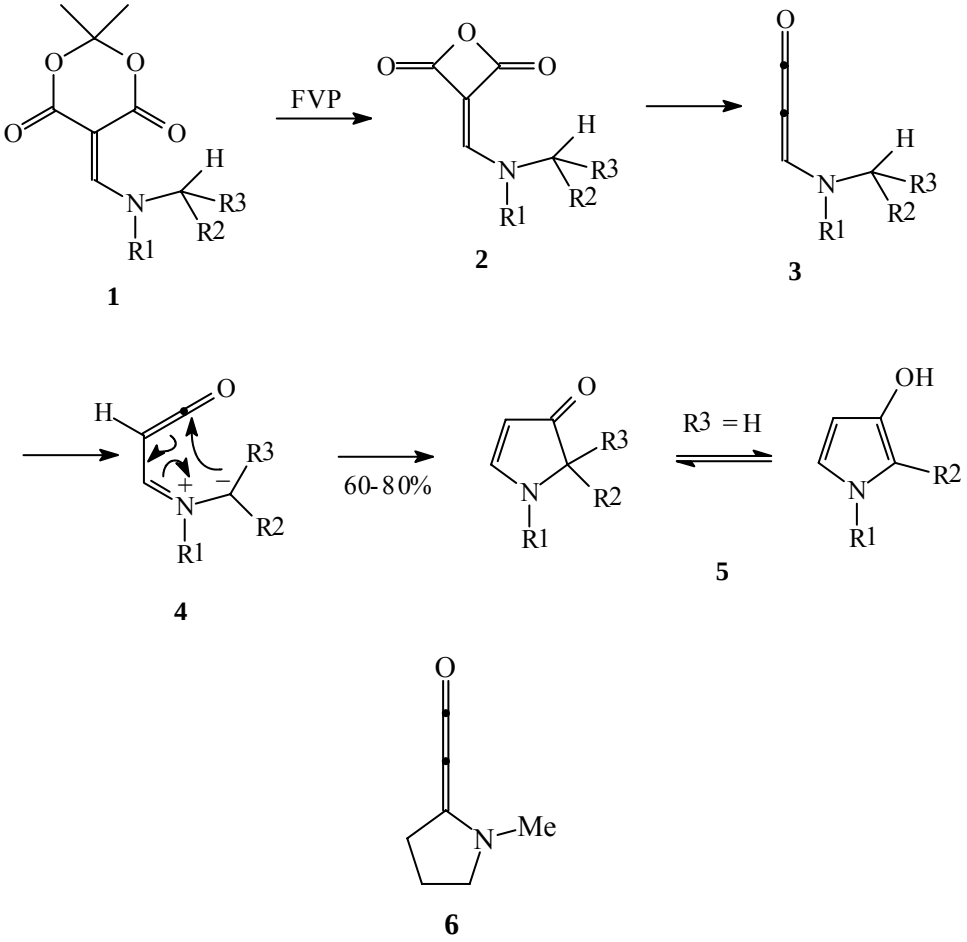
Keywords: Viehe's reagent, flash vacuum pyrolysis, pyrrolones, ketene intermediates

Introduction

Flash vacuum pyrolysis (FVP) of readily available *N,N*-disubstituted aminomethylene Meldrum's acid derivatives **1** provides a simple and direct synthetic route to 1-substituted 3-hydroxypyrroles and their tautomers, 1*H*-pyrrol-3-(2*H*)-ones **5** (Scheme 1).[1,2] The general method can also be applied to the synthesis of the corresponding thiophenones (Scheme 1, S replacing NR^1).[2]

The early stages of the pyrolytic mechanisms of many Meldrum's acid derivatives have been thoroughly investigated by Brown and Eastwood[3] and more recently by Wentrup *et al.*,[4] and the involvement of methyleneketenes and related intermediates has been rigorously established. Indeed, a detailed study by matrix isolation of the course of such reactions of **1** has shown that an intermediate anhydride **2** is formed as the precursor of the methyleneketene, **3**.[5] A particularly stable methyleneketene, **6**, whose spectra in solution persist even up to room temperature, has been isolated from such precursors.[5] However, the later stages of the formation of 1*H*-pyrrol-

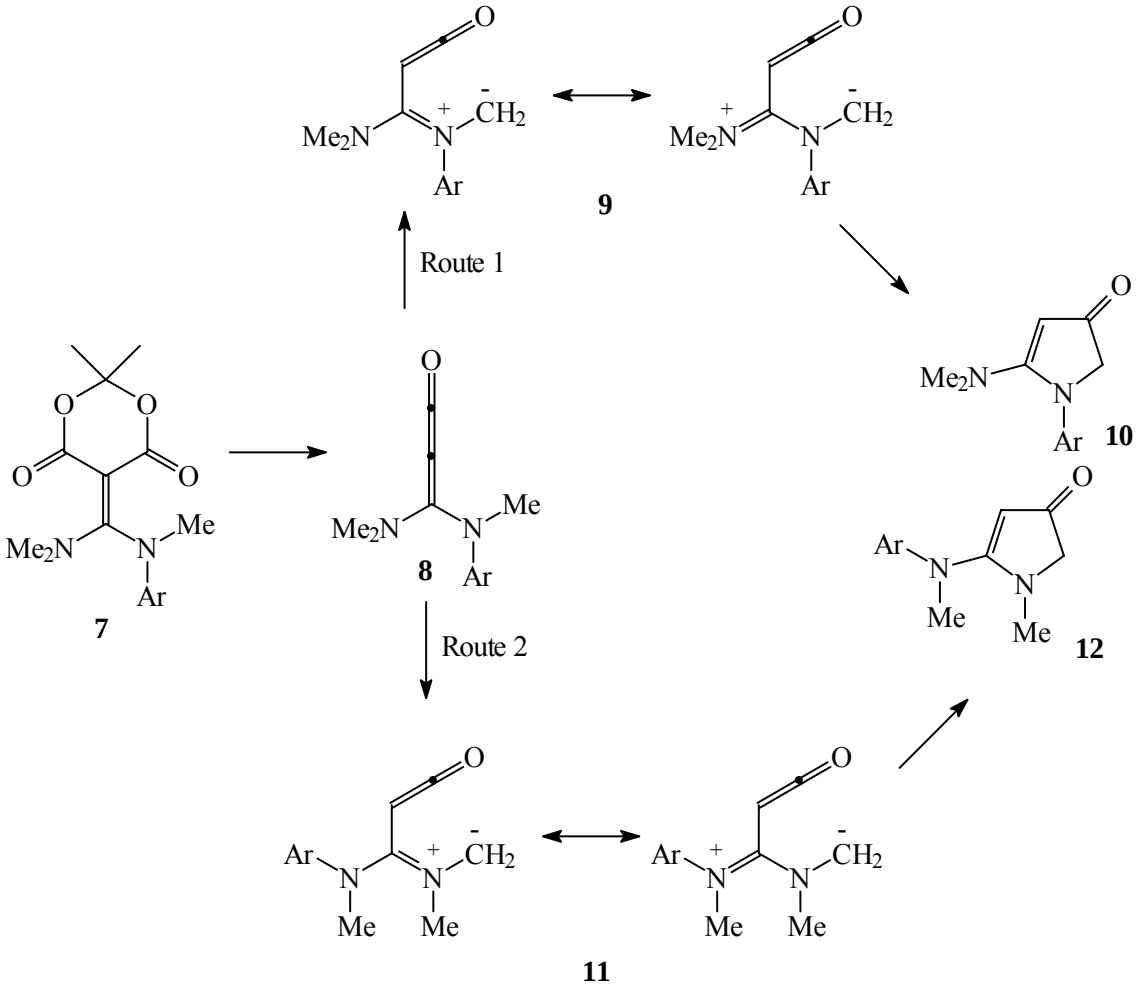
3(2*H*)-ones **5** (and the corresponding thiophenones) from the methyleneketenes **3** are less well defined (Scheme 1) because no further intermediates have been detected by matrix isolation.[6]



Scheme 1

More information on these stages has been inferred by chemical methods. Thus the 1,4-hydrogen transfer from a site adjacent to the nitrogen atom (*e.g.,* **3** → **4**) has been confirmed by deuterium labelling.[7] The measured value for the deuterium isotope effect (k_H/k_D = 1.9) is typical of FVP processes.[7] The hydrogen transfer (*e.g.*, **3** → **4**) and the new C-C bond formation (*e.g.*, **4** → **5**) could be either stepwise or concerted processes. Initial assumptions that a diradical intermediate might be involved in the transfer[8] were discounted on the grounds of substituent effects; for example, hydrogen transfer from a primary site is favored over that from a tertiary site by a factor of *ca*. 2:1 (after statistical correction).[9] In addition, a concerted hydrogen-transfer–cyclisation process from the methyleneketene **3** can be excluded because the configuration of an asymmetric center at the site of hydrogen transfer (*e.g.*, Scheme 1, R^1 = Pr_i, R^2 = Me, R^3 = Ph) is partially lost in the final pyrrolone.[10] It has been proposed that it is the 1,5-dipolar species **4** which undergoes the final electrocyclic ring closure to give the products **5** in both the nitrogen and the sulfur series,[9–11] but why are such intermediates not observable spectroscopically?

In this paper we report the results of a series of Hammett-type experiments designed to shed further light on these questions. Thus, the substrates **7** were designed so that they can react via the methyleneketene **8** by two different hydrogen-transfer modes, either from the *N*-aryl-*N*-methyl group (route 1) or from the *N,N*-dimethyl group (route 2), leading to the pyrrolones **10** and **12**, respectively (Scheme 2). Applying the mechanism of Scheme 1, route 1 provides a potential resonance-stabilized dipolar intermediate **9**, whereas route 2 provides the alternative structure **11**. Variation of substituents in the Ar group might then be expected to influence the stability of these intermediates in different ways and hence affect the ratio of the two pyrrolone products.

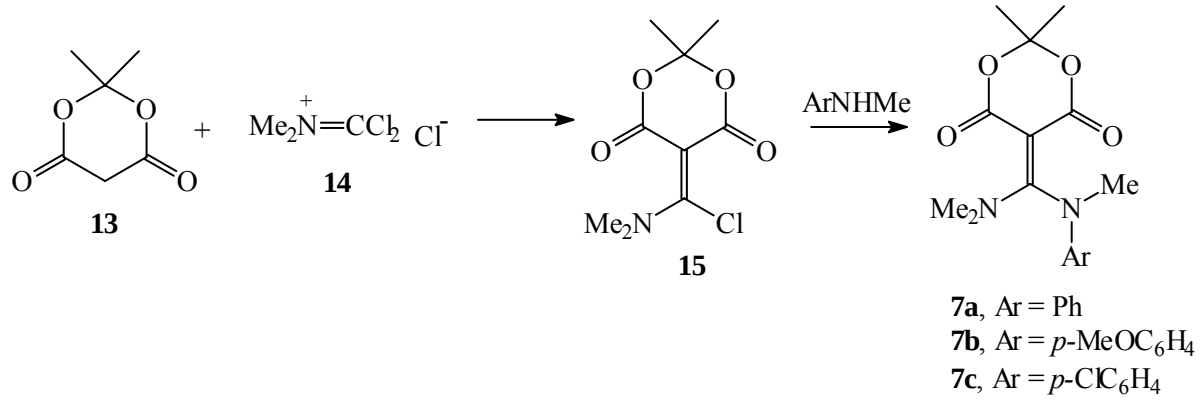


Scheme 2

Results and Discussion

The precursors **7a**–**7c** were made in two steps from Meldrum's acid **13** (Scheme 3). Treatment with phosgeniminium chloride (Viehe's reagent, **14**) under neutral conditions in chloroform

gives the chlorodimethylaminomethylene derivative **15** (60%).[12] This procedure is occasionally temperamental, but works best when fresh reagent and dry solvent are used and the product is purified as described in the Experimental Section. The product **15** is very reactive towards nucleophiles and has proved invaluable in the preparation of a wide variety of dimethylaminomethylene Meldrum's acid derivatives.[13] Treatment of **15** with appropriate *N*-methylanilines in the presence of triethylamine in acetonitrile solution at room temperature for 1–5 days gave the pyrolysis precursors **7a**–**7c** in 65–81% yield; in contrast, reaction of **15** with *N*-methyl-4-nitroaniline was unsuccessful, owing to the low nucleophilicity of the amine. The substituents were chosen to give a range of Hammett σ-values (see Table) for the final analysis.

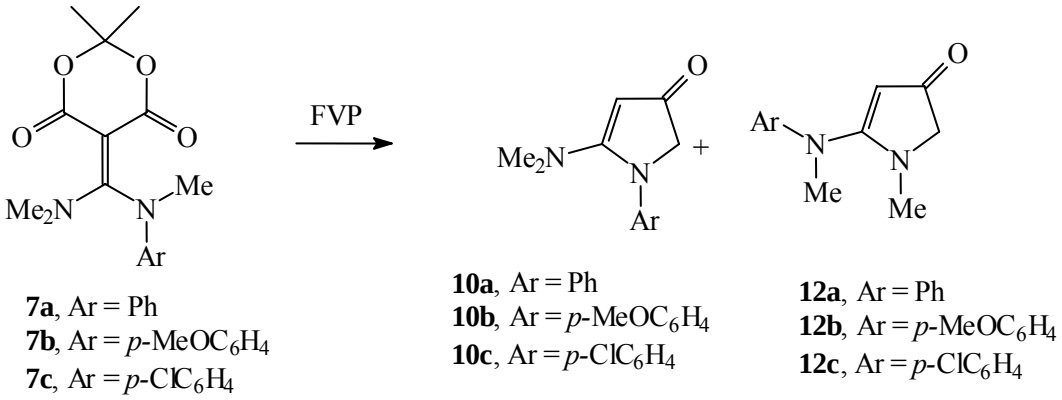


Scheme 3

The products **7a**–**7c** all gave molecular ions in their electron-impact mass spectra and showed typical breakdown patterns of Meldrum's acid derivatives [*e.g.*, ($M–C_3H_6O–CO_2$) peak generally present]. However, the major initial breakdown peak observed in all cases (base peak for **7a** and **7c**) is formed by loss of fragment(s) totaling 76 Da from the molecular ions. This may be owing to cleavage of C_3H_6O and H_2O (as we have previously confirmed in the special case of *N*-amino groups with saturated cyclic substituents)[9] but the nature of the species formed requires further investigation. The NMR spectra of **7a**–**7c** are in accord with the proposed structures. The appearance of the *C*-methyl groups of the Meldrum's acid ring as two singlets (particularly in the ^{13}C-NMR spectra) indicates that the methylene double bond is substantially twisted, as recently reported by Wentrup and co-workers for some related Meldrum's acid derivatives.[14] It is also noteworthy that the quaternary signals for C(5) of the Meldrum's acid ring resonate at very low frequency in the ^{13}C NMR spectrum (δC *ca*. 76) in accord with the electron-rich nature of this site (*cf*. ref. 14).

Flash vacuum pyrolysis (FVP) reactions of the Meldrum's acid derivatives **7a**–**7c** were carried out under our standard conditions for such substrates (600 °C and 0.001–0.005 Torr). In each case two pyrrolone products were obtained, as shown by the two signals at δH *ca*. 4.8 owing to the proton at the 4-position of the heterocycle (Scheme 4). Assignment of the two

products as **10a**–**c** and **12a**–**c** was readily established by the ratios of the aliphatic protons (6:2 in the cases of the dimethylamino compounds **10** and 3:3:1 in the case of the anilino- compounds **12**) (see Experimental Section). The ratios of the two pyrrolones **10** and **12** in each pyrolysis were therefore easily obtained by comparison of the integral values. The results are shown in the Table 1.



7a, Ar = Ph
7b, Ar = *p*-$MeOC_6H_4$
7c, Ar = *p*-ClC_6H_4

10a, Ar = Ph
10b, Ar = *p*-$MeOC_6H_4$
10c, Ar = *p*-ClC_6H_4

12a, Ar = Ph
12b, Ar = *p*-$MeOC_6H_4$
12c, Ar = *p*-ClC_6H_4

Scheme 4

In the first place, these results show that hydrogen transfer from the dimethylamino groups is consistently favored over that from the *N*-methylarylamino groups (statistical ratio 67:33). This may be owing to the relative electron donating abilities of a methyl group *vis-à-vis* an aryl group (*e.g.,* Me, σ_m –0.07; Ph, σ_m +0.06) stabilizing **11** more effectively than **9**. Secondly, it is clear that the two pyrrolones **12a**–**c** and **10a**–**c** were obtained in *ca.* 17:83 ratio (within ± 5% experimental error), independent of the nature of the aryl substituent. In other words, the Hammett ρ parameter for the reaction is 0.0.

Table 1. Relative yields of **10** and **12** in FVP reactions of **7**

Substituent	σ_p	12[a]	10[a]
H	0.0	89	11
p-OMe	–0.27	78	22
p-Cl	+0.23	83	17

[a] Estimated error from integral values, ±5%.

What are the implications of these results for the mechanism of the cyclization, given that both concerted and stepwise radical processes have already been ruled out? It is possible that the reaction has a very early transition state with little charge build-up on the nitrogen atom(s) prior to the actual cyclization event. This may explain why no late intermediates could be detected by matrix isolation and also why only partial racemization of an asymmetric center takes place

during the cyclization process. A theoretical study of the reaction profile would now be of great interest.

Experimental Section

General Procedures. ^{1}H- and ^{13}C- NMR spectra were recorded at 80 (or 200) and 20 MHz respectively for solutions in [^{2}H]-chloroform. ^{13}C-NMR signals are for one CH resonance unless otherwise stated; assignments were generally confirmed by DEPT experiments. Mass spectra were obtained under electron impact (EI) ionization conditions unless otherwise stated.

5-(1-Chloro-1-*N,N*-dimethylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione (15)[12]**.** Meldrum's acid **13** (14.4 g, 0.1 mol) was dissolved in scrupulously purified and dried chloroform (100 ml). To this solution was added fresh phosgeneiminium chloride **14** (20 g, 0.12 mol) and the reaction mixture was heated at reflux for 1.5 h, during which there was a brief evolution of HCl gas. The solution was then concentrated (rotary evaporator) to approximately one third of the initial volume. The product was precipitated as a sticky solid by the portionwise addition of dry ether (250 ml). However, with prolonged scratching and vigorous overnight stirring, the quality of the product was improved. The crude material was then filtered, washed with dry ether, and *immediately* dried under reduced pressure. The *5-(1-chloro-1-*N,N-*dimethylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione* **15** (11.2–14.9 g, 48–64%), mp 158 °C (from benzene), so obtained was sufficiently pure for further reactions, but decomposed on standing and was best stored at low temperatures and used within a few weeks. (Found: C, 46.4; H, 5.2; N, 5.8. $C_9H_{12}ClNO_4$ requires C, 46.25; H, 5.15; N, 6.0%), δ_H 3.42 (6H, s), and 1.67 (6H, s); δ_C 166.51 (quat.), 161.02 (2 quint.), 102.68 (quint.), 83.95 (quint.), 46.02 (br), and 26.48 (CH_3); *m/z* (FAB) 236 (M+1, 17%), 234 (M+1, 40), 176 (100), 142 (43), 132 (50) and 96 (20). Despite many attempts to find a suitable alternative, benzene was found to be the best solvent for the recrystallization.

In the reactions of the above compound with nitrogen nucleophiles, it should be noted that the success depended largely on the quality of the starting material. Often with poor quality starting material the yields decreased dramatically from the norm and work-up became increasingly difficult.

5-(Bis-amino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione derivatives (7). To a stirred solution of 5-(1-chloro-1-*N,N*-dimethylamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione **15** (1 mmol) in acetonitrile (5 ml) was added the appropriate secondary amine (1 mmol) and an excess of triethylamine (3–5 mmol). The reaction mixture was stirred at room temperature for 20 h, although for the less reactive amines it was necessary to lengthen the period for up to 5 days. Water (10 ml) was then added and the mixture was acidified to remove any excess amine. After extraction with dichloromethane (3x10 ml) the combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield the crude product. In

some cases a gum was obtained, but trituration with a mixture of cyclohexane and ethanol always gave the required solid in good yield.

The following compounds were synthesized by this general procedure; in each case, the amine used and the reaction time are indicated.

5-(1,1-*N'*-Phenyl-*N',N,N*-trimethyldiamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione (7a). *(N*-methylaniline, 3 days) (76%), mp 209–210 °C (from toluene) (Found: C, 62.9; H, 6.75; N, 9.0. $C_{16}H_{20}N_2O_4$ requires C, 63.15; H, 6.6; N, 9.2%); δ_H 7.42–7.16 (5H, m), 3.46 (3H, br s), 3.03 (3H, br s), 2.51 (3H, br s) and 1.71 (6H, br s); δ_C 167.98 (quint.), 163.09 (2 quint.), 145.29 (quint.), 129.90 (2-CH), 126.25, 124.08 (2-CH), 102.19 (quint.), 76.08 (quint.), 42.51 (2xCH_3), 41.53 (CH3), 26.79 (CH_3), and 26.53 (CH_3); *m/z* 304 (M+, 25%), 228 (100), 201 (27), 187 (10), 158 (68), 130 (13), 96 (50), 77 (38), 69 (31) and 68(9).

5-(1,1-*N'*-*p*-Methoxyphenyl-*N',N,N*-trimethyldiamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione (7b). (*N*-methyl-*p*-anisidine, 20 h) (81%), mp 174 °C (from toluene) (Found: C, 60.7; H, 6.6; N, 8.45. $C_{17}H_{22}N_2O_5$ requires C, 61.1; H, 6.6, N, 8.4%); δ_H 7.21 (2H, d, 3J 9.0), 6.89 (2H, d, 3J 9.0), 3.79 (3H, s), 3.43 (3H, s), 3.03 (3H, s), 2.53 (3H, s), 1.71 (3H, s), and 1.70 (3H, s); δ_C 168.06 (quint.), 163.14 (2 quint.), 157.69 (quint.), 138.31 (quint.), 125.74 (2-CH), 115.00 (2-CH), 102.17 (quint.), 75.76 (quint.), 55.36 (CH3), 42.99 (CH3), 42.44 (CH3), 41.50 (CH3), 26.87 (CH3) and 26.43 (CH3); *m/z* 334 (M^+, 28%), 258 (70), 243 (36), 217 (20), 188 (44), 160 (37), 150 (12), 121 (33), 120 (19), 85 (100), 81 (28) and 69 (20).

5-(1,1-*N'*-*p*-Chlorophenyl-*N',N,N*-trimethyldiamino)-methylene-2,2-dimethyl-1,3-dioxane-4,6-dione (7c). (*p*-chloro-*N*-methylaniline, 5 days) (65%), mp 160–163 °C (from cyclohexane/ethanol) (Found: C, 55.9; H, 5.6; N, 8.0. $C_{16}H_{19}ClN_2O_4 \cdot 0.25\ H_2O$ requires C, 56.0; H, 5.70; N, 8.15%) (Found: M^+ 340.100 and 338.103. $C_{16}H_{19}ClN_2O_4$ requires *M*, 340.100 and 338.103); δ_H 7.35 (2H, br d, 3J 8.4), 7.13 (2H, br d, ^{3}J 8.4), 3.43 (3H, br s), 3.04 (3H, br s), 2.56 (3H, br s) and 1.71 (6H, br s); δ_C 168.16 (quint.), 163.01 (2 quint.), 143.85 (quint.), 131.66 (quint.), 130.06 (2CH), 125.29 (2CH), 102.30 (quint.), 42.66 (CH_3), 42.46 (CH_3), 41.57 (CH_3), 26.78 (CH_3) and 26.56 (CH_3) (one quaternary C overlapping with $CDCl_3$ signal); *m/z* 340 (M+, 9%), 338 (M+, 24), 262 (100), 235 (17), 221 (18), 192 (72), 152 (28), 125 (21), 96 (78), 85 (56), 69 (29) and 68 (10).

Attempts to prepare the *p*-nitro analogue by the same method were unsuccessful owing to the reduced reactivity of the amine.

Flash vacuum pyrolysis experiments. Small-scale experiments were carried out in which the entire pyrolysate was dissolved in a deuterated solvent and analyzed immediately by ^{1}H-NMR spectroscopy. The precursor, pyrolysis conditions [quantity of precursor, furnace temperature (T_f), inlet temperature (T_i), pressure range (P) and pyrolysis time (t)] and, where appropriate, approximate yields are given.

5-(1,1-*N'*-Phenyl-*N',N,N*-trimethyldiamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione (7a). T_f 600 °C, T_i 185 °C, P 0.001 Torr, t 30 min, gave two products in a 11:89 ratio (both quoted); 5-dimethylamino-1-phenyl-1H-pyrrol-3(2H)-one **10a**, δ_H 7.37–7.12 (5H, m), 4.83 (1H,

s), 3.95 (2H, s) and 2.74 (6H, s); and 5-(*N*-methyl-*N*-phenylamino)-1-methyl-1*H*-pyrrol-3(2*H*)-one 12a, δ_H 7.37–7.12 (5H, m), 4.80 (1H, s), 3.68 (2H, s), 3.24 (3H, s) and 2.36 (3H, s).

5-(1,1-*N'*-*p*-Methoxyphenyl-*N'*,*N*,*N*-trimethyldiamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione (7b). T_f 600 °C, T_i 150 °C, P 0.005 Torr, t 30 min, gave two products in a 22:78 ratio (both quoted): 5-dimethylamino-1-(*p*-methoxyphenyl)-1*H*-pyrrol-3(2*H*)-one **10b**, δ_H 7.10 (2H, d, ^{3}J 9.0), 6.87 (2H, d, ^{3}J 9.0), 4.83 (1H, s), 3.93 (2H, s), 3.76 (3H, s) and 2.75 (6H, s); and 4-[*N*-(*p*-methoxyphenyl)-*N*-methylamino]-1-methyl-1*H*-pyrrol-3(2*H*)-one **12b**, δ_H 7.10 (2H, d, 3J 9.0), 6.87 (2H, d, 3J 9.0), 4.79 (1H, s), 3.77 (3H, s), 3.70 (2H, s), 3.21 (3H, s) and 2.38 (3H, s).

5-(1,1-*N'*-*p*-Chlorophenyl-*N'*,*N*,*N*-trimethyldiamino)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione (7c). T_f 600 °C, T_i 190 °C, P 0.005 Torr, t 30 min, gave two products in a 17:83 ratio both quoted): 1-(*p*-chlorophenyl)-5-dimethylamino-1*H*-pyrrol-3(2*H*)-one 10c, δ_H 7.32 (2H, m), 7.09 (2H, m), 4.88 (1H, s), 3.95 (2H, s) and 2.76 (6H, s); and 5-[*N*-(*p*-chlorophenyl)-*N*-methyl]-1-methyl-1*H*-pyrrol-3(2*H*)-one **12c**, δ_H 7.32 (2H, m), 7.11 (2H, m), 4.84 (1H, s), 3.71 (2H, s), 3.24 (3H, s) and 2.41 (3H, s).

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References

1. McNab, H.; Monahan, L. C. In *Pyrroles* Part 2; R.A. Jones; Ed.; Wiley: New York, 1992; p 525.
2. McNab, H.; Gaber, A. M. *Synthesis* **2001**, 2059.
3. Brown, R.F.C.; Eastwood, F. W. *Synlett* **1993**, 9, and references therein
4. For example, Wentrup, C.; Rao, V. V. R.; Frank, W.; Fulloon, B. E.; Moloney, D. W. J.; Mosandl, T. *J. Org. Chem*. **1999**, *64*, 3608.
5. Lorencak, P.; Pommelet, J. C.; Chuche, J.; Wentrup, C. *J. Chem. Soc., Chem. Commun.* **1986**, 369.
6. Bibas, H.; Kappe, C. O.; Wong, M. W. Wentrup, C. *J. Chem. Soc., Perkin Trans. 2* **1998**, 493.
7. Hickson, C. L.; Keith, E. M.; Martin, J. C.; McNab, H.; Monahan, L. C.; Walkinshaw, M. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1465.
8. Gordon, H. J.; Martin, J. C.; McNab, H. *J. Chem. Soc., Chem. Commun*. **1983**, 957.
9. McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 863.
10. (a) McNab, H.; Monahan, L. C. *J. Chem. Soc., Chem. Commun*. **1987**, 138. (b) McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 869.

11. Ben Cheikh, A.; Dhimane, H.; Pommelet, J. C.; Chuche, J. *Tetrahedron Lett.* **1988**, *29*, 5919.
12. Viehe, H. G.; Janousek, Z. unpublished work. We are grateful to Professor Viehe for access to an unpublished preparation for this compound.
13. Morrow, M. Ph. D. Thesis, The University of Edinburgh, 1994.
14. Bernhardt, P. V.; Koch, R.; Moloney, D. W. J.; Shtaiwi, M; Wentrup, C. *J. Chem. Soc., Perkin Trans. 2* **2002**, 515.