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LETTERS

Diels–Alder cycloaddition of 5-aryl-2-pyrones

Kamyar Afarinkia[a,]* and Jose Berna-Canovas[b]

[a]*Department of Chemistry, King's College, The Strand, London WC2R 2LS, UK*
[b]*Departamento de Quimica Organica, Universidad de Murcia, Campus de Espinardo, Murcia, Spain*

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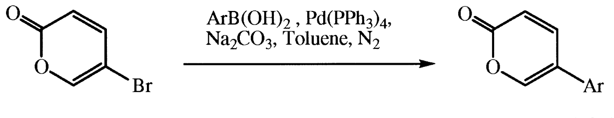
Abstract

Regio- and stereoselectivity of the Diels–Alder cycloadditions of a range of 5-aryl-2-pyrones are reported.

Diels–Alder cycloaddition of 2-pyrones are widely investigated and are shown to be a useful methodology for the synthesis of natural products.[1] Since cycloadditions of unsubstituted 2-pyrone itself are known to be barely selective, this methodology has commonly employed 2-pyrones with strongly polar substituents to ensure regio- and stereoselectivity in cycloadditions.[2] To date, study of the cycloadditions of electronically 'neutral' pyrones, which extend the scope of the methodology as well as the range of natural products accessible, has been limited to those of 3- and 5-bromo-2-pyrone. Interestingly, these two pyrones are more versatile than their 'polar' counterparts since, in addition to their cycloadditions with electronically biased alkenes being highly regio- and stereoselective, they undergo cycloaddition with both electron rich and electron deficient alkenes.[3] Here, we report on the regio- and stereoselectivity of the Diels–Alder cycloadditions of 5-aryl-2-pyrones and conclude that they are equally versatile, ambident dienes.

We prepared a range of novel 5-aryl-2-pyrones by the palladium-catalysed coupling of 5-bromo-2-pyrone with the corresponding arylboronic acid (Scheme 1).[4,5]



Ar = Ph (65%); Ar = 4-(MeO)-C_6H_4 (57%); Ar = 2-(MeO)-C_6H_4 (73%);
Ar = 4-(MeS)-C_6H_4 (58%); Ar = 4-(F)-C_6H_4 (81%)

Scheme 1.

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* Corresponding author.

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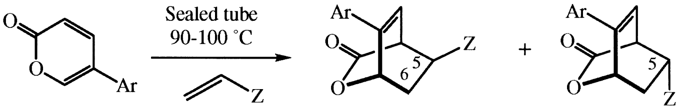
Cycloadditions were carried out in a sealed tube at 100°C with a slight excess of dienophile.[6] The *endo*:*exo* ratios of the cycloadducts were determined by examination of the NMR spectra of the crude product mixtures. Assignment of the *endo*/*exo* configuration of cycloadducts was carried out in accordance with empirical rules established in a previous publication.[3c,d]

The results are outlined in Table 1. As can be seen, good to excellent yields of cycloadducts are obtained in these reactions. Cycloadditions with electronically biased alkene dienophiles can be highly regio- and stereoselective, affording the 5-*endo* cycloadduct as the major product. On the other hand, cycloadditions of weakly activated alkenes are non-stereoselective. All reactions are very regioselective and except on two occasions no 6-*endo* cycloadduct is observable within the limits of detection by NMR (> 97:3).

Table 1



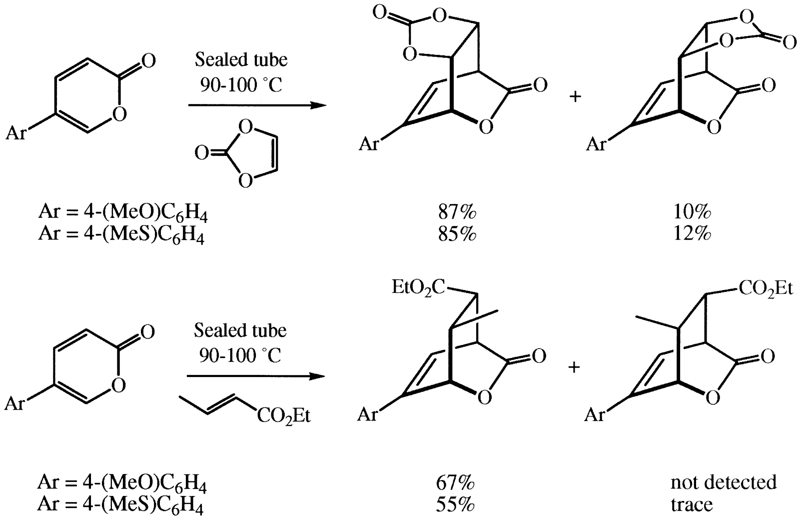
	Ar	Z	endo : exo	Yield %
1	C_6H_5	OBu	75 : 25	72
2	C_6H_5	OAc	50 : 50	60
3	C_6H_5	CO_2Me	85 :15	96
4	C_6H_5	COMe	80 : 20	100
5	4-F-C_6H_4	OBu	91 : 9	69
6	4-F-C_6H_4	CO_2Me	80 : 20	76
7	4-F-C_6H_4	COMe	78 : 22	56
8	4-(MeO)-C_6H_4	OBu	79 : 21	80
9	4-(MeO)-C_6H_4	COMe	93 : 7*	69
10	4-(MeO)-C_6H_4	CH_2OAc	50 : 50	90
11	2-(MeO)-C_6H_4	COMe	70 : 30	63
12	4-(MeS)-C_6H_4	OAc	66 : 33**	82

* 5 : 6 ratio is 95 : 5 ** 5 : 6 ratio is 91 : 9

We conducted a number of competition experiments to compare the reactivity of 5-phenyl-2-pyrone to that of 5-bromo-2-pyrone. These were conducted by exposing an equimolar mixture of the two pyrones to dienophile (butylvinylether and methyl acrylate) and analysing the reaction at intervals. By comparing the quantity of the respective cycloadducts obtained from each pyrone, we concluded that the rate of cycloaddition of 5-phenyl-2-pyrone towards electron rich alkenes is about half that of 5-bromo-2-pyrone. However, the rate of reactions of the two pyrones towards electron deficient alkenes were similar. Similarly, we found only slight differences in the rate of cycloadditions of 5-aryl-2-pyrones bearing electron-deficient, electron neutral and electron-rich substituents on the aryl ring.

We can conclude that 5-phenyl-2-pyrone, as is the case with 5-bromo-2-pyrone, is significantly more reactive towards electron deficient alkenes than towards electron rich alkenes; and that the reactivity towards electron neutral alkenes is slightly lower than that towards electron rich alkenes. Nevertheless, it is important to note that 5-aryl-2-pyrones are ambident dienes with excellent regioselectivity and very good stereoselectivity in cycloadditions.

Finally, we carried out the cycloaddition of two typical 5-aryl-2-pyrones with vicinally disubstituted dienophiles vinylene carbonate and ethyl crotonate (Scheme 2). The cycloadditions proceeded in excellent yield and stereoselectivity, and the pure *endo* cycloadducts were isolable in both cases.



Scheme 2.

In summary, we have demonstrated that 5-aryl-2-pyrones undergo efficient and stereoselective cycloadditions with a range of both electron rich and electron deficient dienophiles.

Acknowledgements

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4. For other examples of aryl coupling of 5-bromo-2-pyrone, see: (a) Liu, Z.; Meinwald, J. *J. Org. Chem.* **1996**, *61*, 6693–6699. (b) Danieli, B.; Lesma, G.; Martinelli, M.; Passarella, D.; Peretto, I.; Silvani, A. *Tetrahedron* **1998**, *54*, 14081–14088.

5. Typical experimental procedure: A 50 mL two-necked round-bottomed flask was charged with 5-bromo-2-pyrone (0.200 g, 1.14 mol), tetrakis (triphenylphosphine)palladium (53 mg, 0.05 mmol) and toluene (27 ml). To this vigorously stirred mixture were added phenylboronic acid (0.153 g, 1.25 mol) dissolved in a minimum amount of 95% ethanol (ca. 1 ml) and 2 M aqueous sodium carbonate solution (1.26 ml, 2.52 mmol). This reaction mixture was heated for 7 hours at 75°C under a nitrogen atmosphere. The cooled reaction mixture was stripped of solvent and the black residue was extracted with dichloromethane (50 mL). The extracts were washed with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was removed and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate in petroleum ether (60–80°C bp fraction) (30% v/v). Removal of solvent from appropriate fractions afforded the desired product as yellow solid. Mp 68°C; ^{1}H NMR (CDCl$_3$) δ 6.45 (dd, J = 9.6, 1.1 Hz, 1H, H-3), 7.44 (m, 5H, aromatic H), 7.64 (dd, J = 9.6, 2.6 Hz, 1H, H-4), 7.69 (dd, J = 2.6, 1.1 Hz, 1H, H-6); ^{13}C NMR (CDCl$_3$) δ 116.5 (d, C-3), 120.6 (s, C-5), 126.0 (d, aromatic C), 128.4 (d, aromatic C), 129.3 (d, aromatic C), 133.5 (s, aromatic C), 144.0 (d, C-4), 148.3 (d, C-6), 161.2 (s, C-2); IR (Nujol) 1695 (C=O), 1223, 1153, 1125, 844, 760 cm^{-1}; MS m/e (EI) 172 (77, M$^+$), 144 (40), 115 (100), 89 (16), 63 (20) and 44 (18); HRMS calcd for $C_{11}H_8O_2$: 172.05245 (M$^+$); found: 172.0524.
6. Typical experimental procedure: A sealed pressure tube (purchased from Aldrich Chemical Co. Cat No Z18,109-9) was charged with 5-phenyl-2-pyrone (0.1 g, 0.57 mmol), methyl acrylate (1.0 mL), a few drops of dichloromethane, a few crystals of butylated hydroxytoluene (BHT) and a small magnetic stirrer bar. The pressure tube was sealed and then immersed in an oil bath maintained at 95°C. After 5 days, the tube was cooled and the contents were stripped of volatile materials to leave a brown gum. The crude sample was analysed by NMR prior to silica gel chromatography using 20% v/v ethyl acetate in petroleum ether (60–80°C bp fraction). Removal of solvent from the appropriate fractions afforded an inseparable mixture of the *endo* and *exo* cycloadducts as an oil; ^{1}H NMR (CDCl$_3$) *endo* cycloadduct: δ 2.17 (ddd, J = 13.8, 4.0, 1.4 Hz, 1H, H-6_{endo}), 2.59 (ddd, J = 13.8, 9.9, 4.0 Hz, 1H, H-6_{exo}), 3.14 (ddd, J = 9.5, 3.3, 2.7 Hz, 1H, H-5), 3.70 (s, 3H, CO$_2$CH$_3$), 4.01 (ddd, J = 6.2, 2.7 Hz, 1H, H-5), 5.70 (m, 1H, H-1), 6.55 (dd, J = 6.2, 2.4 Hz, 1H, H-8), 7.37 (m, 5H, aromatic H); *exo* cycloadduct: δ 2.22 (m, 1H, H-6_{endo}), 3.49 (ddd, J = 9.4, 5.5, 3.9 Hz, 1H, H-6_{exo}), 3.53 (s, 3H, CO$_2$CH$_3$), 3.65 (dd, J = 6.6, 2.8 Hz, 1H, H-4), 3.73 (m, 1H, H-5), 5.96 (m, 1H, H-1), 6.73 (dd, J = 6.6, 2.8 Hz, 1H, H-8), 7.39 (m, 5H, aromatic H); ^{13}C NMR (CDCl$_3$) *endo* cycloadduct: δ 29.75 (t, C-6), 37.1 (d, C-5), 43.4 (d, C-4), 52.6 (q, CO$_2$*C*H$_3$), 76.1 (d, C-1), 122.2 (d, aromatic C), 125.3 (d, aromatic C), 128.8 (d, C-8), 129.0 (d, aromatic C), 133.9 (s, C-7), 145.0 (s, aromatic C), 171.9 (s, *C*O$_2$Me), 172.5 (s, bridge CO$_2$); *exo* cycloadduct: δ 23.5 (t, C-6), 40.5 (d, C-5), 43.0 (d, C-4), 52.1 (q, CO$_2$*C*H$_3$), 76.1 (d, C-1), 122.3 (d, aromatic C), 125.1 (d, aromatic C), 128.6 (d, aromatic C), 128.8 (d, C-8), 134.0 (s, C-7), 145.0 (s, aromatic C), 171.9 (s, *C*O$_2$Me), 172.5 (s, bridge CO$_2$); IR (Nujol) 1736 (C=O), 1632 (C=C), 1265, 1041, 951, 737 cm^{-1}; MS m/e (EI) 258 (5, M$^+$), 214 (13), 155 (58), 129 (45), 115 (11), 88 (51), 86 (92), 84 (100); HRMS calcd for $C_{15}H_{14}O_4$: 258.8920 (M$^+$); found: 258.8925.