HETEROCYCLES, Vol. 55, No. 11, 2001, pp. 2139 - 2145, Received, 27th August, 2001

SYNTHESIS OF A THIINO[2,3,4-*d,e*]PHTHALAZINE

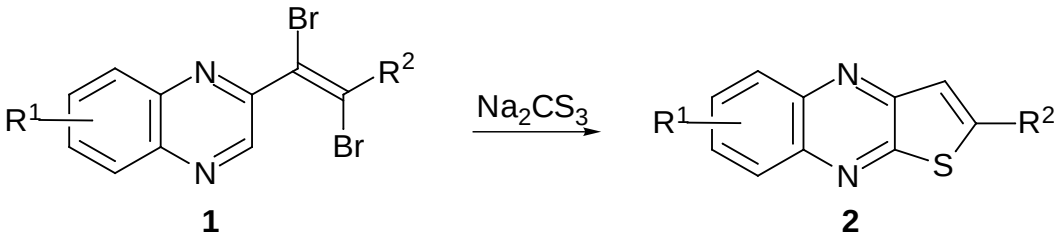
Abdel Karim Karim[#] , Montserrat Armengol, and John A. Joule*

Department of Chemistry, The University of Manchester, Manchester M13 9PL, U.K.

Abstract – The reaction of 5-(1,2-dibromo-2-phenylethenyl)-phthalazine (**16**) with Na_2CS_3 gives 5-phenylthiino[2,3,4-*d,e*]phthalazine (**17**).

Introduction

We have described[1] a route (Scheme 1) in which 2-(1,2-dibromoalkenyl)quinoxalines (**1**) are reacted with disodium trithiocarbonate[2] resulting in cyclising ring closures giving thieno[2,3-*b*]quinoxalines (**2**), with the loss of both bromine atoms. We proposed[1] a mechanism for the process which involved initial addition of trithiocarbonate to the double bond reflecting both the electron-withdrawing nature of the halogens and conjugation with the ring imine.



1 **2**

Scheme 1

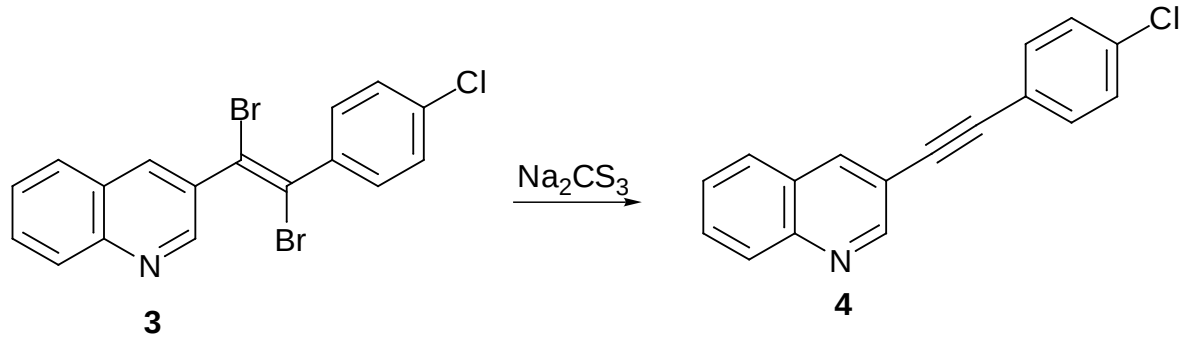
On the basis of the mechanism proposed,[1] we speculated[3] that there are two essential criteria for a successful thiophene-cyclisation: (1) there must be a ring imine, in conjugation with the dibromoalkene, in order to encourage correctly oriented dithiocarbonate addition *and* (2) there must be ring imine to encourage a subsequent intramolecular cyclising sulfur addition; both of these requirements are present in the quinoxaline series as (N-1–C-2) and (C-3–N-4) respectively. Confirmation for these ideas came when we attempted a ring closure with the dibromoalkenylquinoline (**3**) – no ring closure occurred, only elimination

---

On leave from Department of Chemistry, Al-Baath University, Homs, Syria.

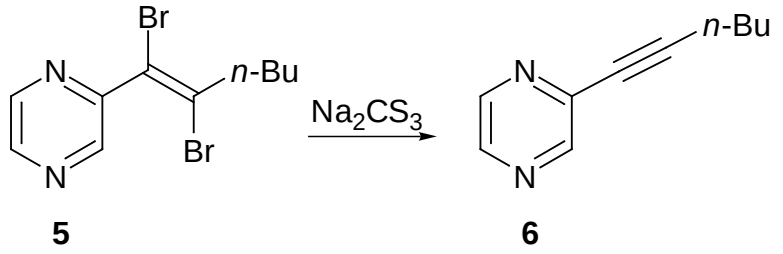
of bromine was observed on treatment of **3** with disodium trithiocarbonate giving **4** (Scheme 2).

The requirements for success in this process were further delineated when we found that neither the dibromoalkenylpyrazine (**5**) nor the dibromoalkenylpyrimidine (**7**) allowed the thiophene ring closing process, once again exposure to disodium trithiocabonate resulting only in bromine elimination, giving **6** and **8** respectively (Scheme 3). We concluded that a second fused aromatic ring (present in **1** but not in either **5** or **6**) is also a necessary requirement for the success of these ring closing processes.

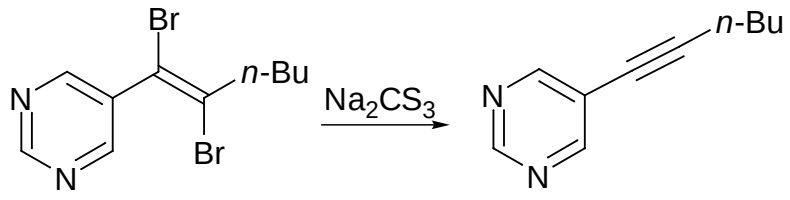


3 **4**

Scheme 2



5 **6**



7 **8**

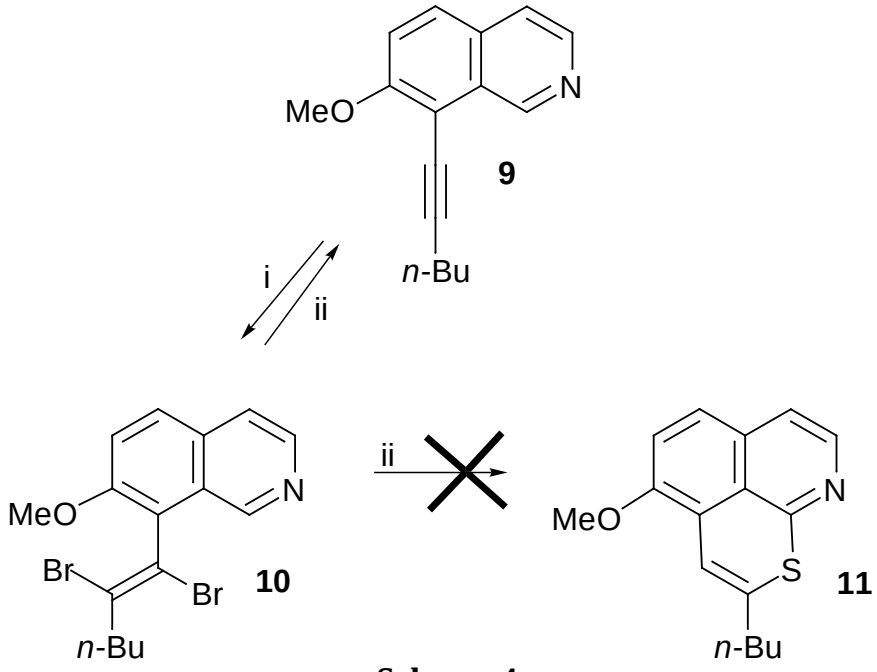
Scheme 3

Results and discussion

We have now turned to examine the possibility of extrapolating the process to the formation of six-membered sulfur-containing rings. We prepared dibromoalkenyl-isoquinoline (**10**) hoping that reaction with trithiocarbonate would yield the tricyclic system

(**11**), but instead only elimination to the alkyne (**9**) was observed (Scheme 4). As in the previous work[1,3] the dibromoalkene (**10**) was prepared by bromine addition to alkyne (**9**).[4]

With all the results described above in mind, we examined the possibility of forming a six-membered ring in a comparable fashion, but using a dibromoalkenylphthalazine (**16**) as our substrate, the heterocyclic ring now having an additional electron-withdrawing component, compared with the isoquinoline situation, in the second imine unit at C-3–N-4.

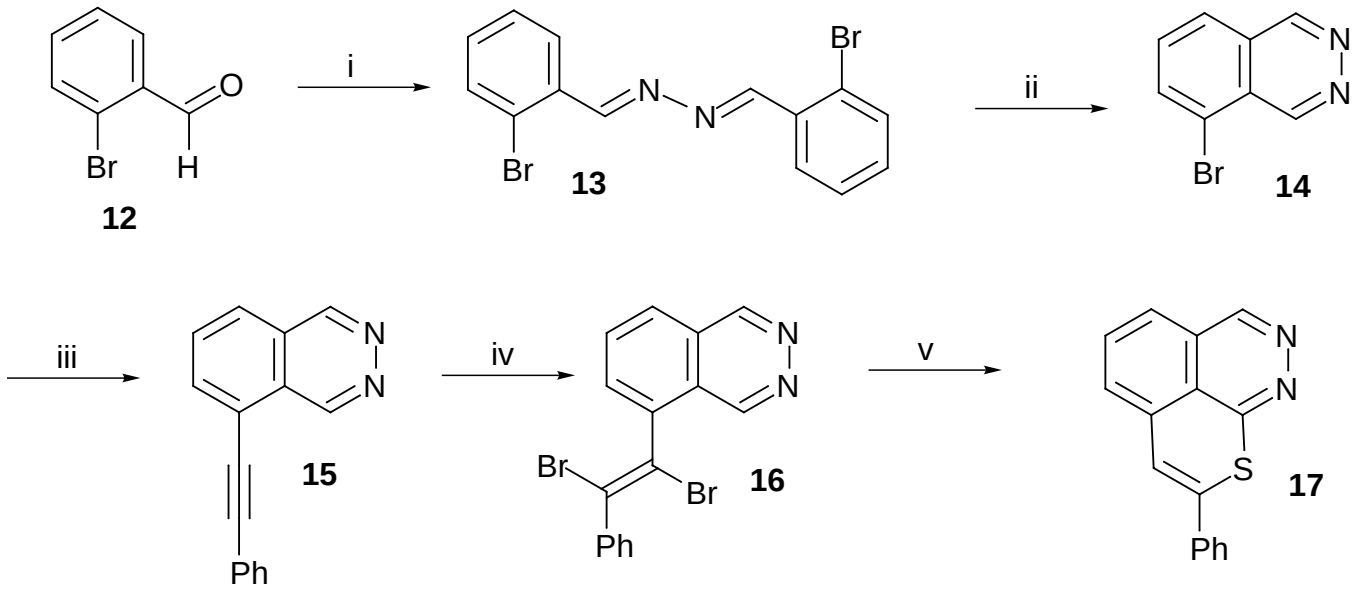


Scheme 4

Reagents: i, Br_2, CH_2Cl_2, rt (34%); ii, Na_2CS_3, MeOH, reflux (*ca.* 100%).

Our route to the substrates (**1**, **3**, **5**, **7**, and **10**), involved in each case the Pd(0)-catalysed coupling of a heteroaryl halide with an alkyne followed by bromine addition. Relatively few methods are available for the synthesis of halogenated phthalazines: 5-bromophthalazine was unknown when we began this work, however 5-chlorophthalazine (which would be unsuitable for the coupling step) had been prepared, along with several other phthalazines, by a process involving reaction of arylaldehyde azines with a mixture of aluminum chloride and aluminum bromide.[5]

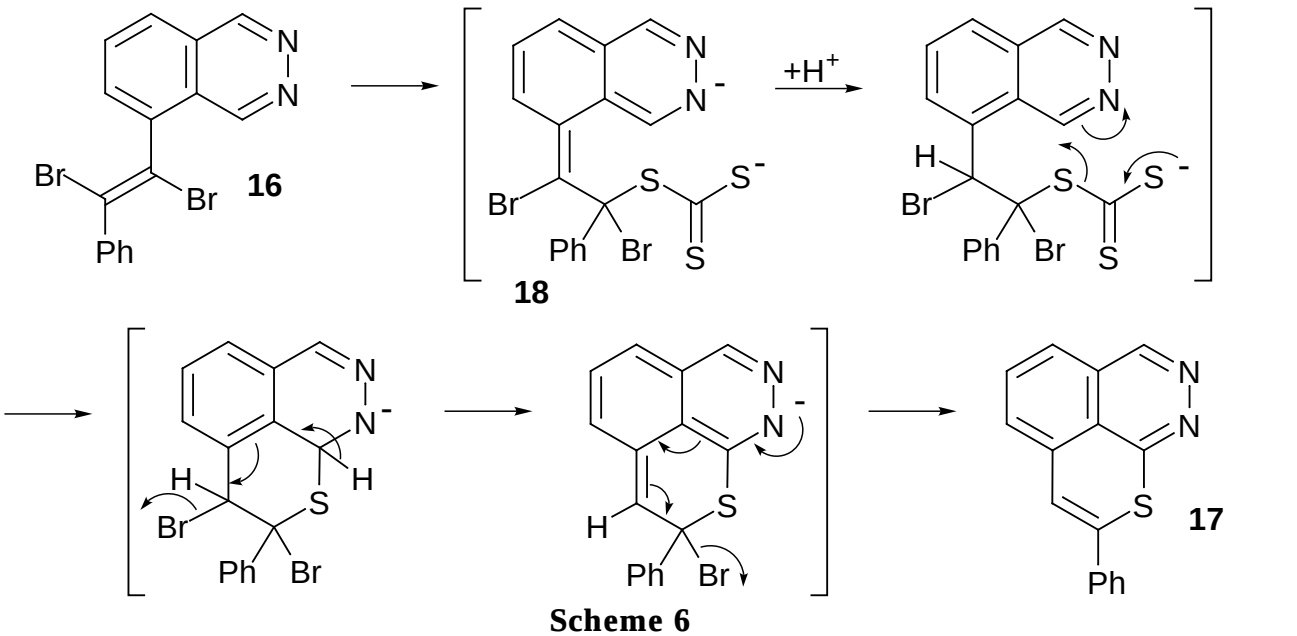
Reaction of 2-bromobenzaldehyde (**12**) with hydrazine gave crystalline, yellow azine (**13**). Application of Robev's method[5] produced the desired 5-bromophthalazine (**14**), though only in 13% yield after purification; an alternative route will be required for future work. Coupling with phenylethyne was efficient, giving the alkyne (**15**) in 76% yield, as was addition of bromine producing the desired cyclisation substrate (**16**) (Scheme 5).



Scheme 5

Reagents: i, $N_2H_4.H_2SO_4$, aq. NH_3, rt (85%); ii, $AlCl_3$, $AlBr_3$, 185 °C, N_2 (13%); iii, PhC≡CH, $Cl_2Pd(PPh_3)_2$, CuI, Et_3N, 62 °C (76%); iv, Br_2, CH_2Cl_2, rt (59%); v, aq. Na_2CS_3, MeOH, reflux (50%).

After some experimentation to find suitable conditions, we were gratified to find that the interaction of the dibromoalkenylphthalazine (**16**) with disodium trithiocarbonate led to the target tricyclic compound (**17**), a crystalline material, in 50% yield. In support of the structural assignment, **17** showed two singlets in its ^{1}H NMR spectrum, at δ 9.55 and 9.98, corresponding to H-6 and H-1 respectively, and had the appropriate molecular composition, now having one sulfur and no bromine atoms. This compound (**17**) is the first example of this tricyclic ring system.



Scheme 6

Following our earlier mechanistic speculation[1] we propose the sequence shown in Scheme 6 to rationalise the formation of **17**. Thus, addition to the dibromoalkene unit, taking advantage of conjugation to the imine (intermediate (**18**)), then intramolecular sulfur addition forming the six-membered ring, is followed by successive losses of two mol equivalents of HBr. It is interesting that the only substantial structural difference between **16**, in which the cyclisation is successful, and **10**, for which no ring closure as observed, is the presence in **16** of a second imine unit – we suggest that this provides sufficient extra electron withdrawal to allow the nucleophilic sulfur addition.

EXPERIMENTAL

General

See reference 1.

8-(1,2-Dibromohex-1-en-1-yl)-7-methoxyisoquinoline (10)

A solution of Br_2 (0.032 mL, 0.61 mmol) in CH_2Cl_2 (1.25 mL) was added dropwise to a stirred solution of 8-(hex-1-yn-1-yl)-7-methoxyisoquinoline (**9**)[4] (135 mg, 0.56 mmol) in CH_2Cl_2 (2.5 mL). The resultant mixture was stirred for 2 h at rt. Addition of 10% sodium metabisulphite and CH_2Cl_2 followed by separation, drying, and evaporation of the organic phase under reduced pressure gave a yellow oil. Purification by column chromatography over silica gel, eluting with petroleum ether/EtOAc (1:1) gave 8-(1,2-dibromohex-1-en-1-yl)-7-methoxyisoquinoline (**10**) (77 mg, 34%) as a brown solid, mp 131-132 °C, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, t, *J* = 7.3 Hz), 1.57 (2H, m), 1.80 (2H, m), 3.02 (2H, m), 7.51 (1H, d, *J* = 9.2 Hz), 7.64 (1H, br s), 7.88 (1H, d, *J* = 9.2 Hz), 8.52 (1H, br s), 9.13 (1H, br s); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 13.9, 21.7, 29.7, 39.9, 56.7, 109.1, 118.0 (2 x C), 123.5, 128.5, 129.4 (2 x C), 130.9, 141.2, 149.1, 153.9; MS (CI) *m/z* 402, 400, 398 (M+1, 19, 37, 19), 240 (100); HRMS: Found: M^+, 396.9682, $C_{16}H_{17}N_2O^{79}Br_2$ requires *M* 396.9677.

2-Bromobenzaldehyde azine (13)

To a stirred mixture of powdered hydrazine sulfate (2.4 g, 13 mmol), water (18 mL) and aq. ammonia (saturated, 2.4 mL) was added 2-bromobenzaldehyde (7.6 g, 41 mmol) dropwise during 1 h. The solid produced was filtered off, washed with water and recrystallised from *n*-hexane/toluene (3:1) to give the *azine* (**13**) (6.3 g, 85%), as yellow needles, mp 170-171 °C, ν_{max} (film) 1587 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.06 (2H, s, 2xCH=N), 8.25 (2H, dd, *J* = 7.2, 1.8 Hz, 2xArH), 7.66 (2H, dd, *J* = 7.8, 1.4 Hz, 2xArH), 7.43 (2H, bd, *J* = 7.3 Hz, 2xArH), 7.35 (2H, dd, *J* = 7.4, 1.8 Hz, 2xArH); MS (CI) *m/z* 369, 367, 365 (M+1, 55, 100, 56%), 287 (25), 285 (20), 206 (45); Anal. Calcd for $C_{14}H_{10}N_2Br_2$: C, 45.9; H, 2.7; N, 7.7, Found: C, 45.9; H, 2.6; N, 7.6,

5-Bromophthalazine (14)

A mixture of 2-bromobenzaldehyde azine (**13**) (2.4 g, 2 mmol), aluminum chloride (16 g, 120 mmol) and aluminium bromide (14.7 g, 22 mmol) was heated at 180-185 °C under N_2 for 30 min. Following addition of H_2O (125 mL) to the cooled mixture, then aq. HCl (5%, 15 mL), the mixture was filtered. The filtrate was made alkaline using aq. KOH (15%) and then extracted thoroughly with toluene. The organic extract was dried and evaporated leaving crude material (0.61 g) which was purified by column chromatography over silica eluting with EtOAc/petroleum ether (4:1) giving *5-bromophthalazine* (**14**) (0.25 g, 13%), mp 118-119 °C, ν_{max} (film) 1553 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.89 (1H, s, H-4), 9.52 (1H, br s, H-1), 8.18 (1H, dd, *J* = 7.6, 1.0 Hz, H-8), 7.98 (1H, d, *J* = 8.1 Hz, H-6), 7.80 (1H, t, *J* = 7.7 Hz, H-7); MS (CI) *m / z* 211, 209 (M+1, 89, 100%), 131 (20); Anal. Calcd for $C_8H_5N_2Br$: C, 45.9; H, 2.4; N, 13.4, Found: C, 45.0; H, 2.2; N, 13.0.

5-Phenylethynylphthalazine (15)

A mixture of 5-bromophthalazine (**14**) (209 mg, 1.0 mmol), phenylethyne (0.13 mL, 1.2 mmol), bis(triphenylphosphine)palladium(II) chloride (1.8 mg), copper(I) iodide (8 mg), and Et_3N (2 mL) were heated together at 62 °C for 24 h. After evaporation of the Et_3N, the residue was treated with aq. HCl (1M, 20 mL) and extracted with CH_2Cl_2. The dried extract was evaporated and the residue purified by column chromatography over silica, elution with EtOAc/petroleum ether (4:1) giving the *alkyne* (**15**) (176 mg, 76%), mp 106-108 °C, λ_{max} 320 nm; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.08 (1H, br s, H-4), 9.58 (1H, d, *J* = 1.5 Hz, H-1), 8.12 (1H, dd, *J* = 6.2, 2.3 Hz, H-8), 7.95 (2H, m, ArH), 7.70 (2H, m, ArH), 7.46 (3H, m, ArH); MS (CI) *m / z* 231 (M+1, 100%); Anal. Calcd for $C_{16}H_{10}N_2$: C, 83.5; H, 4.3; N, 12.1, *M* 230.0842, Found: C, 82.2; H, 4.4; N, 11.8, M^+ 230.0847.

5-(1,2-Dibromo-2-phenylethenyl)phthalazine (16)

A solution of Br_2 in CH_2Cl_2 (0.12 mL in 10 mL, 3 mL) was added dopwise to a stirred solution of 5-phenylethynylphthalazine (92 mg, 0.4 mmol) in CH_2Cl_2 (5 mL). The resultant mixture was stirred for 3 h at rt then aq. sodium metabisulfite (20%, 10 mL) was added, the layers separated and the CH_2Cl_2 layer dried and evaporated leaving crude material (120 mg). Purification by column chromatography over silica, eluting with Et_2O/CH_2Cl_2 (1:3) gave the *dibromide* (**16**) (60 mg, 59%), mp >230 °C decomp, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.82 (1H, d, *J* = 1.2 Hz, H-4), 9.65 (1H, d, *J* = 1.5 Hz, H-1), 8.05 (3H, m, ArH), 7.70 (2H, m, ArH), 7.55 (3H, m, ArH); MS (CI) *m / z* 391 (M+1, 10%), 231 (16%); Anal. Calcd for $C_{16}H_{10}N_2Br_2$: Br, 41.0, Found: Br, 41.1, M^+ 387.9214, , $C_{16}H_{10}N_2{}^{79}Br_2$ requires *M* 387.9212.

5-Phenylthiino[2,3,4-*d,e*]phthalazine (17)

An aqueous solution of Na_2CS_3[2] (33%, 2 mL) was added dropwise to a solution of 5-(1,2-dibromo-2-phenylethenyl)phthalazine (**16**) (60 mg) in MeOH/THF (16:1, 8.5 mL) with stirring at 62 °C. After a further 18 h at reflux, the solvent was evaporated, the residue treated with H_2O and organic material extracted into CH_2Cl_2. The dried organic extract was evaporated leaving crude product (50 mg) which was purified by colum chromatography over silica when elution with Et_2O/CH_2Cl_2 (1:1) gave the *tricycle* (**17**) (20 mg, 50%), mp >215 °C, λ_{max} 266, 334 nm; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.98 (1H, s, H-1), 9.55 (1H, s, H-6), 8.20 (2H, m, ArH), 7.75 (3H, m, ArH), 7.42 (3H, m, ArH); MS (CI) *m/z* 263 (M+1, 100%); Found M^+: 262.0565, $C_{16}H_{10}N_2S$ requires *M* 262.0565.

ACKNOWLEDGEMENTS

AKK thanks Al-Baath University and the Syrian Government for financial support. We thank the Nissan Chemical Company, Tokyo, Japan for support for the initial part of this work (MA).

REFERENCES

1. M. Armengol and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 2001, 154.
2. D. J. Martin and C. C. Greco, *J. Org. Chem.*, 1968, **33**, 1275.
3. M. Armengol and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 2001, 978.
4. M. Armengol, M. Helliwell, and J. A. Joule, *Arkivoc*, 2000, **1**, 829.
5. S. K. Robev, *Tetrahedron Lett.*, 1981, **22**, 345.