Diels–Alder Reactions of 2-(Isoquinolin-1-yl)-5-phenyl-3*H*-pyrrole-3-carboxylic Esters with *N*-Methyl- and *N*-Phenyl-maleimides†

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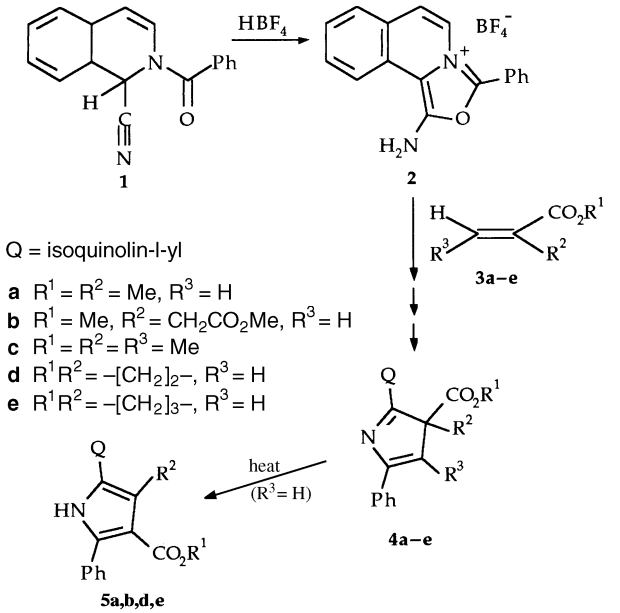
The reaction between the title compounds produces [4 + 2] Diels–Alder cycloadducts; the stereochemistry of the reaction is deduced from ^{1}H NMR data.

As part of our research on the reactivity of the tetrafluoroborate salts of Reissert compounds,[1] we have already described the preparation of 3*H*-pyrrole-3-carboxylic esters **4** by the reaction of the Reissert compound tetrafluoroborate salt **2** with suitably gem-disubstituted α,β-ethylenic esters **3**.[2] When R^3 = H, prolonged heating in toluene converts the



Scheme 1

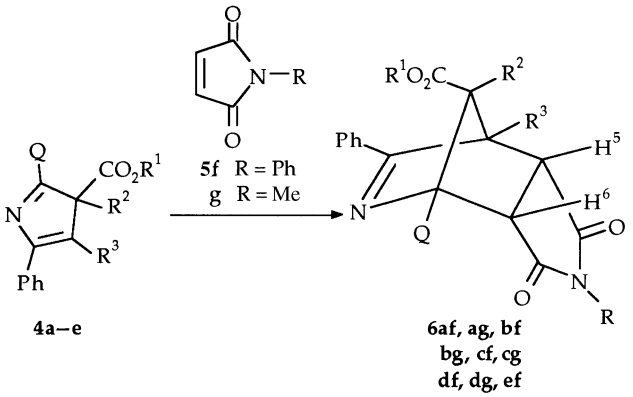
3*H*-pyrrole **4** into the isomeric 1*H*-pyrrole **5** *via* a [1,5] sigmatropic rearrangement[2] (Scheme 1).

Since Diels–Alder reactions, in which the azole functions as an azadiene, have been observed either directly from 3*H*-pyrroles[3] or from 2*H*-pyrroles *via* a [1,5] sigmatropic rearrangement to 3*H*-pyrroles,[3–6] it was of interest to study reactions of the 3*H*-pyrroles derivatives **4** with some dienophiles.[7]

In preliminary studies, the 3*H*-pyrrole **4a** was treated with a variety of dienophiles in toluenic solutions at various temperatures (20–110 °C). Dimethyl acetylenedicarboxylate and methyl esters of propiolic, acrylic, fumaric and maleic acids gave complex mixtures in which the 1*H*-pyrrole **5a** was the major component.

N-Methyl- and *N*-phenyl-maleimides proved to be the most useful dienophiles for reactions with the 3*H*-pyrrole derivatives **4**. 3*H*-Pyrroles **4** in toluene under reflux gave moderate to good yields of stable 1:1 adducts **6** (Scheme 2). Physical, analytical, IR (ν C=O) and ^{1}H and ^{13}C NMR data for the adducts are given in Tables 1 and 2.

^{1}H NMR data allowed the diastereochemistry of the cycloadducts **6** to be assigned. According to the literature,[8,9]



Scheme 2

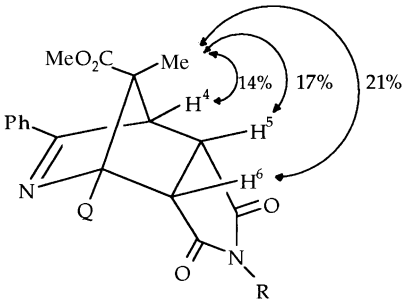


Fig. 1 NOE enhancements for the cycloadduct **6af**

the *exo* oriented H-5 gives a signal in the form of a doublet of doublets owing to two vicinal couplings $^3J_{4,5}$ 4.3–4.6 Hz (R^3 = H) and $^3J_{5,6}$ 7.2–7.6 Hz whereas an appropriate *endo* oriented H-5 proton would give only a doublet, since one of the two vicinal proton couplings ($^3J_{4,5}$) would be close to zero. This *endo* configuration is also the stereochemistry described by Sammes *et al.*[3] for the Diels–Alder adducts of other 3*H*-pyrroles with *N*-phenylmaleimide.

In order to determine the diastereochemistry of the approach between the two reactants towards the ester group of the azadienic 3*H*-pyrroles **4**, NOE difference experiments were carried out with the cycloadducts **6**. The observed enhancements are examplified in the case of the cycloadduct **6af** (Fig. 1).

These observations may be extended to all cycloadducts **6** and lead to the choice of the *endo–anti* approach of the maleimide group to the ester group of the azadienic 2*H*-pyrroles **4**. Thus, the cycloaddition is diastereoselective and the cycloadducts **6** are obtained with simultaneous control of the relative stereochemistry of five chiral centres.

Experimental

All mps are uncorrected. IR spectra (KBr) were recorded on a Bio-Rad FTS spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-Spectrospin AC 200 spectrometer in $CDCl_3$.

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Table 1 Physical and analytical data for 3*H*-pyrrole Diels–Alder adducts **6**

Adduct	R^1	R^2	R^3	R	Yield (%)	Mp *T*/°C)	Reaction time (*t*/h)	IR (νC=O)/ cm^{-1}	Analysis (%) Found (required) C	H	N
6af ($C_{32}H_{25}N_3O_4$)	Me	Me	H	Ph	53	288	20	1713 1773	74.55 (74.37	4.89 4.86	8.15 7.99)
6ag ($C_{27}H_{23}N_3O_4$)	Me	Me	H	Me	64	187	8	1700 1710 1773	71.51 (71.67	5.11 5.22	9.27 9.07)
6bf ($C_{34}H_{27}N_3O_6$)	Me	CH_2CO_2Me	H	Ph	26	270	24	1718 1736 1758	71.19 (71.23	4.74 4.91	7.33 7.27)
6bg ($C_{29}H_{25}N_3O_6$)	Me	CH_2CO_2Me	H	Me	47	208	8	1702 1736	68.09 (67.98	4.93 4.96	8.21 8.32)
6cf ($C_{33}H_{27}N_3O_4$)	Me	Me	Me	Ph	16	248	24	1715 1770	74.85 (74.77	5.14 5.22	7.93 7.86)
6cg $C_{28}H_{25}N_3O_4$)	Me	Me	Me	Me	28	223	8	1700 1735 1769	71.93 (72.07	5.39 5.28	8.99 8.92)
6df ($C_{33}H_{23}N_3O_4$)	—CH_2CH_2—		H	Ph	46	312	3	1710 1764	74.85 (74.78	4.51 4.62	8.18 8.12)
6dg ($C_{27}H_{21}N_3O_4$)	—CH_2CH_2—		H	Me	49	293	3	1691 1764	71.84 (71.93	4.67 4.82	9.31 9.17)
6ef ($C_{33}H_{25}N_3O_4$)	—$CH_2CH_2CH_2$—		H	Ph	40	263	16	1709 1774	75.13 (75.27	4.78 4.69	7.96 7.89)

Table 2 ^{1}H NMR data (δ ppm/$CDCl_3$; *J* in Hz) for 3*H*-pyrrole Diels–Alder adducts **6**

Adduct	R^1	R^2	R^3	H^5	H^6	R	Aromatic protons
6af	2.97 (s, 3 H),	1.48 (s, 3 H)	4.53 (d, 1 H)	3.80 (dd, 1 H) $J_{4,5}$ 4.7; $J_{5,6}$ 7.6	5.57 (d, 1 H)		6.55–6.65 (m, 2 H, ar.) 7.10–8.95 (m, 14 H, ar.)
6ag	2.95 (s, 3 H)	1.43 (s, 3 H)	4.41 (d, 1 H)	3.64 (dd, 1 H) $J_{4,5}$ 4.6; $J_{5,6}$ 7.9	5.40 (d, 1 H)	2.58 (s, 3 H)	7.40–8.85 (m, 11 H, ar.)
6bf	2.99 (s, 3 H)	2.95 (AB syst., 2 H) J_{AB} 17.4 3.68 (s, 3 H)	4.82 (d, 1 H)	3.79 (dd, 1 H) $J_{4,5}$ 4.3; $J_{5,6}$ 7.6	5.57 (d, 1 H)		6.55–6.65 (m, 2 H, ar.) 7.10–8.85 (m, 14 H, ar.)
6bg	2.97 (s, 3 H)	2.90 (AB syst., 2 H) J_{AB} 17.4 3.67 (s, 3 H)	4.70 (d, 1 H)	3.62 (dd, 1 H) $J_{4,5}$ 4.3; $J_{5,6}$ 7.4	5.39 (d, 1 H)	2.58 (s, 3 H)	7.40–8.75 (m, 11 H, ar.)
6cf	2.90 (s, 3 H)	1.33 (s, 3 H)	2.01 (s, 3 H)	3.42 (d, 1 H) $J_{5,6}$ 7.7	5.56 (d, 1 H)		6.74–6.80 (m, 2 H, ar.) 7.15–8.95 (m, 14 H, ar.)
6cg	2.88 (s, 3 H)	1.29 (s, 3 H)	1.93 (s, 3 H)	3.26 (d, 1 H) $J_{5,6}$ 7.5	5.39 (d, 1 H)	2.69 (s, 3 H)	7.40–8.82 (m, 11 H, ar.)
6df	4.11 (m, 1 H) 3.83 (m, 1 H)	2.12 (t, 2 H)	4.40 (d, 1 H)	4.71 (dd, 1 H) $J_{4,5}$ 4.6; $J_{5,6}$ 7.5	4.57 (d, 1 H)		6.65–6.75 (m, 2 H, ar.) 7.10–9.60 (m, 14 H, ar.)
6dg	3.91 (t, 1 H)	2.48 (m, 1 H) 2.70 (m., 2 H)	4.28 (d,. 1 H)	3.58 (dd, 1 H) $J_{4,5}$ 4.4; $J_{5,6}$ 7.5	5.50 (d, 1 H)	2.60 (s., 3 H)	7.45–8.95 (m, 11 H, ar.)
6ef	3.95 (m, 1 H) 4.30 (m, 1 H)	1.50–1.90 (m, 4 H)	4.45 (d, 1 H)	3.68 (dd, 1 H) $J_{4,5}$ 4.5; $J_{5,6}$ 7.56	5.71 (d, 1 H)		6.65–6.75 (m, 2 H, ar.) 7.20–9.55 (m, 14 H, ar.)

Analytical data were performed by the CNRS Vernaison (France). 3*H*-Pyrroles **4** were obtained by literature methods.[2]

Preparation of Cycloadducts **6**.—*General procedure.* A solution of 3*H*-pyrrole **4** (2 mmol) and *N*-methyl- or *N*-phenyl-maleimide (2.2 mmol) toluene (20 ml) was heated under reflux for an appropriate time (Table 1). The reaction mixture was then left at room temperature for 12 h. In the case of **6df**, **dg** and **ef**, a small quantity of the rearranged 1*H*-pyrrole **5** crystallised. After filtration, the solution was evaporated and the obtained solid recrystallised from ethanol.

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References

1 D. Adnani, G. Schmitt, K. Monnier, B. Laude, M. M. Kubicki and M. Jannin, *J. Chem. Res*., 1996, (*S*) 74; (*M*) 0534 and references cited therein.
2 S. Perrin, K. Monnier and B. Laude, *Bull. Soc. Chim. Belg*., 1996, **105**, 777.
3 K. H. Lui, T. F. Lai and M. P. Sammes, *J. Chem. Res*., 1989, (*S*) 244; (*M*) 1759.
4 A. Eddaïf, A. Laurent, P. Mison and N. Pelissier, *Tetrahedron Lett*., 1984, **26**, 2779; A. Eddaïf, A. Laurent, P. Mison, N. Pelissier, P. A. Carrupt and P. Vogel, *J. Org. Chem*., 1987, **52**, 5548.
5 P. H. Daniels, J. L. Wong, J. L. Atwood, L. G. Canada and R. D. Rogers, *J. Org. Chem*., 1979, **45**, 435; B. K. Rammash, C. M. Gladstone and J. L. Wong, *J. Org. Chem*., 1981, **46**, 3036.
6 M. E. Jung and J. J. Shapiro, *J. Am. Chem. Soc*., 1980, **102**, 7862.
7 M. P. Sammes, personal communication.
8 T. Lakhlifi, A. Sedqui, B. Laude, Nguyen Dinh An and J. Vebrel, *Can. J. Chem*., 1991, **69**, 1156.
9 H. Krawczyk and A. Gryff-Keller, *J. Chem. Res*., 1996, (*S*) 452; (*M*) 2583.