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Spiroheterocyclic compounds: old stories with new outcomes

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ABSTRACT

An efficient and straightforward method for the preparation of spirodiazine derivatives is reported which involves mild reaction conditions and easily accessible reactants. A new class of spiroazaheterocycles, spiro[pyrrolidine-pyrrolo[3,4-*c*]pyrroles], is obtained. A feasible explanation is given for the unexpected results obtained at high energy (high temperatures, MW and ultrasound irradiation).

Fused and non-fused diazines, particularly those based on pyrimidine, pyridazine and phthalazine, have demonstrated versatile biological activities such as antiviral and anti-HIV,[1–4] anticancer,[5–7] antihypertensive, cardiotonic and antiplatelet,[8–10] analgesic, anxiolytic and antidepressant,[11–13] antimicrobial, antiinflammatory, antimalarial and antituberculosis[14–20]. The development of simple and efficient routes to such compounds is of interest. Various strategies have been adopted in order to reach this goal, but most are energy- and time-consuming and also rather expensive. One of the strategies adopted for obtaining fused nitrogen compounds[16–18,21,22] involves ylides as versatile and reactive intermediates. As regard to spiroazaheterocycles, few studies have been performed.[23–25] In the early 70s there were isolated studies (by treating 1,2-diazine with dienophiles), leading to cycloadducts[24] or spirocompounds.[25] As for pyrimidine, this type of reaction has not been studied at all.

Microwave and ultrasound irradiation have become increasingly valuable tools in organic chemistry, since they offer versatile and facile pathways for a large variety of syntheses.[26,27] So far, few studies have been reported regarding diazinium ylides and most of these have been conducted by our group.[16–18,28,29]

The overall goal of this work was to develop a new, efficient and general preparation of spirodiazine heterocycle derivatives of potential biological interest.

Pyridazine **1** was treated with dienophiles (*N*-ethylmaleimide (NEMI) or *N*-phenylmaleimide (NPMI)), leading to spiropyridazine compounds **3** and **4**, Scheme 1 and Figure 1. No cycloadducts of type **5** were observed (pathway *ii*). We suggest that the reaction mechanism involves two steps: the first is nucleophilic attack of pyridazine on the dienophile, with the formation of the ylide species **2**; the second is a [3+2] dipolar cycloaddition of the ylide **2a** to a second molecule of the dienophile with the formation of the spirocompound (pathway *i*).

Spirophthalazine compounds **8** and **9** were obtained using similar chemistry (Scheme 2, Fig. 2) and, again, no cycloadducts of type **5** were observed.

Unexpectedly, when we treated pyrimidine **10** with dienophiles, spiropyrroles **12** and **13** were obtained instead of the expected spiropyrimidine **14** (Scheme 3, Fig. 3).

In order to explain the formation of the spiropyrrolidine-pyrroles, we postulate a reaction mechanism that involves several steps. The first two are similar to those described above for the 1,2-diazine, leading to the unstable spiropyrimidine intermediate **15**. In this structure the imine N-2 becomes extremely electron deficient and adds a molecule of acetic acid leading to **16**. Due to the acidic medium, **16** undergoes complex processes of oxidative rearrangements and hydrolysis, via **17**, leading to the spiropyrrolidine-pyrrole derivatives (Scheme 4).

Using conventional methods, we have varied the reaction conditions with respect to molar ratio, solvents, temperatures, times, etc. The only reasonable route to the desired spiroazaheterocycle derivatives in good yields (≈50%) involved stirring of the reaction mixture for five days for the 1,2-diazines and for twenty days for the pyrimidines, at room temperature, in acetic acid as solvent.

The temperature is critical; temperatures above ambient conditions led to a mixture of diazine starting material and a polymeric derivative **18** of the dienophile. A reasonable explanation could be

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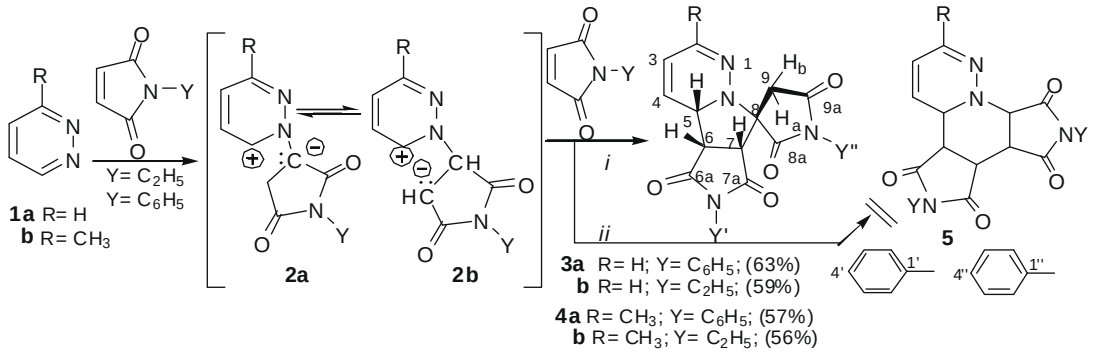


Scheme 1. Reaction pathway to spiropyridazines.

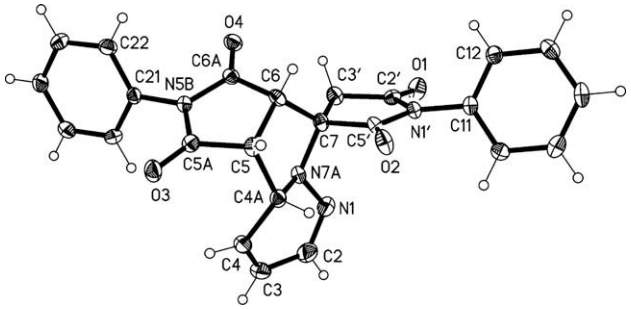


Figure 1. ORTEP representation at 50% probability and atom numbering scheme for spiropyridazine **3a**.

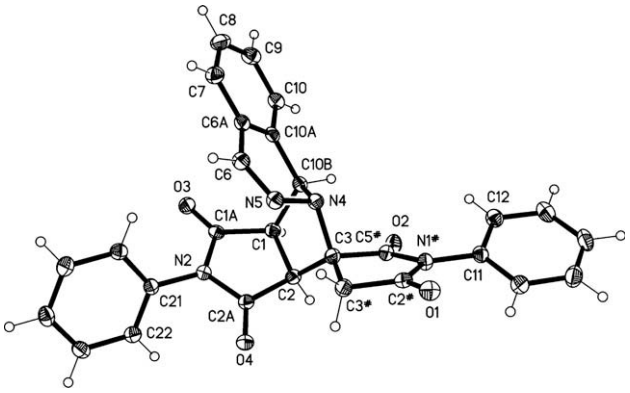


Figure 2. ORTEP representation at 50% probability and atom numbering scheme for spirophthalazine **8a** (one of the two independent molecules).

that, at high energy, the bond between the ylide carbanion and ylide nitrogen atom breaks leading to a diazine and the polymer **18** (pathway *ii*), Scheme 5. The literature describes similar results in the case of polymerization of maleimides in AcOH in the presence of zwitterionic species.[30]

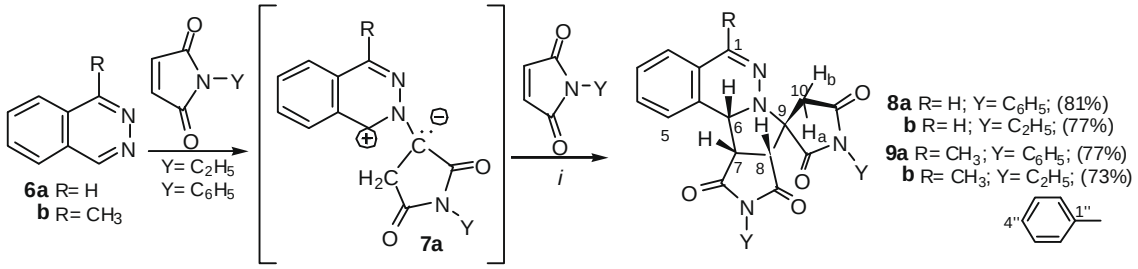
In the next step we examined the influence of microwaves and ultrasound irradiation on the reaction pathway. Unexpectedly, under MW and ultrasound irradiation, no matter what conditions were employed (different power for the reactor, different molar ratios, solvents, temperatures, times, etc.), a mixture of diazine starting material and the polymeric dienophile **18** was obtained. The same explanation as noted above for high temperature reactions could be valid.

The structures of the spiro derivatives were proven by elemental and spectral analysis (IR, ^{1}H NMR, ^{13}C NMR, DEPT 45, DEPT 90, DEPT 135, COSY, HMQC and HMBC) and X-ray analysis of compounds **3a**, **8a** and **12b**.[31]

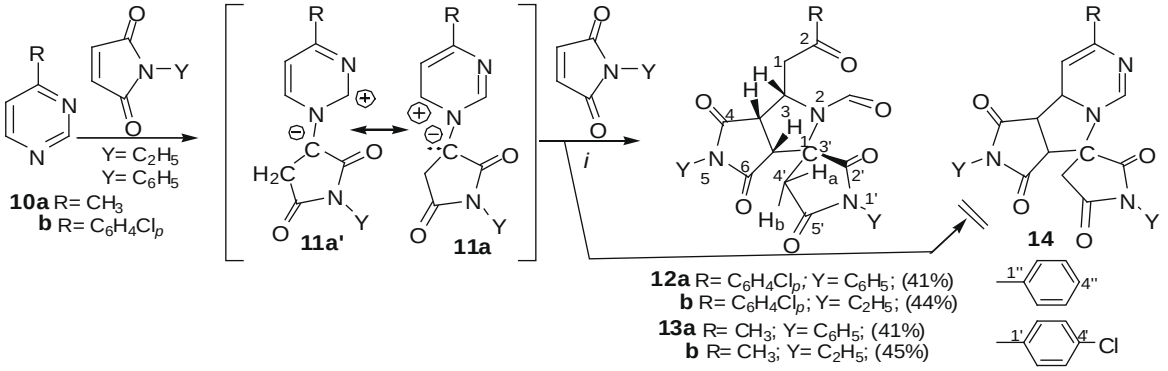
In conclusion, we have reported a general, efficient and straightforward method for the preparation of two classes of spiroazaheterocycles: spiropyrroles and spiro-1,2-diazines. A new class of spiroazaheterocycles, namely spiro[pyrrolidine-pyrrolo[3,4-*c*]pyrroles], has been obtained.

The reaction mechanism for the formation of spiro[pyrrolidine-pyrrolo[3,4-*c*]pyrrole] involves several steps: nucleophilic attack of pyridazine on the dienophile, a [3+2] dipolar cycloaddition of the ylide thus formed to a second molecule of the dienophile, and finally complex processes of oxidative-hydrolysis rearrangements in the acidic media. An explanation for the unexpected results obtained at high temperature, under MW and under ultrasound irradiation is also given.

Typical procedure for the synthesis of spiro derivatives: NEMI or NPMI (10 mmol) was dissolved in glacial acetic acid (10 mL) and the nitrogen heterocycle (pyrimidine, pyridazine, phthalazine, 5 mmol) was added. The resulting mixture was stirred at room temperature for 10 days for the reaction with NPMI and 20 days for the reaction with NEMI. The crude product obtained was filtered and dried in vacuum, then purified by washing with diethyl ether (20 mL).



Scheme 2. Reaction pathway to the spirophthalazines **8** and **9**.



Scheme 3. Reaction pathway to spiropyrrolidine-pyrroles **12** and **13**.

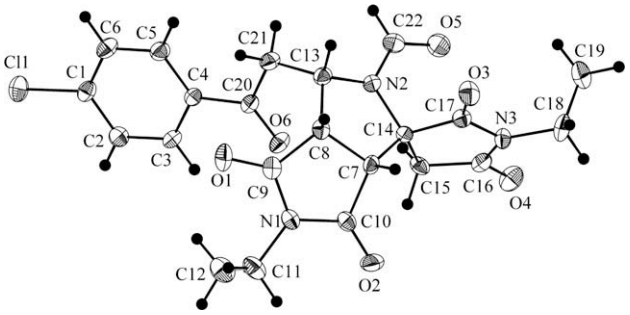
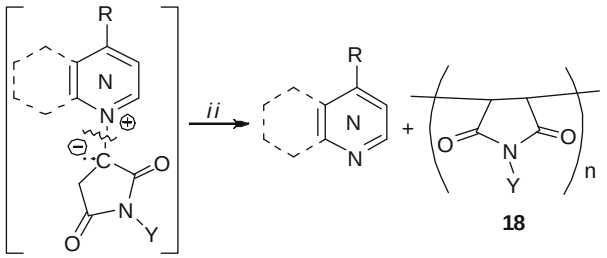


Figure 3. ORTEP representation at 30% probability and atom numbering scheme for spiropyrrolidine-pyrrole **12b**.

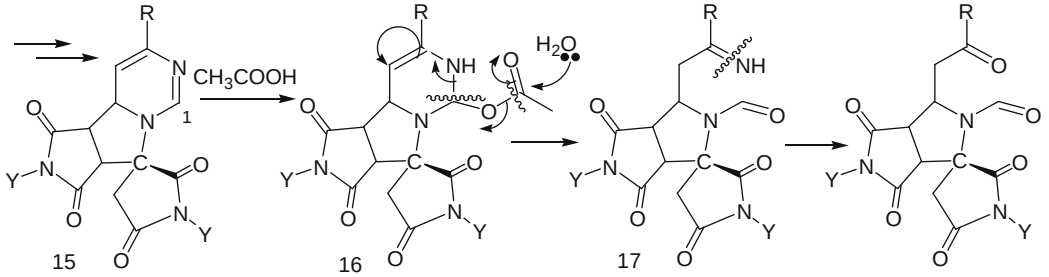


Scheme 5. Cleavage of diazinium ylides.

Spiro-pyrrolopyridazine (**3a**). This compound was obtained as yellow acicular crystals, mp 209–210 °C. IR: 3068, 2970 (C–H), 1756 (C=O imide), 1600, 1498, 1469, 1409, 1242 (C=C, C=N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55–7.45 (m, 4H, 2H3′, 2H3″), 7.43–7.38 (m, 2H, H4′, H4″), 7.31–7.24 (m, 4H, 2H2′, 2H2″), 7.08 (dd, J = 3.2 Hz, J = 1.2 Hz, 1H, H2), 6.52 (dt, J = 10.4 Hz, J = 5.6 Hz, J = 1.6 Hz, 1H, H3), 5.89 (dt, J = 10.4 Hz, J = 2.8 Hz, J = 1.2 Hz, 1H, H4), 4.66–4.60 (m, 1H, H5), 3.93 (d, J = 18.0 Hz, 1H, H9a), 3.70–3.65 (m, 2H, 1H6, 1H7), 3.00 (d, J = 18.0 Hz, 1H, H9b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.87 (C8a), 174.56 (C6a), 174.24 (C7a), 173.38 (C9a), 142.32 (C2), 131.34 (C1′), 131.25 (C1″), 129.27 (C3′), 129.22 (C3″), 129.09 (C4′), 128.90 (C4″), 127.60 (C3), 126.62 (C2′), 126.30 (C2″), 119.29 (C4), 68.30 (C8), 54.33 (C5), 44.94 (C6), 43.55 (C7), 34.72 (C9). Anal. Calcd for $C_{24}H_{18}N_4O_4$ (426.42): C, 67.60; H, 4.25; N, 13.14. Found: C, 67.54; H, 4.23; N, 13.10.

Spiro-pyrrolophthalazine (**8a**). This compound was obtained as yellow acicular crystals, mp 210–211 °C. IR: 3065, 2972 (C–H), 1752 (C=O imide), 1601, 1505, 1470, 1409 (C=C, C=N). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (t, J = 8.0 Hz, 1H, H3), 7.48–7.29 (m, 9H, H1, H2, H4, 2H2′, 2H2″, H4′, H4″), 7.18 (d, J = 7.2 Hz, 1H, H5), 7.14 (t, J = 7.6 Hz, 4H, 2H2′, 2H3″), 5.49 (d, J = 7.6 Hz, 1H, H6), 3.96–3.89 (m, 2H, H10a, H7), 3.76 (d, J = 8.0 Hz, 1H, H8), 3.47 (d, J = 18.4 Hz, 1H, H10b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.25 (C9a), 174.09 (C8a), 173.50 (C7a), 173.40 (C10a), 143.35 (C1), 131.39 (C1′), 131.37 (C1″), 131.16 (C3), 130.10 (C1a), 129.22 (C3′), 129.18 (C3″), 128.90 (C4′), 128.87 (C4″), 128.53 (C4), 127.39 (C2), 126.59 (C2′), 126.13 (C2″), 126.02 (C5), 124.79 (C5a), 70.77 (C9), 59.03 (C6), 46.50 (C8), 45.95 (C7), 34.45 (C10). Anal. Calcd for $C_{28}H_{20}N_4O_4$ (476.48): C, 70.58; H, 4.23; N, 11.76. Found: C, 70.55; H, 4.20; N, 11.68.

Spiro-pyrrolopyrrolidine-carbaldehyde (**12b**). This compound was obtained as yellow acicular crystals, mp 163–164 °C. Yield 44%. IR: 3070, 2965 (C–H), 1758 (C=O imide), 1696 (C=O ketone), 1600, 1504, 1470, 1403, 1236 (C=C, C=N), 1129. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (s, 1H, H-aldehyde), 7.82 (d, J = 7.2 Hz, 2H, 2H2′), 7.46 (d, J = 7.2 Hz, 2H, 2H3′), 4.95 (q, J = 9.0 Hz, J = 2.0 Hz, 1H, H3), 3.93 (t, J = 10.0 Hz, 1H, H3a), 3.82–3.63 [m, 8H, 1H6a, 1H4′a, CH_2 (keto), 2×CH_2 (ethyl)], 2.90 (d, J = 18.4 Hz, 1H, H4′b), 1.22 (t, J = 7.2 Hz, 3H, CH_3), 1.10 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.20 (C=O ketone), 176.89 (C=O, C4), 174.88 (C=O, C5), 173.87 (C=O, C5′), 173.45 (C=O, C2′), 160.48 (C=O, aldehyde), 140.61 (C4′, phenyl), 134.10 (C1′, phenyl), 129.37 (C3, phenyl′), 129.26 (C2′, phenyl), 66.93 (C3′, spiro),



Scheme 4. Reaction mechanism for obtaining spiropyrrolidine-pyrrole derivatives.

55.08 (C1, α-ketone), 50.60 (C3), 46.17 (C6a), 40.23 (C3a), 37.27 (C4′), 34.49 (CH_2), 34.41 (CH_2), 12.71 (CH_3), 12.49 (CH_3). Anal. Calcd for $C_{22}H_{22}ClN_3O_6$ (459.88): C, 57.46; H, 4.82; N, 9.14. Found: C, 57.51; H, 4.78; N, 9.05.

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31. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 735317 (**3a**), 735318 (**8a**) and 732133 (**12b**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).