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Synthesis of pyrrolo[3,4-*c*]quinolines by 1,5-electrocyclisation of non-stabilised azomethine ylides

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Abstract—A new route to the pyrrolo[3,4-*c*]quinoline ring system has been developed via the 1,5-dipolar electrocyclisation reactions of azomethine ylides derived from easily available 3-formylquinoline derivatives. The intermediacy of azomethine ylides was shown by the trapping of the proposed dipoles with *N*-phenylmaleimide.

Quinolines are an important group of heterocyclic compounds. Among the quinolines 2-chloro-3-formylquinolines occupy a prominent position as they are key intermediates for further [*b*]-annelation of a wide variety of rings and for various functional group interconversions.[1] The applications of these methodologies have yielded beside the huge number of new quinoline derivatives new synthetic approaches for alkaloids such as camptothecin,[2] luotonin A,[3] or nothapodytine (Fig. 1).[4]

In this paper we report the first [*c*]-annelation of this type of quinoline by 1,5-electrocyclisation of azomethine ylides.[5] This conversion gives a direct route to the otherwise hardly accessible pyrrolo[3,4-*c*]quinoline ring system.[6]

The quinolines (**1a**–**c**) were prepared by the method described by Meth-Cohn from the corresponding acetanilides by treatment with the Vilsmeier reagent in a single step.[7] The non-stabilized azomethine ylides **2** were generated from these aldehydes **1a**–**c** using the decarboxylation method.[8] The reaction of 2-chloro-3-formylquinolines **1a**–**c** with sarcosine in refluxing xylene gave 2-methyl-2,4,5,9*b*-tetrahydro-1*H*-pyrrolo[3,4-*c*]-quinolin-4-ones **4a**–**c** in acceptable yields via the expected 1,5-electrocyclisation reaction accompanied by hydrolysis of the chlorine function under the applied reaction conditions in the presence of the water formed in the first step[9] (Scheme 1).

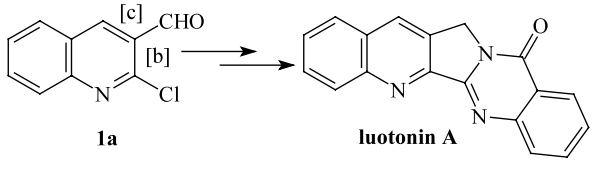

Figure 1.

The intermediacy of azomethine ylides **2** was shown by trapping the proposed dipoles with *N*-phenylmaleimide to give the two isomeric cycloadducts **5** and **6** (*endo–exo* ratio ≈1:1) in a quantitative yield (Scheme 1).[10]

After the successful 1,5-electrocyclisation of non-stabilised azomethine ylides, we studied the reactivity of the analogous ester-stabilised system generated from the corresponding Schiff-base **7** by thermal 1,2-prototropy.[11] In contrast, in these cases, no 1,5-electrocyclisation was observed, the **7** imine remained unchanged even after a prolonged reaction time in refluxing xylene (Scheme 2). This result is in good agreement with our earlier observations on the reactivity of azomethine ylides in electrocyclisation reactions.[12]

We performed the next series of experiments with 2-phenyl-3-formylquinolines **8a**–**c**. In these, with azomethine ylides **9** derived from the aldehydes there is a possibility—besides the 1,5-electrocyclisation—of a 1,7-electrocyclic ring closure onto the phenyl group.[13] The starting material was prepared in three simple steps from the 2-chloro-3-formylquinolines including a palladium-catalysed Suzuki coupling with phenylboronic acid (Scheme 2).

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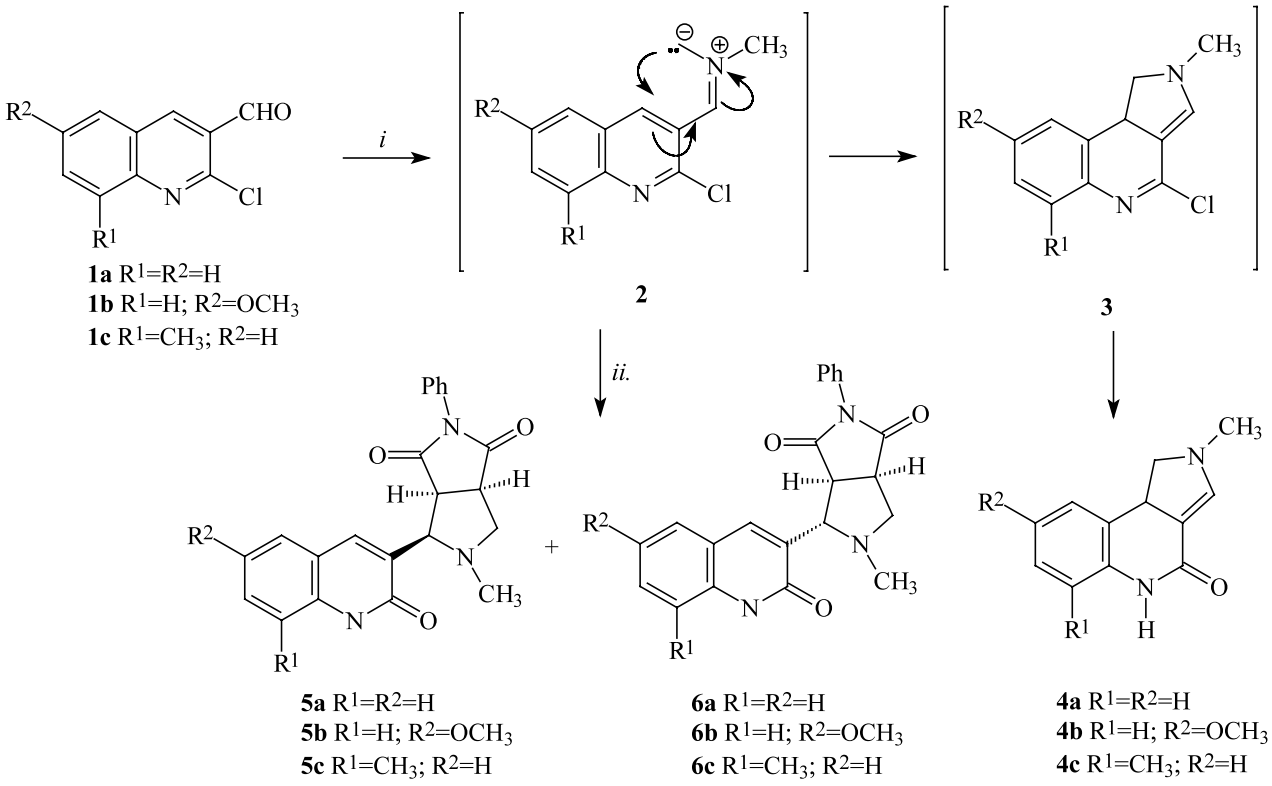
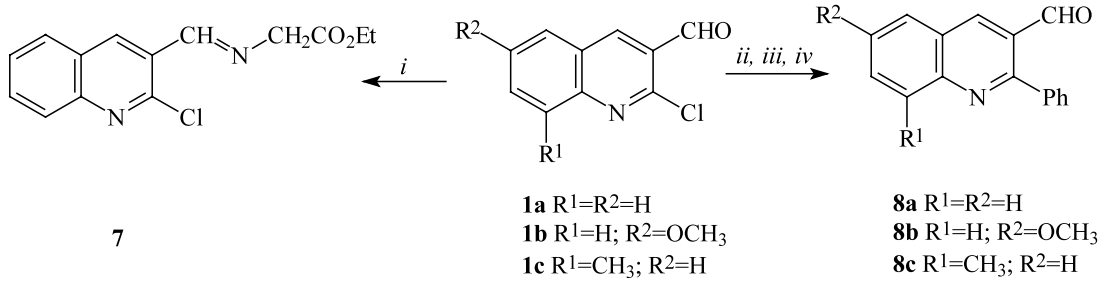


Scheme 1. *Reagents and conditions*: (i) sarcosine (2 equiv.), xylene, 140°C; (ii) *N*-phenylmaleimide (1 equiv.), sarcosine (2 equiv.), xylene, 140°C.



Scheme 2. *Reagents and conditions*: (i) $EtO_2CCH_2NH_2{\cdot}HCl$, Et_3N, CH_2Cl_2, rt; (ii) $HOCH_2CH_2OH$, PTSA, benzene, reflux; (iii) $PhB(OH)_2$, $Pd(OAc)_2$ (cat.), K_2CO_3, DME, H_2O; (iv) 5% HCl, THF, 80°C.

The reaction of the resultant quinolines **8a**–**c** with sarcosine in refluxing xylene gave 2-methyl-4-phenyl-1*H*-pyrrolo[3,4-*c*]quinolines **12a**–**c** as products in moderate yields (Scheme 3).[9] The 1,5-electrocyclisations in these cases were followed by full aromatisation to the tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline **11** ring system. This slightly different result compared to the transformation **1** ⇒ **4**, may be explained by the delocalisation energy difference between the lactam products **4** and compounds **12** having a more extended conjugation.

The intermediacy of azomethine ylides was again shown by trapping the dipole with *N*-phenylmaleimide to give the two isomeric cycloadducts **13** and **14** (ratio ≈1:5) in good yield.[10] The stereochemistry of the major isomer (**14**) was proved by NOE experiments (Scheme 4).

Acknowledgements

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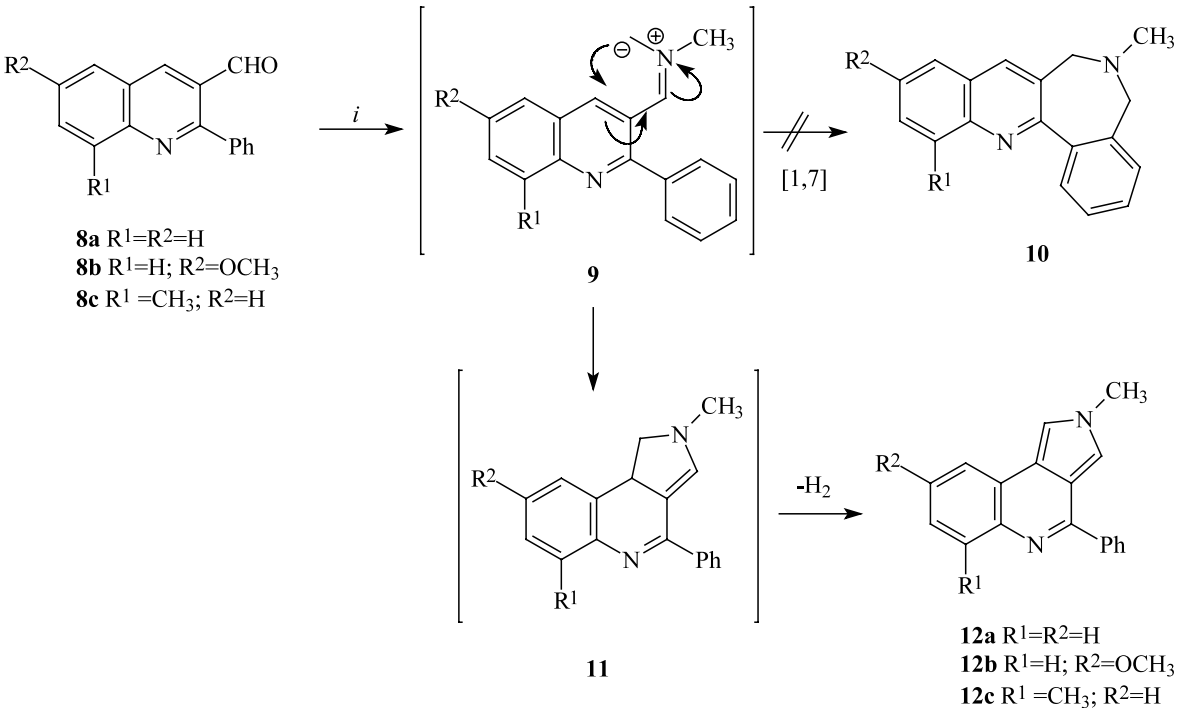
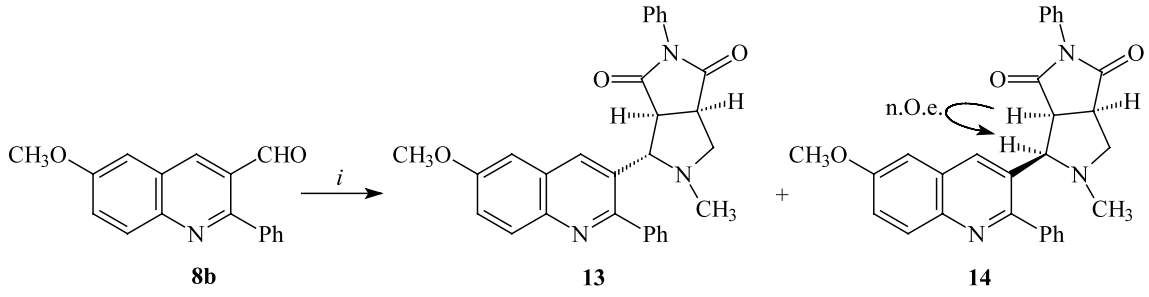


Scheme 3. *Reagents and conditions*: (i) sarcosine (2 equiv.), xylene, 140°C.



Scheme 4. *Reagents and conditions*: (i) *N*-phenylmaleimide (1 equiv.), sarcosine (2 equiv.), xylene, 140°C.

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9. *General procedure for the preparation of compounds* ***4a–c*** *and* ***12a–c***: The aldehyde (3 mmol) was dissolved in xylene (30 cm^3) and sarcosine (0.54 g, 6.0 mmol) was added. The reaction mixture was refluxed until the starting aldehyde completely disappeared (judged by TLC). All the solvent was removed in vacuo and the residue

purified by flash chromatography (eluent petroleum ether–acetone 3:1) to give the crystalline product in 40–60% yield. All new compounds afforded correct elemental analyses and spectroscopic data. *2-Methyl-2,4,5,9b-tetrahydro-1H-pyrrolo[3,4-c]quinolin-4-one* (***4a***): ^{1}H NMR (250 MHz, d_6-DMSO): 7.79 (s, 1H), 7.66 (d, 1H, *J* 8 Hz), 7.54 (d, 1H, *J* 8 Hz), 7.44 (t, 1H, *J* 8 Hz), 7.14 (t, 1H, *J* 8 Hz), 5.77 (br s, 1H, NH), 5.17 (br s, 1H), 3.69 (t, 1H, *J* 9.0 Hz), 3.30 (dd, 1H, *J* 2.2 and 9.0 Hz), 2.99 (s, 3H, NCH_3); ^{13}C NMR (63 MHz, d_6-DMSO): 160.4 (q), 148.5 (q), 130.8 (CH), 128.9 (q), 128.8 (CH), 128.0 (CH), 125.4 (CH), 123.6 (q), 121.3 (CH), 66.0 (CH), 59.8 (CH_2), 31.2 (CH_3); *2-Methyl-4-phenyl-1H-pyrrolo[3,4-c]quinoline* (***12a***): ^{1}H NMR (250 MHz, $CDCl_3$): 8.10 (dd, 1H, *J* 1.5 and 8.0 Hz), 7.97 (dd, 2H, *J* 1.3 and 7.8 Hz), 7.92 (dd, 1H, *J* 1.5 and 8.0 Hz), 7.53–7.38 (m, 5H), 7.27 (d, 1H, *J* 1.5 Hz), 7.20 (d, 1H, *J* 1.5 Hz), 3.77 (s, 3H, NCH_3); ^{13}C NMR (63 MHz, $CDCl_3$): 155.6 (q, C-4), 142.8 (q, C-5a), 140.3 (q), 129.7 (CH), 129.0 (CH), 128.5 (2×CH), 128.4 (2×CH), 126.0 (CH), 125.8 (CH), 122.9 (q), 122.2 (CH), 121.9 (q), 117.6 (CH), 117.5 (q), 112.8 (CH), 37.4 (CH_3).

10. *General procedure for 1,3-dipolar cycloadditions of azomethine ylides* ***2*** *and* ***9*** *to N-phenyl-maleimide*: The aldehyde (1 mmol) was dissolved in xylene (50 cm^3) and *N*-phenyl-maleimide (0.17 g 1.0 mmol) and sarcosine (0.36 g 4.0 mmol) were added. The reaction mixture was refluxed for 1 h. On cooling the solvent was removed in vacuo and the residue was purified by flash chromatography (eluent petroleum ether–acetone, 3:1) to give the crystalline product in 90–95% yield. *Cycloadduct* (***14***): ^{1}H NMR (250 MHz, d_6-DMSO): 8.32 (s, 1H), 8.06 (d, 1H, *J* 9 Hz), 7.52–7.37 (m, 9H), 7.10 (m, 3H), 3.93 (s, 3H), 3.84 (d, 1H, *J* 7.3 Hz), 3.65–3.50 (m, 4H), 2.07 (s, 3H); ^{13}C NMR (63 MHz, d_6-DMSO): 176.2 (q), 175.5 (q), 158.4 (q), 157.9 (q), 143.4 (q), 139.9 (q), 134.7 (CH), 131.4 (q), 131.0 (q), 130.8 (CH), 129.8 (2×CH), 129.1 (2×CH), 128.6 (CH), 128.1 (2×CH), 127.9 (CH), 127.8 (q), 126.4 (2×CH), 123.1 (CH), 104.5 (CH), 68.0 (CH), 57.3 (CH_2), 55.5 (CH_3), 54.8 (CH), 44.2 (CH), 38.6 (CH_3).
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