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1,5-Electrocyclisation of azomethine ylides leading to pyrrolo[2,1-*a*]isoquinolines—concise construction of the lamellarin skeleton

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Abstract—A new, general route to the 1,2-diaryl-substituted pyrrolo[2,1-*a*]isoquinolines has been developed via the 1,5-dipolar electrocyclisation reactions of azomethine ylides derived from readily available stilbenic acid derivatives. This method was applied to the concise construction of a lamellarin skeleton.

The 1,3-dipolar cycloaddition of azomethine ylides represents perhaps the most important example of the variety of reaction pathways available to these dipoles.[1] There are, however, many other synthetically useful reactions of these dipoles, including the 1,5-electrocyclic ring closure of appropriately substituted dipolar systems.[2] Recently, we[3] and others[4] published the first examples of the 1,7-electrocyclisation of azomethine ylides with α,β:γ,δ-unsaturation.[5] This method was shown to be general for the annelation of a benzazepine ring to different heterocycles in one step.[6]

We have also demonstrated the first 1,7-electrocyclisation of azomethine ylides (**2**, $R^1 = H$, $R^2 = Ph$) stabilised with an electron-withdrawing group (R = e.g., CO_2Me), providing a useful route to the tetrahydrobenz[5,6]azepino[2,1-*a*]isoquinoline ring system **3** (Scheme 1).[7]

As a continuation of these studies, we have examined the reactivity of some closely related azomethine ylides (**2**, $R^1 = Ar$, $R^2 = H$) and investigated the effect of the additional aryl substituents (G) on the course of the 1,7-electrocyclisation process.

The starting materials for this study were prepared via the appropriate stilbenic acids **6** (themselves readily available from substituted benzaldehydes **4** and phenylacetic acids **5**) by the treatment of the corresponding acid chlorides with a slight excess of 2-(3,4-dimethoxyphenyl)ethylamine **7**. The cyclisation of amide **8** was carried out using the Bischler–Napieralski procedure,[8] in the presence of $POCl_3$, resulting in the formation of 3,4-dihydroisoquinolines **9**. The subsequent reaction of these isoquinolines **9** with various bromoalkyl derivatives in anhydrous ether gave the quaternary salts **10** (Scheme 2).

To our surprise, reacting these isoquinolinium salts **10a** ($R^5 = CO_2Et$, $CH{=}CH_2$) with triethylamine at ambient temperature in dry ethanol, did not give the expected tetrahydro-benz[5,6]azepino[2,1-*a*]isoquinolines **3**, originating from a 1,7-electrocyclisation, but the pyrrole derivatives **12a** ($R^5 = CO_2Et$, $CH{=}CH_2$) were obtained, after column chromatography, in 52–59% yield (Scheme 2).

We propose that the mechanism for the formation of these pyrroles involves the 1,5-electrocyclisation of the azomethine ylide, followed by the aerobic oxidation of the **11** pyrroline intermediate, which was not isolated in these cases.

In the reaction of isoquinolinium salt **10a** ($R^5 = Ph$) with base, using similar conditions, a white precipitate

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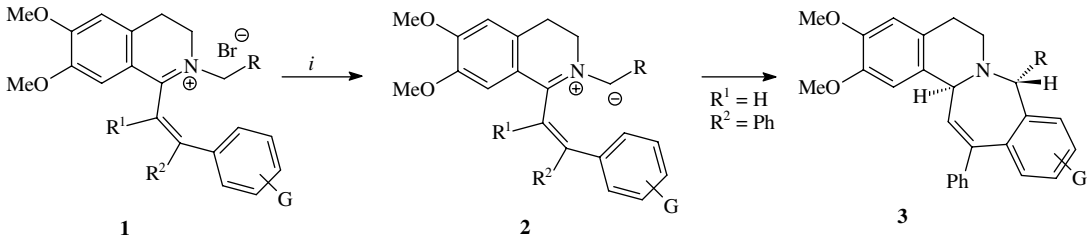
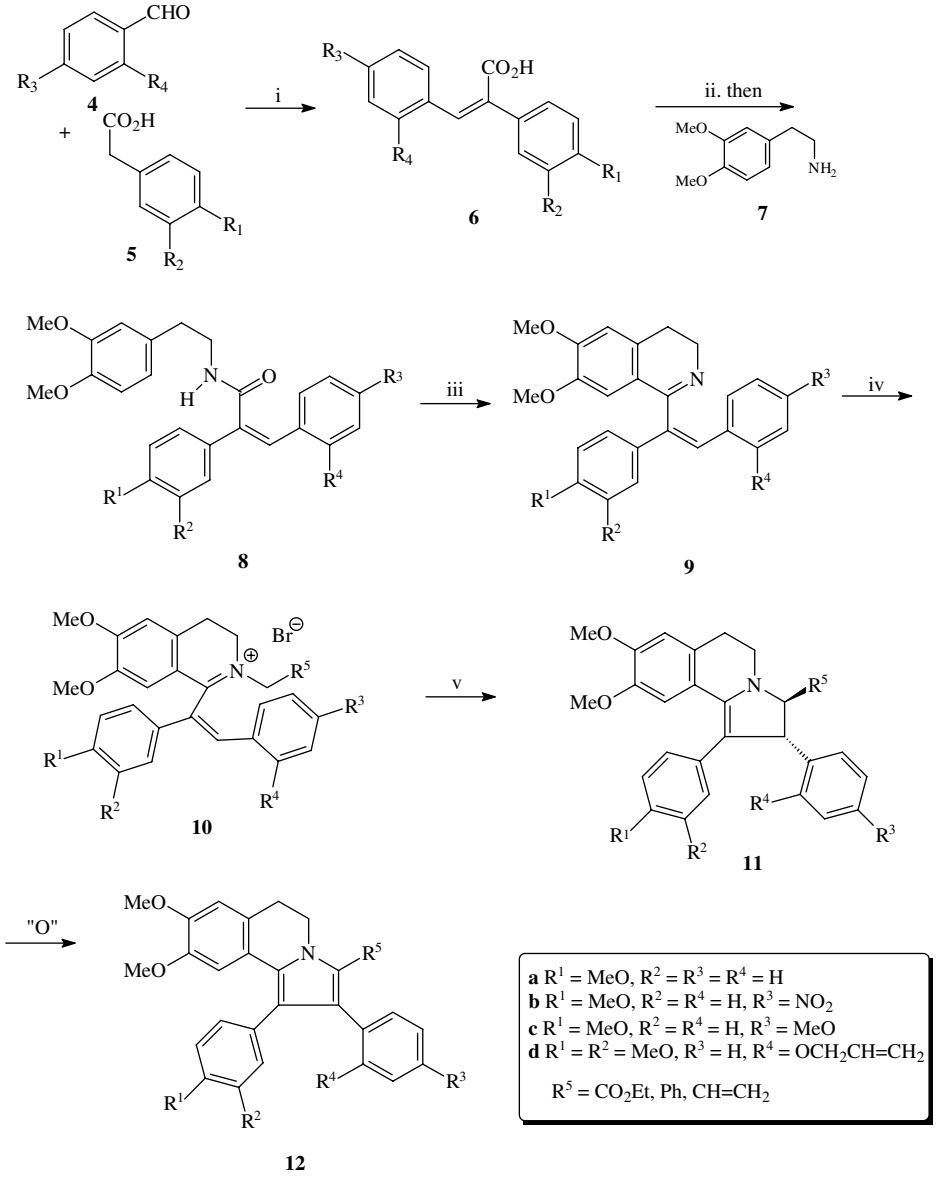


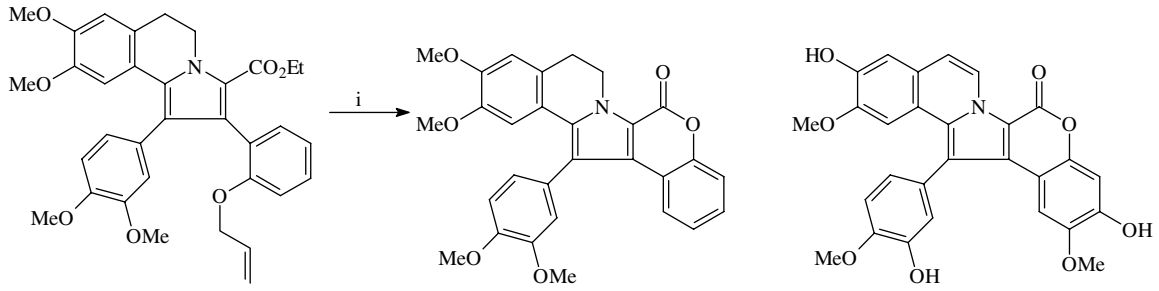
Scheme 1. Reagents and conditions: (i) Et_3N, EtOH, rt.



Scheme 2. Reagents and conditions: (i) Et_3N, Ac_2O, reflux (48–66%); (ii) $SOCl_2$, reflux (90–95%); (iii) $POCl_3$, toluene, reflux (90–96%); (iv) $BrCH_2R^5$, Et_2O, rt (95–98%); (v) Et_3N, EtOH, rt (52–68%).

was collected (in 55–68% yield) and the expected pyrrole derivative **12a** ($R^5 = Ph$) was isolated from the filtrate, but only in 5–12% yield. The main crystalline product proved to be the pyrroline derivative **11a** ($R^5 = Ph$). The relative stereochemistry of this cycloadduct was deduced by NOE studies. Similar results were obtained with two isoquinolinium bromide analogues (**10b** and **10c**).

We next examined the synthesis of the lamellarin skeleton using this 1,5-electrocyclisation methodology. The lamellarins, described for the first time in 1985 by



12d 13 Lamellarin D

Scheme 3. Reagents and conditions: (i) 10% Pd/C, TsOH, EtOH, H_2O, reflux (68%).

Faulkner and co-workers,[9] are a group of approximately 40 compounds, isolated from marine invertebrates such as sponges, tunicates and molluscs.[10] A wide array of interesting biological activity has been found in the lamellarins, including inhibition of cell division, cytotoxicity (against several multidrug-resistant cell lines),[11] HIV-1 integrase inhibition[12] and immunomodulatory activity.[10a] Lamellarin D (Scheme 3) was also found to be a novel potent inhibitor of topoisomerase I.[13] To establish some structure–activity relationships (SAR) and to find out the mechanism of action of these alkaloids, relatively large quantities of lamellarins are required. However, because the natural sources of lamellarins provide these compounds in only small quantities, total synthesis is a vital alternative in providing these compounds. In order to satisfy this demand, a number of research groups have reported elegant strategies for total syntheses of lamellarins[14] including solid-phase methods.[15]

Based on the results depicted in Scheme 2, we have developed a simple, general method for the synthesis of the core of the lamellarin alkaloids. The synthesis starts from *O*-allylsalicylaldehyde **4d** and in five steps gives the pyrrole derivative (**12d**, $R^5 = CO_2Et$) in 31% yield. Removal of the allylic protecting group by Pd/C in the presence of TsOH[16] resulted in the formation of pyrroloisoquinoline **13**, containing the 8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolin-6-one skeleton of some of the lamellarin alkaloids (Scheme 3),[17] in one step via simultaneous lactone formation.

In summary, we have explored a convenient reaction sequence which provides a useful route to pyrrolo[2,1-*a*]isoquinoline ring system via the 1,5-dipolar electrocyclisation reactions of azomethine ylides derived from easily available stilbenic acid derivatives.[18] The synthesised pyrrolo[2,1-*a*]isoquinolines—as we have demonstrated in one example—could be novel building blocks for the synthesis of otherwise difficultly obtainable lamellarin alkaloids and analogues.

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17. *All new compounds afforded correct elemental analyses and spectroscopic data. Selected data of representative examples*: Compound **11a** (R^5 = Ph): ^{1}H NMR (500 MHz, $CDCl_3$): 7.29–7.25 (m, 5H, Ph^3–H), 7.18–7.12 (m, 5H, Ph^2–H), 7.09 (d, 2H, *J* 8.8 Hz, Ar^1–2 and 6H), 6.92 (s, 1H, H-10), 6.72 (d, 2H, *J* 8.8 Hz, Ar^1–3 and 5H), 6.60 (s, 1H, H-7), 4.17 and 4.16 (2 × d, 2H, *J* 11.9 Hz, H-2 and H-3), 3.83 (s, 3H, 8-OMe), 3.66 (s, 3H, OMe), 3.32 (s, 3H, 9-OMe), 3.19 (m, 1H, H-6), 3.07 (m, 1H, H-5), 2.84 (m, 1H, H-5), 2.78 (m, 1H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): 157.9 (q), 148.6 (q), 146.6 (q), 142.2 (q), 141.6 (q), 140.3 (q), 131.3 (2 × CH), 130.5 (q), 129.3 (2 × CH), 128.2 (2 × CH), 128.1 (q), 127.9 (2 × CH), 127.3 (2 × CH), 127.2 (CH), 126.3 (CH), 121.2 (q), 113.7 (2 × CH), 112.4 (q), 110.6 (CH), 109.3 (CH), 78.6 (CH), 64.0 (CH), 55.7 (CH_3), 55.0 (CH_3), 54.95 (CH_3), 46.9 (CH_2), 29.9 (CH_2). Compound **12d** ($R^5 = CO_2Et$): ^{1}H NMR (500 MHz, $CDCl_3$): 7.50 (d, 1H, *J* 7.8 Hz, Ar^2–3′H), 7.25 (t, 1H, *J* 7.8 Hz, Ar^2–4′H), 7.13 (t, 1H, *J* 7.8 Hz, Ar^2–5′H), 7.02 (d, 1H, *J* 7.8 Hz, Ar^2–6′H), 6.79–6.69 (m, 5H, H-7, H-10, and Ar^1–H), 5.82 (m, 1H, allyl–CH), 5.14 (m, 2H, allyl–CH_2), 4.53 (m, 2H, allyl–CH_2), 4.00 (m, 2H, H-6), 3.90 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.36 (s, 3H, OMe), 3.05 (t, 2H, *J* 6.6 Hz, H-5); ^{13}C NMR (125 MHz, $CDCl_3$): 162.0 (q), 156.5 (q), 148.4 (q), 148.0 (q), 147.5 (q), 147.2 (q), 138.7 (CH), 133.9 (CH), 132.2 (CH), 130.8 (q), 129.0 (q), 128.4 (q), 127.8 (CH), 127.4 (q), 125.9 (q), 124.4 (CH), 123.1 (CH), 121.7 (q), 121.2 (q), 119.8 (q), 116.4 (CH_2), 116.3 (CH), 114.1 (CH), 111.9 (CH), 110.8 (CH), 108.8 (CH), 69.0 (CH_2), 59.5 (CH_2), 56.1 (CH_3), 55.9 (CH_3), 55.8 (CH_3), 55.3 (CH_3), 42.8 (CH_2), 29.1 (CH_2), 13.6 (CH_3). Compound **13**: ^{1}H NMR (500 MHz, $CDCl_3$): 7.37 (d, 1H, *J* 8 Hz, H-4), 7.27 (t, 1H, *J* 8 Hz, H-3), 7.23 (d, 1H, *J* 8 Hz, H-1), 7.07 (m, 2H, Ar^{14}–5′ and 6′H), 7.02 (s, 1H, Ar^{14}–2′H), 7.00 (t, 1H, *J* 8 Hz, H-2), 6.76 (s, 1H, H-13), 6.66 (s, 1H, H-10), 4.81 (m, 2H, H-8), 3.99 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.36 (s, 3H, OMe), 3.12 (t, 2H, *J* 7.0 Hz, H-9); ^{13}C NMR (125 MHz, $CDCl_3$): 155.2 (q), 151.2 (q), 149.8 (q), 149.0 (q), 148.9 (q), 147.5 (q), 136.1 (q), 127.8 (q), 127.5 (q), 127.3 (CH), 126.6 (q), 123.7 (CH), 123.3 (CH), 123.25 (CH), 120.0 (q), 118.3(q), 117.1 (CH), 115.8 (q), 114.5 (q), 113.7 (CH), 112.0 (CH), 110.9 (CH), 108.7 (CH), 56.1 (2 × CH_3), 55.9 (CH_3), 55.1 (CH_3), 42.5 (CH_2), 28.7 (CH_2).
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