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Inverse-electron-demand Diels–Alder reactions of 4-aryl-2-pyrones with electron-rich dienophiles

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Abstract

The Diels–Alder reaction of 4-aryl-pyrones with electron-rich dienophiles afforded substituted biaryl derivatives in most cases. At the minimal temperatures necessary for a measurable conversion of the starting pyrones, the bicyclic lactones, the primary products of the condensation, underwent cycloreversion by extruding carbon dioxide and then aromatised through further eliminations. In the case of the more active 4-aryl-6-chloro-pyrone, a formal substitution was observed instead of the expected cycloaddition with an active dienophile, while in its reaction with a Schiff-base the primary product of the cycloaddition was trapped through the formation of a new tetrahydropyridine derivative.

Keywords: Diels–Alder reaction; 4-aryl-2-pyrones; biphenyls.

Lycoricidine (**1**) is a herbal growth regulator[1] and an important representative of the Amaryllidaceae alkaloids with a neutral character and also possesses significant antitumour activity.[2] Its challenging structure, especially the substitution and stereochemistry of the C-ring has evoked considerable synthetic work.[3] The Diels–Alder reaction of α-pyrones is an efficient route to polysubstituted cyclohexenes without aromatic substituents, with excellent control of relative and absolute stereochemistry.[4–8] In our work this methodology was tried for the construction of the C-ring of lycoricidine analogues. The structurally and stereochemically rich bicyclic lactones, the primary products of the cycloaddition, were successfully isolated in several cases despite their thermal lability even from reactions conducted above 100°C.[6,7] Based on our former experiences,[9] the intermediates obtained by the opening of the lactone ring and the necessary functional group transformations were expected to cyclise via a modified Bischler–Napieralski reaction (Scheme 1).

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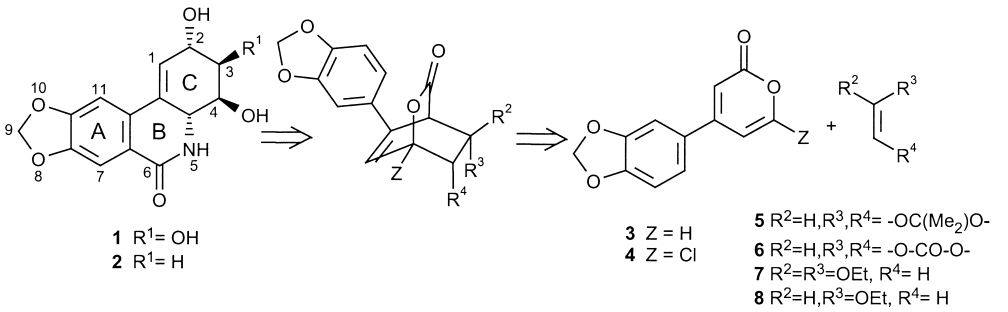


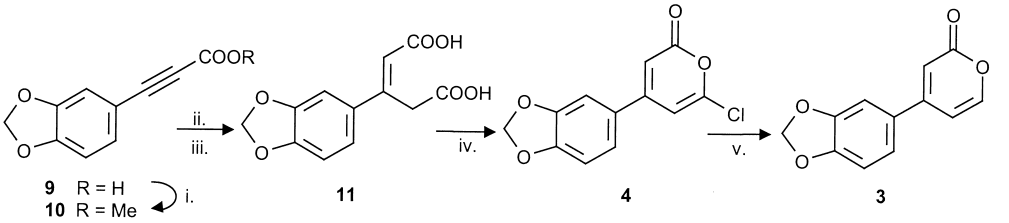
Scheme 1.

As starting dienophiles 2,2-dimethyl-1,3-dioxole (**5**), vinylene carbonate (**6**), 1,1-dimethoxyethylene (**7**) and ethoxyethylene (**8**) were selected corresponding to the substitution of the target lycoricidine (**1**) and 3-deoxy-lycoricidine (**2**) molecules. Cycloaddition of these electron-rich dienophiles to aryl-pyrones can be described using FMO theory as an inverse electron-demand process in which the LUMO of the diene component is combined with the HOMO of the dienophile[10] (for the corresponding energy values of the reactants calculated by the AM1 method see Table 1).

Table 1

Dienophile	E_{HOMO} (eV)	E_{LUMO} (eV)	Diene	E_{HOMO} (eV)	E_{LUMO} (eV)
5	−8.89	1.12	**3**	−9.14	−1.14
6	−10.33	0.02	**4**	−9.22	−1.32
7	−8.69	1.70			
8	−9.35	1.50			

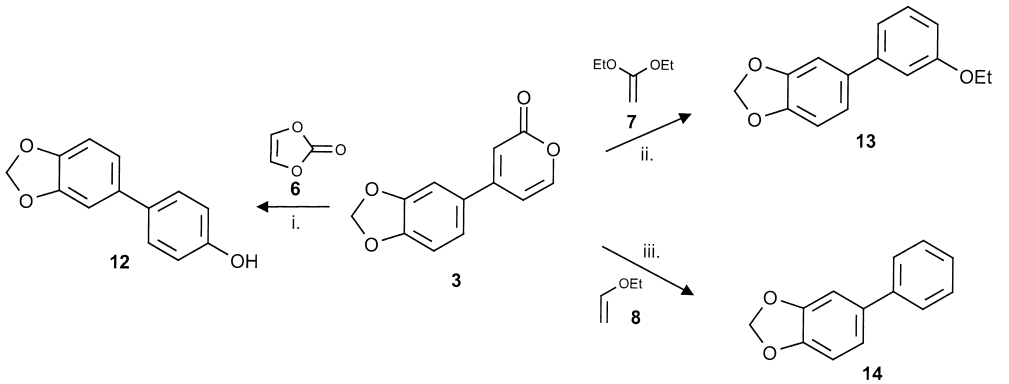
The synthesis of 4-aryl-pyrone (**3**) was achieved by a route which also involved the preparation of the 6-chloro-derivative (**4**) with a more pronounced electron-poor character and therefore higher reactivity (Scheme 2).



Scheme 2. (i) MeOH, H_2SO_4, rt, 24 h, 91%; (ii) NaOMe, $CH_2(COOMe)_2$, benzene, MeOH, THF, reflux, 8 h, 93%; (iii) KOH, EtOH, reflux, 24 h, 69%; (iv) PCl_5, chlorobenzene, rt, 3 h, 54%; (v) Zn, AcOH, 3 h, 89%

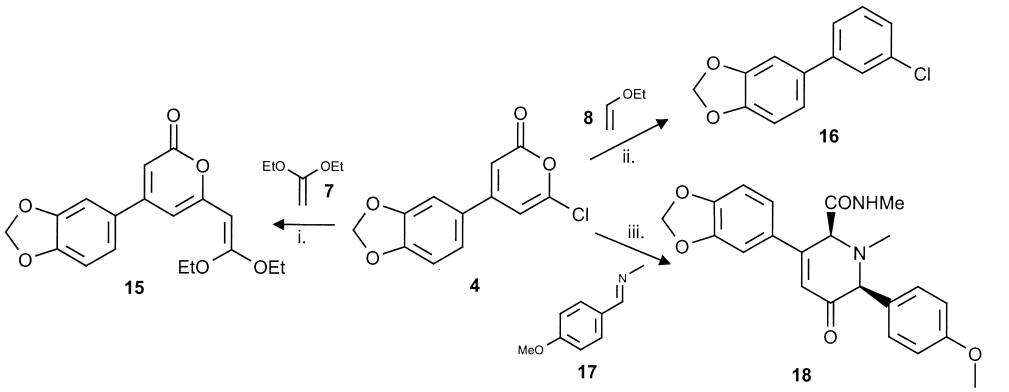
In order to minimise the chance of the decomposition of the primary adduct by cycloreversion, the reactions were conducted at the lowest possible temperature at which considerable conversion could be detected by HPLC, using the dienophile also as a solvent (except for **5**). In the case of **5**, none of pyrones **3** and **4** were reactive enough to combine with the fairly labile dienophile before its decomposition, allowing only the regeneration of starting compounds from a tarry reaction mixture. At the same time the reaction of aryl-pyrone **3** with vinylene carbonate

6 gave biphenyl derivative **12** as the only isolable product (in 80% yield after 10 days at 115°C beside the regeneration of 60% of the starting pyrone) with the regioselective formation of the *para*-hydroxy derivative following the extrusion of two moles of carbon dioxide from the primary adduct. Under similar conditions the reaction of chloro-pyrone (**4**) resulted in slow decomposition. In the case of both dienophiles **7** and **8** only aromatic products could be isolated from their reaction mixture even after 10% conversion of the starting diene **3** (5 days at 60–70°C). The biphenyls were generated by cycloreversion followed by ethanol elimination. Dienophile **7** yielded *meta*-substituted derivative (**13**) due to the regioselectivity of the cycloaddition (Scheme 3).



Scheme 3. (i) Sealed tube, **6**, 115°C, 10 days, 80% (based on recovered starting material); (ii) sealed tube, **7**, 70°C, 5 days, 18%, or 90°C, 3 days, 75%; (iii) sealed tube, **8**, 70°C, 10 days, 7%, or 120°C, 2 days, 55%

The course of the reaction of ethoxyethylene (**8**) and 6-chloropyrone (**4**) was similar. Surprisingly, trisubstituted ethylene **15** was obtained in the reaction of 1,1-diethoxyethylene (**7**) and pyrone (**4**), the formation of which can be explained by an attack of the electron-rich olefin on the electron-deficient C-6 of the pyrone followed by HCl elimination. On the other hand cycloreversion of the primary product could be averted in the hetero Diels–Alder cycloaddition of pyrone **4** with an electron-rich olefin of another type, the Schiff-base **17**, obtained from 4-methoxy-benzaldehyde and methylamine. The initial lactone was 'trapped' by the methyl amine present in equilibrium with the starting imine, affording the tetrahydropyridinyl carboxylic amide (**18**) following HCl elimination. The stereochemistry of compound **18** was established by NOE experiments, the essential observations being significant NOE enhancements between H_2 and H_6 (Scheme 4).



Scheme 4. (i) Sealed tube, **7**, CH_2Cl_2, 50°C, 4 h, 68%; (ii) sealed tube, **8**, 70°C, 10 days, 15%, or 120°C, 2 days, 85%; (iii) sealed tube, **17**, CH_2Cl_2, 110°C, 2 days, 25%

Under thermal conditions, at temperatures necessary for a minimal conversion the Diels–Alder reaction of 4-aryl-pyrones led to the formation of biaryl compounds. Our experiences suggest that isolation of the initial bicyclic products would need lower temperatures and necessarily higher pressures (5–20 kbar).[11]

Characterisation of compound **4**: colourless crystals, mp 208–212°C. $C_{12}H_7ClO_4$ (250.641) requires: C, 57.51; H, 2.82; Cl, 14.14%. Found: C, 57.40; H, 2.78; Cl, 14.25%. IR (KBr), cm^{-1}: 3420, 3086, 2970, 2796, 1722, 1611, 1524, 1505, 1437, 1408, 1263, 1086, 1038, 1028. ^1H NMR (200 MHz, $CDCl_3$): 7.12 (dd, 1H, $J=8.0$, 1.8, H-6′), 7.02 (d, 1H, $J=1.8$, H-4′), 6.92 (d, 1H, $J=8.0$, H-7′), 6.49 (d, 1H, $J=1.4$, H-3), 6.31 (d, 1H, $J=1.4$, H-5), 6.07 (s, 2H, H-2′).

Characterisation of compound **13**: colourless oil. HRMS ($C_{15}H_{14}O_3$) calcd 242.0943, found 242.0941 (M^+). IR (film), cm^{-1}: 2979, 2891, 1601, 1233, 1041. ^1H NMR (400 MHz, $CDCl_3$): 7.31 (t, 1H, $J=7.9$, H-5′), 7.09 (dt, 1H, $J=7.9$, 0.8, H-6′), 7.06 (m, 3H, H-4, H-6, H-2′) 6.88 (d, 1H, $J=7.7$, H-7), 6.83 (dt, 1H, $J=7.9$, 1.5, H-4′), 6.00 (s, 2H, H-2), 4.09 (q, 2H, $J=7.0$, OCH_2), 1.44 (t, 3H, $J=7.0$, CH_3).

Characterisation of compound **15**: pale brown crystals, mp 135–140°C. $C_{18}H_{18}O_6$ (330.340) requires: C, 65.45; H, 5.45%. Found: C, 65.22; H, 5.58%. IR (KBr), cm^{-1}: 2978, 1695, 1628, 1587, 1512, 1452, 1378, 1347, 1317, 1243, 1076, 1033. ^1H NMR (200 MHz, $CDCl_3$): 7.12 (dd, 1H, $J=8.1$, 1.8, H-6′), 7.06 (d, 1H, $J=1.8$, H-4′), 6.88 (d, 1H, $J=8.0$, H-7′), 6.73 (d, 1H, $J=1.5$, H-3), 6.03 (s, 2H, H-2′), 6.02 (d, 1H, $J=1.5$, H-5), 4.50 (s, 1H, CH=C), 4.27 (q, 2H, $J=7.0$, CH_2), 4.00 (q, 2H, $J=7.0$, CH_2), 1.41 (t, 6H, $J=7.0$, $2\times CH_3$).

Characterisation of compound **18**: pale yellow crystals, mp: 132°C. $C_{22}H_{22}N_2O_5$ (394.152) requires: C, 66.98; H, 5.63; N, 7.11%. Found: C, 66.75; H, 5.54; N, 7.20%. IR (KBr), cm^{-1}: 3295, 2924, 2854, 1649, 1610, 1511, 1495, 1444, 1251, 1037. ^1H NMR (400 MHz, $CDCl_3$): 7.14 (d, 2H, $J=8.8$, H-2″, H-6″), 6.89 (d, 1H, $J=1.5$, H-4′), 6.87 (dd, 1H, $J=8.7$, 1.5, H-6′), 6.84 (d, 2H, $J=8.8$, H-3″, H-5″), 6.76 (d, 1H, $J=8.7$, H-7′), 6.50 (s, 1H, CH=C), 5.98 (s, 2H, H-2′), 5.82 (q, 1H, $J=4.8$, NH), 5.20 (s, 1H, H-6), 3.76 (s, 3H, OCH_3), 3.68 (s, 1H, H-2), 3.00 (s, 3H, NCH_3), 2.78 (d, 3H, $J=4.8$, NH–CH_3).

Acknowledgements

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