Tetrahedron 64 (2008) 9561–9566

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The synthesis of highly functionalised pyridines using Ghosez-type reactions of dihydropyrazoles

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ARTICLE INFO

Article history:
Received 14 April 2008
Received in revised form 3 July 2008
Accepted 17 July 2008
Available online 22 July 2008

Keywords:
Diels–Alder reaction
Microwave
4,5-Dihydropyrazole
Heterocycles

ABSTRACT

The aza-Diels–Alder reaction of αβ-unsaturated hydrazones is a general methodology that has been applied both to the synthesis of natural products and to the development of multicomponent reactions. Trends have emerged as to the effect of substituents on the efficiency of this reaction with substituents at the C2 and C4-positions of the aza-diene in general suppressing the reaction. Here we report that 4,5-dihydropyrazoles can function as substrates in this process despite the presence of substituents at both of these positions. A one pot, four chemical step sequence carried out under standard thermal or microwave conditions results in the formation of the corresponding pyridine-containing compounds. The scope of the reaction is explored and additional insights into the proposed mechanism of this reaction are provided.

1. Introduction

The aza-Diels–Alder reaction of αβ-unsaturated hydrazones, originally reported by Ghosez,[1] provides rapid access to substituted pyridine-containing compounds (for example, the conversion of **1** to **2**, Scheme 1). Compound **2** is thought to be formed, following the initial hetero-Diels–Alder reaction, by the cleavage of the *N*–*N* bond in **3** and subsequent oxidation of the resulting dihydropyridine **4**. This robust and general methodology[2] has been applied in both natural product synthesis[3] and in the development of multicomponent reactions.[4] Here we report our studies on the use of dihydropyrazoles of general structure **5** (Scheme 2) as substrates in this reaction. These substrates are readily accessed in two steps from commercially available ketones and when combined with the Ghosez methodology provide a fast route to relatively complex structures in only a few chemical steps. Dihydropyrazoles provide a considerable challenge for the Ghosez methodology due to the presence of substituents at both the C2- and the C4-position of the aza-diene. The incorporation of substituents at these positions has previously been shown to suppress the desired Diels–Alder reaction.[5,6] Our studies show that dihydropyrazoles can function as a substrate in this reaction under standard thermal or microwave conditions. We also present an exploration of the scope of this reaction and provide some additional insight into its mechanism.

2. Results and discussion

Initial studies focused on dihydropyrazole **6** (Scheme 2), which was formed by the reaction of cyclohexanone (**7**) with excess benzaldehyde in acetic acid containing HCl to give the known *E*,*E*-dibenzylidene ketone **8** in 67% isolated yield.[8] Whilst **8** precipitated from this reaction on work up and was stable as a solid, a solution of **8** was found to degrade rapidly in the presence of light resulting in the formation of the *E*,*Z*- and *Z*,*Z*-isomer of **8** (see Supplementary data). Subsequent reaction of freshly dissolved *E*,*E*-**8** with *N*-methylhydrazine under microwave irradiation conditions gave **6** in 90% yield following recrystallisation from methanol.[9] Despite being significantly more stable than **8**, **6** also degraded on standing in solution in the light for prolonged periods of time (see Supplementary data). Degradation of **6** by isomerisation of the benzylidene functional group and by air oxidation as well as formation of **9** (Scheme 2) was observed. This relative lack of stability of **6** coupled with the presence of the substituents at C2 and C4 of the aza-diene initially suggested that **6** would be a very poor substrate for the Ghosez methodology,[5,6] although electron-donating substituents at the C3 position of the aza-diene are known to be advantageous for this reaction.[10] In addition, analysis of the X-ray crystal structure of **6** (Fig. 1) supported a view that the presence of the bicyclic ring structure in **6** forces the N2 lone pair into conjugation with the aza-diene. Therefore, in contrast to the reported observation that the

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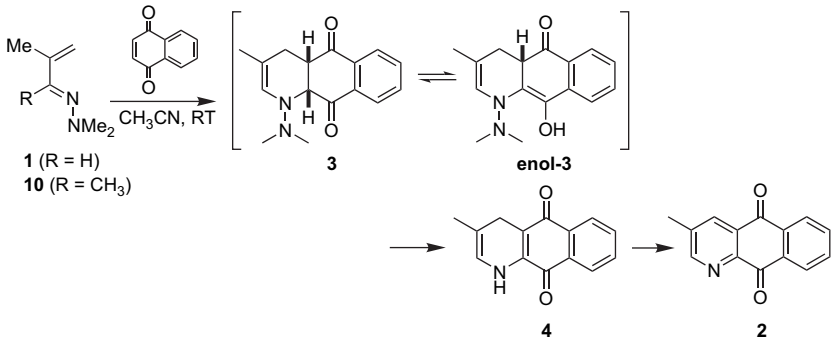
doi:10.1016/j.tet.2008.07.063

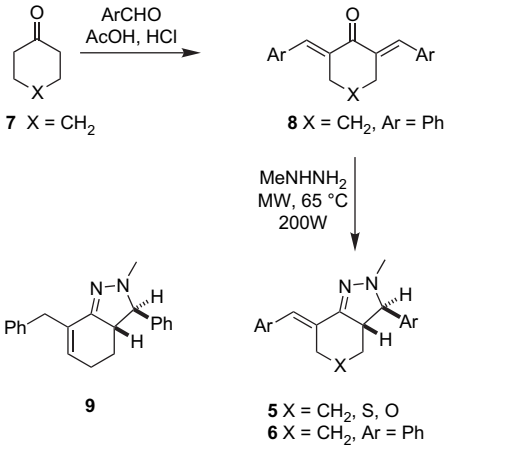


Scheme 1. Examples of the Ghosez methodology.[1,7]

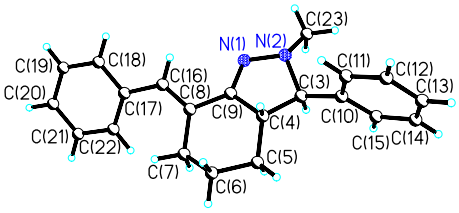
C2-substituent in **10** (Scheme 1) suppresses the reaction,[5] the C2-substituent in the dihydropyrazole system would be expected to have minimal detrimental effect.

In line with the literature precedent[6] for substrates substituted at C4 of the diene (see Supplementary data for an additional example) it was decided to carry out the Ghosez reaction of **6** with 1,4-naphthoquinone at 105 °C in toluene. Additional precautions of degassing the solvent and running the reaction in the absence of light were taken to minimise the expected degradation of **6**, although potential oxidation of **6** by the dienophile could not be avoided. It should also be noted that at least three chemical steps (Diels–Alder reaction, *N*–*N* bond cleavage and oxidation) were expected to take place in this one pot transformation with a fourth step, amine elimination, also possible. In practice, **6** reacted with 2 equiv of 1,4-naphthoquinone to give the penta-substituted pyridine **11** as a yellow crystalline solid in 30% isolated yield after heating for 6 days (Fig. 1, Table 1, entry 1). When the reaction was repeated using 4 equiv of the dienophile, an improved yield of 40% of **11** was obtained although product purification was more laborious (Table 1, entry 2). Whilst the yield of formation of **11** was low, ^{1}H NMR analysis of the crude reaction mixture indicated that **11** was the major product suggesting that issues relating to product purification, in addition to the complexity of the reaction sequence, contributed to the low yield. Interestingly, **11** does not contain the methylamino group, which was presumably eliminated as methylamine and, at least partially, trapped by the dienophile, as judged by the isolation of the known compound, 2-(methylamino)-1,4-naphthoquinone from this reaction (see Supplementary data).[11] X-ray crystallographic analysis of **11** (Fig. 1) confirmed its structure including the presence of the exocyclic *E*-double bond. It also emphasised the non-planarity of this compound presumably resulting from steric interactions between the C12 phenyl ring, the C11 carbonyl group and the adjacent C1 methylene (see Fig. 1 for numbering system). To the best of our knowledge, there are very few reports of the synthesis of this or closely related ring systems and those that exist use different synthetic approaches.[12] Interestingly, one set of related heterocycles containing a pyrido[2,3,4-*kl*]acridine system has reported cytotoxic activity through a DNA damaging mechanism.[13]

Analogous reaction conditions were used to explore the scope of this reaction as a function of the substituents in the aryl ring. The results of these studies are shown in Table 1. As expected, the incorporation of an electron-donating group resulted in similar or improved yields with the *p*-methoxy analogue **12** giving the desired pyridine **13** in 42% overall yield (Table 1, entries 3 and 4). The incorporation of an electron-withdrawing group in the *para*-position of the aromatic ring resulted in the formation of only trace amounts of the desired product (Table 1, entries 5 and 6). In light of this plans to incorporate electron-deficient heteroaryl rings in the

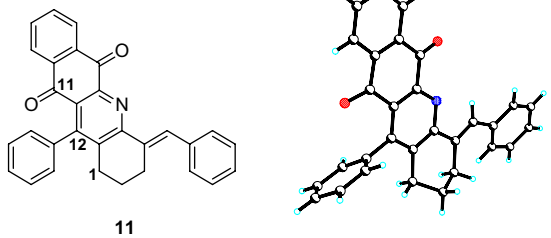


Scheme 2. Synthesis of the dihydropyrazole substrates.



Selected torsional angles for **6**

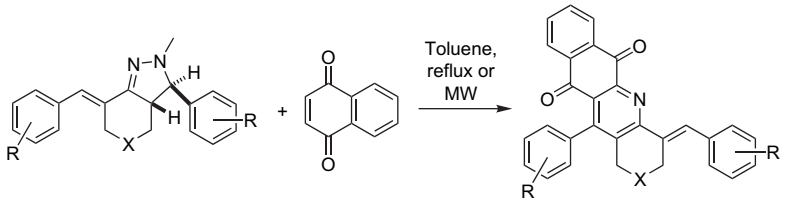
C(16)-C(8)-C(9)-N(1)	–17.1(3)
N(2)-N(1)-C(9)-C(8)	–178.6(16)



11

Figure 1. X-ray crystallographic analysis of **6** and **11**. The structure of **6** illustrates the near planar nature of the N(2)–C(16) region of **6** and the correct alignment of the N(2) lone pair for donation of electron density into the aza-diene unit. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 693374–693377. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table 1
Investigating the scope of the Ghosez reaction of dihydropyrazoles



6,12,14,16, 18, 20, 22, 24 **11, 13,15,17, 19, 21, 23, 25**

Entry	Substrate number	X	R	Product number	Standard thermal conditions isolated % yield	MW irradiation isolated % yield (NMR yield)
1	**6**	CH_2	H	**11**	30[a]	23 (31)[a]
2	**6**	CH_2	H	**11**	40[b]	27 (45)[b]
3	**12**	CH_2	*p*-OCH_3	**13**	42[a]	29 (40)[b]
4	**14**	CH_2	*p*-CH_3	**15**	22[a]	20 (29)[b]
5	**16**	CH_2	*p*-NO_2	**17**	n.d.[a]	n.d. (<10)[b]
6	**18**	CH_2	*p*-Br	**19**	n.d.[a]	n.d. (<10)[b]
7	**20**	CH_2	*o*-Br	**21**	47[a]	0 (6)[b]
8	**22**	O	*p*-OCH_3	**23**	24[a]	26 (33)[b]
9	**24**	S	*p*-OCH_3	**25**	12[a]	4 (6)[b]

Not determined (n.d.) as only trace quantities of the desired product were observed in the ^{1}H NMR analysis of the crude reaction mixture.
[a] Dienophile: 2 equiv.
[b] Dienophile: 4 equiv.

4,5-dihydropyrazole substrate were abandoned. Unexpectedly, the *o*-bromo analogue **20** gave **21** in 47% yield (Table 1, entry 7). X-ray crystal structure analysis of **20** (Fig. 2) provides a plausible rationalisation for the unexpected success of this reaction. The presence of the *ortho*-bromo-substituent appears to force the ring of the diene's aryl substituent further out of the plane of the diene (see Fig. 2 legend for relevant torsional angle). The resulting loss of conjugation of the aryl ring with the diene would be expected to lead to a net increase in electron density associated with the aza-diene (cf. **18**) facilitating a normal electron-demand Diels–Alder reaction. Incorporation of a sulfur atom in the cyclohexyl ring in the *p*-methoxy series led to a decrease in the yield of the reaction (Table 1, entry 9), however, exchange of the sulfur for an oxygen atom led to an increase in yield in the same series (Table 1, entry 8). Replacement of the methylene in **12** with $NCH_2CH_2C_6H_4p$-F led to a substrate that decomposed under the reaction conditions.

2.1. Use of microwave irradiation

Attempts to improve further the yields in the successful reactions were carried out including the addition of lithium trifluoromethanesulfonimide ($LiNTf_2$), a Lewis acid previously reported to promote the Ghosez reaction.[14] Our studies focused exclusively on the use of $LiNTf_2$ as it had previously been reported that when a range of Lewis acids including BF_3. OEt_2, $TiCl_4$, $SnCl_4$, $ZnCl_2$ and TMSOTf were used to catalyse the reaction of a related systems with quinone, a competing reaction occurred.[6] No improvement was observed in our hands with $LiNTf_2$ or when the reaction was carried out using ultrasound.[15] Attempts to shorten reaction times by the use of xylene as solvent were also unsuccessful. However, the use of microwave irradiation did have an impact on the synthetic utility of this reaction in line with previous reports for this reaction type.[16] For example, **11** was formed in 27% yield after just 2 h irradiation at an optimal 200 °C in toluene using 4 equiv of 1,4-naphthoquinone (see Supplementary data). Degassing of the reaction was not required in contrast to the reactions carried out under standard thermal conditions. Significant amounts of unreacted **6** were observed when the reaction was repeated at 150 °C under otherwise identical reaction conditions. The use of alternative solvents with higher tan δ values (DMSO, DCE, CH_3CN)[17] resulted in reduced conversion on heating at 200 °C, as judged by ^{1}H NMR analysis of the crude reaction mixture (Table S1 in Supplementary data). The reaction was also successful in the absence of solvent, however, a further reduction in yield was observed (Table S1 in Supplementary data).

The optimal reaction conditions also proved successful for the other substrates (Table 1) with the yields again being limited by the purification procedure as judged by comparison of the NMR and isolated yields (Table 1). The exception was the *ortho*-bromo-containing substrate **20** as in this case only trace amounts of the desired product **21** were obtained with the major compound being **26** resulting from isomerisation of the double bond in **20** (Scheme 3). Further studies on this reaction showed that **20** was not converted to **26** on heating at 200 °C in the microwave in the absence

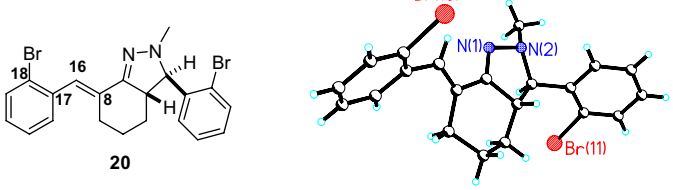
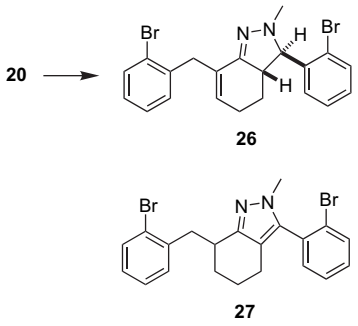
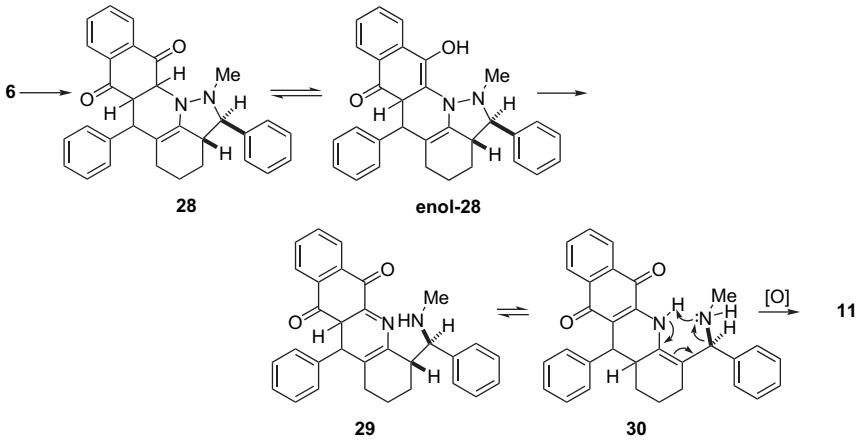


Figure 2. X-ray structure of **20**. Torsional angle C8–C16–C17–C18=135.8(6)°.



Scheme 3. Acid catalysed isomerisation of **20**.



Scheme 4. A plausible mechanism for the formation of **11**.

of 1,4-naphthoquinone. However, repeating the original reaction with **20** after re-purification of the dienophile still resulted in the formation of large quantities of **26**. A likely explanation for this observation is that trace amounts of acid are produced during the reaction and are sufficient to cause the observed isomerisation reaction at the higher temperature (cf. the standard thermal reaction, Table 1, entry 7). In support of this, **20** was shown to isomerise to **26** at 200 °C in toluene under microwave irradiation for 15 min in the presence of catalytic amounts of *p*-toluenesulfonic acid. A second isomerised compound **27** was also isolated in this experiment (Scheme 3).

2.2. Reaction mechanism

Whilst the mechanism of the Ghosez reaction is generally accepted to involve an initial Diels–Alder reaction followed by *N*–*N* bond cleavage and subsequent oxidation to the pyridine (Scheme 1), few direct studies on the mechanism have been reported. We became interested in the *N*–*N* bond cleavage reaction, in particular the possibility that an intramolecular deprotonation involving the enol tautomer of **28** (**enol-28**, Scheme 4) occurred to give **29** en route to **11**. It was unfortunately not possible to access **28**, however, a crude sample of the Diels–Alder adduct **3** (Scheme 1) contaminated with 1,4-naphthoquinone was prepared using a literature procedure.[16] The rate of conversion of **3** to **2** was found to be concentration dependent with no detectable conversion being observed for a 20 mM solution of **3** in 24 h at 25 °C whereas almost complete conversion (**3**/**2** 1:20) was observed for a 80 mM solution of **3** under otherwise identical conditions. No signals corresponding to the formation of **4** were observed in these studies presumably due to the rapid oxidation of **4** to **2** by 1,4-naphthoquinone. This data supports a view that *N*–*N* bond cleavage proceeds via an intermolecular deprotonation of **3** or **enol-3** (Scheme 1 and Supplementary data). An analogous situation presumably also occurs in the formation of **11** from **6** via **28** (Scheme 4).

The observed formation of the *E*-stereochemistry of the alkene functionality in **11** is also of interest. An E2 elimination of methylamine would be expected to result in the formation of the corresponding *Z*-isomer that would have to isomerise under the reaction conditions to give **11**. Alternatively, the intramolecular process shown in Scheme 4 could occur following a series of imine–enamine tautomerisations allowing direct access to **11**.

3. Conclusion

The Ghosez aza-Diels–Alder reaction provides rapid access to compounds containing highly substituted pyridine rings. In this study, we have extended the scope of this methodology further by showing that 4,5-dihydropyrazoles can act as substrates in this reaction with 1,4-naphthoquinone as the dienophile. Inspection of the 3-dimensional structure of two of these substrates (**6** and **20**) implied that, despite the presence of C2- and C4-substituent on the aza-diene, this chemistry could be successfully applied. This was found to be the case both under standard thermal and microwave conditions with the corresponding pyridine-containing compounds being isolated. The scope of this reaction as a function of substituents in the aryl rings was consistent with a normal electron-demand Diels–Alder reaction with the *ortho*-bromo analogue **20** providing an interesting exception. The reaction of 4,5-dihydropyrazoles with alternative dienophiles falls outside the scope of this paper and these results will be reported elsewhere in the near future. Two factors are believed to contribute to the low yields for these transformations, first the fact that four different chemical steps are taking place in the one pot reaction and second that the products contain a penta-substituted pyridine ring, which makes purification using standard chromatographic techniques difficult. Finally, we demonstrated an improvement in the synthetic utility of the reaction through the use of microwave irradiation resulting in a significant reduction in the reaction time.

4. Experimental section

4.1. General procedure for the preparation of 4,5-dihydropyrazoles

A mixture of the *E*,*E*-dibenzylidene ketone (5 mmol) and 2 mL of methylhydrazine (38 mmol) was subjected to microwave heating (200 W) for 25 min at 65 °C. After cooling, the reaction was diluted with dichloromethane (15 mL) and washed with water (2×10 mL). The biphasic mixture was then passed through hydromatrix and the filtrate concentrated in vacuo to give a solid. Subsequent recrystallisation from methanol gave the desired compound in high purity and yield.

*4.1.1. 7-(12-Methoxybenzylidene)-3-(4′-methoxyphenyl)-2-methyl-2,3,3a,4,6,7-hexahydro-pyrano[4,3-c]pyrazole (**22**)*

Isolated as a yellow solid (1.02 g, 2.8 mmol, 56%); mp 166.5–167.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (br d, 2H, J=8.5 Hz, $H_{2'}$), 7.19 (br s, 1H, H_8), 7.13 (br d, 2H, J=8.5 Hz, H_{10}), 6.89 (dd, 4H, J=11.3, 8.5 Hz, $H_{3',11}$), 4.87 (d, 1H, J=14.0 Hz, H_{6a}), 4.39 (dd, 1H, J=14.0, 1.4 Hz, H_{6b}), 4.14 (dd, 1H, J=10.5, 6.7 Hz, H_{4a}), 3.81 (s, 6H, OCH_3), 3.60 (d, 1H, J=14.0 Hz, H_3), 3.57 (t, 1H, J=10.5 Hz, H_{4b}), 3.21 (ddd, 1H, J=14.0, 10.5, 6.7 Hz, H_{3a}), 2.77 (s, 3H, NCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 159.9 (CH), 159.6 (CH), 151.9 (C), 131.4 (CH), 130.7 (C), 128.9

(CH), 128.7 (C), 126.7 (C), 126.0 (CH), 114.5 (CH), 114.2 (CH), 77.6 (CH), 70.2 (CH_2), 68.1 (CH_2), 55.7 (CH_3), 55.6 (CH_3), 53.8 (CH), 42.0 (CH_3); IR (KBr) ν_{max}: 2832, 1600, 1459, 1102 cm^{-1}; LRMS (ES^+) (MeOH): *m/z* 387.21 $[M+Na]^+$ (100%), 365.23 $[M+H]^+$ (20%); HRMS (ES^+): *m/z* calcd for $C_{22}H_{24}N_2O_3$ $[M+H]^+$: 365.1865, found: 365.1866.

4.1.2. 7-(12-Methoxybenzylidene)-3-(4′-methoxyphenyl)-2-methyl-2,3,3a,4,6,7-hexahydro-thiopyrano[4,3-c]pyrazole (**24**)

Isolated as a white solid (1.43 g, 3.77 mmol, 76%); mp 152.0–153.0 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.34 (d, 2H, *J*=8.4 Hz, $H_{2'}$), 7.23 (d, 2H, *J*=8.4 Hz, H_{10}), 7.15 (s, 1H, H_8), 6.90 (dd, 4H, *J*=15.5, 8.4 Hz, $H_{3',11}$), 3.82–3.77 (m, 7H, OCH_3 and H_{6b}), 3.61–3.55 (m, 2H, $H_{6a,3}$), 3.21 (ddd, 1H, *J*=14.5, 10.7, 6.1 Hz, H_{3a}), 2.87–2.69 (m, 2H, $H_{4a,b}$), 2.76 (s, 3H, NCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 159.9 (CH), 159.4 (CH), 153.2 (C), 131.3 (CH), 130.6 (C), 129.0 (CH), 128.9 (C), 127.2 (C), 127.0 (CH), 114.6 (CH), 114.2 (CH), 79.9 (CH), 56.8 (CH), 55.7 (CH_3), 55.6 (CH_3), 42.1 (CH_3), 31.7 (CH_2), 30.0 (CH_2); IR (KBr) ν_{max}: 2833, 2787, 1602, 1455 cm^{-1}; LRMS (ES^+) (MeOH): *m/z* 403.17 $[M+Na]^+$ (100%); HRMS (ES^+): *m/z* calcd for $C_{22}H_{25}N_2O_2S$ $[M+H]^+$: 381.1637, found: 381.1640.

4.2. General procedure for aza-Diels–Alder reaction

A mixture of the substituted indazole (0.5 mmol) and 1,4-naphthoquinone (1 mmol) was allowed to react in a sealed Schlenk tube in the dark for 6 days at 105 °C in freshly distilled and degassed toluene (5 mL). Evaporation of the solvent, purification by column chromatography and recrystallisation from acetonitrile gave the desired product.

4.2.1. 4-(*E*)-Benzylidene-12-phenyl-1,2,3,4-tetrahydro-benzo[b]acridine-6,11-dione (**11**)

Isolated as yellow needles (64.0 mg, 0.15 mmol, 30%); mp 244.5–245.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.47 (s, 1H, H_{13}), 8.38–8.33 (m, 1H, $H_{7/10}$), 8.10–8.05 (m, 1H, $H_{7/10}$), 7.81–7.69 (m, 2H, $H_{8,9}$), 7.58–7.47 (m, 5H, Ar*H*), 7.45–7.37 (m, 2H, Ar*H*), 7.34–7.27 (m, 1H, Ar*H*), 7.17–7.11 (m, 2H, Ar*H*), 2.96–2.88 (m, 2H, H_3), 2.53 (t, 2H, *J*=6.2 Hz, H_1), 1.76 (tt, 2H, *J*=12.3, 6.2 Hz, H_2); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ: 183.0 (C), 182.2 (C), 157.9 (C), 151.3 (C), 147.3 (C), 138.5 (C), 137.2 (C), 137.0 (C), 134.8 (C), 134.3 (CH), 134.0 (C), 133.9 (CH), 133.1 (CH), 132.9 (C), 130.0 (CH), 128.7 (CH), 128.2 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 127.1 (CH), 126.8 (CH), 125.9 (C), 28.3 (CH_2), 27.5 (CH_2), 22.1 (CH_2); IR (KBr) ν_{max}: 2933, 1672, 1545, 1520, 1301, 1252, 978 cm^{-1}; LRMS (ES^+) (MeOH): *m/z* 450.16 $[M+Na]^+$ (10%), 877.29 $[2M+Na]^+$ (100%); HRMS (ES^+): *m/z* calcd for $C_{30}H_{21}NO_2Na$ $[M+Na]^+$: 450.1470, found: 450.1466. Anal. calcd for $C_{30}H_{21}NO_2$: 84.29% C, 4.95% H, 3.28% N; found: 84.04% C, 4.64% H, 3.13% N.

4.2.2. 4-(4′-Methoxybenzylidene)-12-(4″-methoxyphenyl)-1,2,3,4-tetrahydro-benzo[b]acridine-6,11-dione (**13**)

Isolated as an orange solid (102.0 mg, 0.21 mmol, 42%); mp 249.5–250.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.41 (br s, 1H, H_{13}), 8.37–8.32 (m, 1H, $H_{7/10}$), 8.12–8.05 (m, 1H, $H_{7/10}$), 7.80–7.69 (m, 2H, $H_{8,9}$), 7.53–7.46 (m, 2H, $H_{2'}$), 7.04 (s, 4H, $H_{2'',3''}$), 6.98–6.92 (m, 2H, $H_{3'}$), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.96–2.89 (m, 2H, H_3), 2.45 (t, 2H, *J*=6.2 Hz, H_1), 1.69 (tt, 2H, *J*=6.2, 6.0 Hz, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 183.2 (C), 182.4 (C), 159.1 (C), 158.9 (C), 158.1 (C), 151.0 (C), 147.4 (C), 137.2 (C), 134.3 (C), 134.2 (C), 133.8 (CH), 133.1 (C), 132.9 (C), 132.8 (CH), 131.6 (CH), 130.5 (C), 129.9 (C), 128.1 (CH), 127.2 (CH), 127.1 (CH), 114.1 (CH), 113.7 (CH), 55.3 (CH_3), 55.2 (CH_3), 28.3 (CH_2), 27.7 (CH_2), 22.2 (CH_2); IR (KBr) ν_{max}: 2953, 2238, 1677, 1603, 1509 cm^{-1}; LRMS (ES^+) (MeOH): *m/z* 488.20 $[M+H]^+$ (100%); HRMS (ES^+): *m/z* calcd for $C_{32}H_{26}NO_4$ $[M+H]^+$: 488.1862, found: 488.1856.

4.2.3. 4-(4′-Methylbenzylidene)-12-(4″-tolyl)-1,2,3,4-tetrahydrobenzo[b]acridine-6,11-dione (**15**)

Isolated as an orange solid (45.0 mg, 0.10 mmol, 20%); mp 246.5–247.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.44 (s, 1H, H_{13}), 8.35 (d, 1H, *J*=7.5 Hz, $H_{7/10}$), 8.09 (d, 1H, *J*=7.5 Hz, $H_{7/10}$), 7.79–7.70 (m, 2H, $H_{8,9}$), 7.42 (d, 2H, *J*=7.9 Hz, $H_{2'}$), 7.33 (d, 2H, *J*=7.8 Hz, $H_{2''}$), 7.22 (d, 2H, *J*=7.9 Hz, $H_{3'}$), 7.02 (d, 2H, *J*=7.8 Hz, $H_{3''}$), 2.92 (t, 2H, *J*=5.5 Hz, H_3), 2.53 (t, 2H, *J*=6.2 Hz, H_1), 2.48 (s, 3H, $H_{5'}$), 2.39 (s, 3H, $H_{5''}$), 1.75 (m, 2H, H_2); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ: 183.1 (C), 182.3 (C), 158.0 (C), 151.5 (C), 147.4 (C), 137.6 (C), 137.1 (C), 135.5 (C), 134.4 (C), 134.3 (CH), 134.2 (C), 133.8 (CH), 133.1 (CH), 132.9 (C), 130.1 (CH), 128.5 (CH), 128.7 (CH), 127.3 (CH), 127.1 (CH), 126.7 (CH), 125.9 (C), 28.3 (CH_2), 27.6 (CH_2), 22.1 (CH_2), 21.5 (CH_3), 21.4 (CH_3); IR (KBr) ν_{max}: 1677, 1544, 1519, 1298 cm^{-1}; LRMS (ES^+) (MeOH): *m/z* 456.22 $[M+H]^+$ (100%), 933.45 $[2M+Na]^+$ (70%); HRMS (ES^+): *m/z* calcd for $C_{32}H_{26}NO_2$ $[M+H]^+$: 456.1964, found: 456.1962.

4.2.4. 4-(2′-Bromobenzylidene)-12-(2″-bromophenyl)-1,2,3,4-tetrahydrobenzo[b]acridine-6,11-dione (**21**)

Isolated as a green/yellow crystalline solid (137.0 mg, 0.23 mmol, 47%); mp 212.5–213.0 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.45 (br s, 1H, H_{13}), 8.39–8.33 (m, 1H, $H_{7/10}$), 8.13–8.07 (m, 1H, $H_{7/10}$), 7.83–7.70 (m, 3H, $H_{8,9}$ and Ar*H*), 7.65 (dd, 1H, *J*=7.8, 1.0 Hz, Ar*H*), 7.48 (dt, 1H, *J*=7.5, 1.2 Hz, Ar*H*), 7.29–7.19 (m, 3H, Ar*H*), 7.18–7.17 (m, 1H, Ar*H*), 7.10 (dd, 1H, *J*=7.5, 1.6 Hz, Ar*H*), 2.83–2.64 (m, 2H, H_3), 2.51 (dd, 2H, *J*=6.7, 6.7 Hz, H_1), 1.86–1.75 (m, 2H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 182.7 (C), 181.8 (C), 157.8 (C), 149.8 (C), 147.5 (C), 139.4 (C), 137.6 (C), 136.7 (C), 136.1 (C), 134.3 (CH), 134.1 (CH), 133.7 (C), 133.1 (C), 132.8 (CH), 132.7 (CH), 132.4 (CH), 130.8 (CH), 129.3 (CH), 128.9 (CH), 128.1 (CH), 127.9 (CH), 127.3 (CH), 127.3 (CH), 126.8 (CH), 126.0 (C), 125.0 (C), 121.3 (C), 27.7 (CH_2), 27.2 (CH_2), 22.0 (CH_2); IR (KBr) ν_{max}: 3065, 2951, 1671, 1547, 1524, 723 cm^{-1}; LRMS (ES^+) (MeOH): *m/z* 605.93 ($[M+Na]^+$ ^{79}Br) (10%), 607.94 $[M+Na]^+$ (100%), 609.95 ($[M+Na]^+$ ^{81}Br) (10%); HRMS (ES^+): *m/z* calcd for $C_{30}H_{19}NO_2Na^{79}Br^{81}Br$ $[M+Na]^+$: 607.9660, found: 607.9663.

4.2.5. 4-(4′-Methoxybenzylidene)-12-(4″-methoxyphenyl)-3,4-dihydro-1H-2-oxa-5-aza-naphthacene-6,11-dione (**23**)

Isolated as a green/yellow solid (59.0 mg, 0.12 mmol, 24%); mp 260.5–261.0 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.42 (s 1H, H_{13}), 8.39–8.32 (m, 1H, $H_{7/10}$), 8.13–8.07 (m, 1H, $H_{7/10}$), 7.83–7.70 (m, 2H, $H_{8,9}$), 7.34 (d, 2H, $H_{2'}$), 7.10–7.02 (m, 4H, $H_{3',2''}$), 6.99–6.94 (m, 2H, $H_{3''}$), 4.90 (d, 2H, *J*=1.5 Hz, H_3), 4.51 (s, 2H, H_1), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 182.9 (C), 182.1 (C), 159.8 (C), 159.3 (C), 154.8 (C), 148.6 (C), 134.4 (CH), 134.0 (CH), 133.9 (CH), 132.8 (C), 131.9 (CH), 131.7 (CH), 128.9 (C), 128.5 (C), 128.0 (CH), 127.2 (CH), 114.2 (CH), 114.0 (CH), 67.4 (CH_2), 66.8 (CH_2), 55.3 (CH_3), 55.2 (CH_3); IR (KBr) ν_{max}: 2924, 1684, 1668, 1597, 1509, 1114 cm^{-1}; LRMS (ES^+) (MeOH): *m/z* 512.13 $[M+Na]^+$ (100%); HRMS (ES^+): *m/z* calcd for $C_{31}H_{23}NO_5Na$ $[M+Na]^+$: 512.1474, found: 512.1478.

4.2.6. 4-(4″-Methoxybenzylidene)-12-(4′-methoxyphenyl)-3,4-dihydro-2-thia-5-aza-naphthacene-6,11-dione (**25**)

Isolated as a green solid (30.0 mg, 0.06 mmol, 12%); mp 263.0–264.0 °C; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.40 (br s, 1H, H_{13}), 8.37–8.33 (m, 1H, $H_{7/10}$), 8.12–8.08 (m, 1H, $H_{7/10}$), 7.82–7.71 (m, 2H, $H_{8,9}$), 7.46–7.40 (m, 2H, $H_{2'}$), 7.07 (br s, 4H, $H_{2'',3''}$), 6.99–6.94 (m, 2H, $H_{3'}$), 3.95 (br s, 2H, H_3), 3.91 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.58 (br s, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 183.0 (C), 181.9 (C), 159.6 (C), 159.3 (C), 157.7 (C), 150.1 (C), 147.5 (C), 134.7 (C), 134.4 (CH), 134.2 (CH), 133.9 (CH), 132.9 (CH), 131.6 (CH), 130.4 (C), 129.5 (C), 129.0 (C), 128.2 (CH), 127.3 (CH), 127.2 (CH), 125.8 (C), 114.4 (CH), 113.9 (CH), 55.5 (CH_3), 55.2 (CH_3), 29.4 (CH_2), 29.1 (CH_2); IR (KBr) ν_{max}: 2934, 1666, 1597, 1509 cm^{-1}; LRMS (ES^+) (MeOH): *m/z* 506.15 $[M+H]^+$ (100%); HRMS (ES^+): *m/z* calcd for $C_{31}H_{24}NO_4S$ $[M+H]^+$: 506.1426, found: 506.1420.

4.3. General procedure for the microwave aza-Diels–Alder reaction

A mixture of the substituted indazole (0.5 mmol) and 1,4-naphthoquinone (2 mmol) was placed in a 10 mL pressure-proof tube. Freshly distilled toluene (3 mL) was added and the tube sealed with a septum. The mixture was irradiated with stirring for 2 h with initial 300 W microwave power at 200 °C. The toluene was evaporated and the crude mixture was dissolved to 30 mL of CH_2Cl_2; 2 g of the thiol resin (PL-BnSH)[9] was added and the tube was shaken for 24 h. The scavenger resin was filtered off, washed with CH_2Cl_2 and the solvent evaporated. The crude mixture was purified by column chromatography.

*4.3.1. 7-Benzyl-2-methyl-3-phenyl-3,3a,4,5-tetrahydro-2H-indazole (**9**)*

Isolated as a colourless oil (35.6 mg, 0.077 mmol, 23.5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.11 (m, 10H, ArH), 5.51–5.46 (m, 1H, H_6), 3.61–3.57 (m, 2H, H_8), 3.48 (d, 1H, J=13.6 Hz, H_3), 2.91 (dt, 1H, J=13.3, 5.1 Hz, H_{3a}), 2.69 (s, 3H, NCH_3), 2.14–2.07 (m, 2H, H_5), 1.93–1.85 (m, 1H, H_4), 1.64–1.51 (m, 1H, H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.6 (C), 139.8 (C), 139.5 (C), 132.2 (C), 132.2 (CH), 129.6 (CH), 129.1 (CH), 128.6 (CH), 128.2 (CH), 127.4 (CH), 125.9 (CH), 80.4 (CH), 54.2 (CH), 41.9 (CH_3), 36.3 (CH_2), 26.4 (CH_2), 25.4 (CH_2); LRMS (ES^+) (MeOH): m/z 325.12 $[M+H]^+$ (100%); HRMS (ES^+): m/z calcd for $C_{21}H_{22}N_2Na$ $[M+Na]^+$: 325.1681, found: 325.1681.

*4.3.2. 7-(10-Bromobenzyl)-3-(2′-bromophenyl)-2-methyl-3,3a,4,5-tetrahydro-2H-indazole (**26**)*

Isolated as a light yellow oil (123.8 mg, 0.27 mmol, 54%); ^{1}H NMR spectrum (400 MHz, $CDCl_3$) δ: 7.83 (dd, 1H, J=1.6, 7.8 Hz, $H_{3'}$), 7.59–7.54 (m, 2H, $H_{11,5'}$), 7.38–7.32 (m, 1H, H_{13}), 7.32–7.23 (m, 2H, $H_{4',6'}$), 7.19–7.13 (m, 1H, H_{12}), 7.12–7.06 (m, 1H, H_{14}), 5.48–5.43 (m, 1H, H_6), 4.31 (d, 1H, J=13.8 Hz, H_3), 3.87–3.74 (m, 2H, H_8), 3.04–2.94 (m, 1H, H_{3a}), 2.75 (s, 3H, NCH_3), 2.28–2.08 (m, 3H, $H_{5,4}$), 1.90–1.78 (m, 1H, H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.8 (C), 139.4 (C), 139.0 (C), 132.8 (CH), 132.7 (CH), 132.2 (CH), 131.7 (CH), 129.9 (C), 129.0 (CH), 128.9 (CH), 127.9 (CH), 127.3 (CH), 125.3 (C), 124.4 (C), 77.8 (CH), 55.2 (CH), 41.9 (CH_3), 36.5 (CH_2), 26.8 (CH_2), 25.6 (CH_2); LRMS (CI^+): m/z 461.00 $[M+H]^+$ (100%), 458.99 (82%); HRMS (CI^+): m/z calcd for $C_{21}H_{21}N_2^{79}Br^{81}Br$ $[M+H]^+$: 461.0051, found: 461.0036.

4.4. Procedure for the microwave *p*-toluenesulfonic acid reaction

A mixture of **6** (50 mg, 0.11 mmol) and *p*-toluenesulfonic acid (2.1 mg, 0.1 equiv) was placed in a 10 mL pressure-proof tube. Freshly distilled toluene (1.5 mL) was added and the tube was sealed with a septum. The mixture was irradiated for 15 min or 2 h with initial 300 W microwave power at 200 °C. The toluene was evaporated. The crude reaction mixture was dissolved in CH_2Cl_2 (30 mL) and washed with 2 M aqueous NaOH. The organic phase was dried over Na_2SO_4 and concentrated in vacuo then purified by column chromatography.

*4.4.1. 7-(2″-Bromobenzyl)-3-(2′-bromophenyl)-2-methyl-4,5,6,7-tetrahydro-2H-indazole (**27**)*

Yield: 48 mg, 0.11 mmol, 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (m, 1H, J=7.8 Hz, $H_{3'}$), 7.56 (d, 1H, J=7.9 Hz, H_{12}), 7.43–7.21 (m, 5H), 7.10–7.05 (m, 1H, H_{13}), 3.73–3.63 (m, 1H, H_9), 3.67 (s, 3H, NCH_3), 3.21 (m, 1H, H_8), 2.89 (m, 1H, H_9), 2.42–2.21 (m, 2H, H_5), 1.86 (m, 1H, H_6), 1.73 (m, 1H, H_7), 1.62–1.43 (m, 2H, $H_{6,7}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.9*, 150.7* (C), 140.2 (C), 133.0 (CH), 132.7 (CH), 132.3 (C), 132.0 (CH), 131.6 (CH), 131.4 (CH), 130.3 (CH), 127.5 (CH), 127.4 (CH), 127.1*, 127.0* (CH), 125.1 (C), 124.7 (C), 115.7 (C), 40.5*, 40.4* (CH_2), 36.81*, 36.78* (CH), 35.1 (CH_3), 28.4*, 28.1* (CH_2), 22.0*, 21.8* (CH_2), 20.8 (CH_2); LRMS (ES^+) (MeOH): m/z 482.94 $[M+Na]^+$ (100%), 460.95 $[M+H]^+$ (5%); HRMS (ES^+): m/z calcd for $C_{21}H_{21}N_2^{79}Br^{81}Br$ $[M+H]^+$: 461.0044, found: 461.0051. (The symbol asterisks '*' represents rotamers.)

Acknowledgements

This work was supported by a Royal Society University Research Fellowship (NJW) and the Research Foundation of Orion Corporation (PSK fellowship). This work was also supported in part by grant R01AI054961 from the US National Institutes of Health. We would like to thank Dr. Rachel Morgan and Professor Douglas Philp for helpful discussions relating to this work.

Supplementary data

General experimental procedures and copies of ^{1}H and ^{13}C spectra of all additional new compounds. Photodegradation studies on **6** and **8**, and a table of microwave optimisation reactions. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.063.

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