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Synthesis of oxepine-, oxocine- and azepine-annulated carbazole derivatives by combined Claisen rearrangement and diene/enyne metathesis

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Abstract—A new route to various medium ring heterocycle-annulated tetra-, penta- and hexacyclic carbazole derivatives has been developed using successive applications of three atom economic processes, viz. Claisen rearrangement, olefin metathesis and Diels–Alder reactions.

Various hetero-annulated carbazole derivatives have drawn considerable attention because of their natural occurrence and the broad spectrum of biological activity associated with these compounds.[1] Of particular interest have been the natural products[2] containing common heterocyclic rings such as furocarbazoles, pyranocarbazoles, pyrrolocarbazoles, indolocarbazoles, pyridocarbazoles and synthetic analogues[3] thereof. A number of synthetic methodologies have emerged for their preparation.[1a,2] On the other hand, medium ring oxa- and azacycle-fused carbazole derivatives have largely remained unexplored which may, in part, be due to a lack of general methods[4] for their synthesis. We have recently developed[5] a methodology based on combined application of Claisen rearrangement and ring-closing diene metathesis for the synthesis of oxepine- and oxocine-annulated coumarin and quinolone derivatives. We have also recently reported[6] the applications of domino Claisen rearrangement, enyne metathesis and Diels–Alder reactions leading to polycyclic coumarin frameworks. These methodologies have found applications[7] in the synthesis of a range of interesting oxepine-annulated heterocyclic structures and hence we report some new observations.

Our synthesis started from the commercially available 2-hydroxycarbazole **1** which on straightforward allylation under conventional conditions afforded *O*-allyl ether **2** (Scheme 1). Claisen rearrangement[8] of **2** in refluxing *N*,*N*-diethylaniline provided the known[9] phenol **4** as the only regioisomer in very good yield. Further allylation of **4** with allyl bromide led to diene **6**. A comparable sequence led to crotyl ether **3** and thence to diene **7** in an overall yield of 44% over three steps from **1**. Ring-closing metathesis of each of the dienes **6** and **7** using Grubbs' catalyst, benzylidene bistricyclohexylphosphinoruthenium(IV) dichloride[10] **8**, under our developed[5c] conditions led smoothly to the oxepinocarbazoles[11] **11** and **12**, respectively, in very good yields. Similarly, butenyl ethers **9** and **10**, derived from phenols **4** and **5**, reacted with catalyst **8**, albeit sluggishly, to provide oxocinocarbazoles **13** and **14** in good yields.

We then became interested in extending the study for the synthesis of azepine-annulated carbazoles. Thus, phenol **4** was converted to its methyl ether **15** which on further alkylation with allyl bromide under the usual conditions led to *N*-alkylcarbazole **17**. Similarly, compound **18** was prepared by two sequential alkylations of **5**. Ring-closing metathesis of dienes with one alkene unit linked to nitrogen can be problematic[12] because the basic nitrogen atom deactivates the carbene catalyst, however, exceptions do exist.[13] We had doubts whether dienes[14] **17** and **18** would undergo effective RCM. Pleasingly, the reaction of diene **17** with catalyst **8** proved to be easy and an efficient conversion to the desired carbazole

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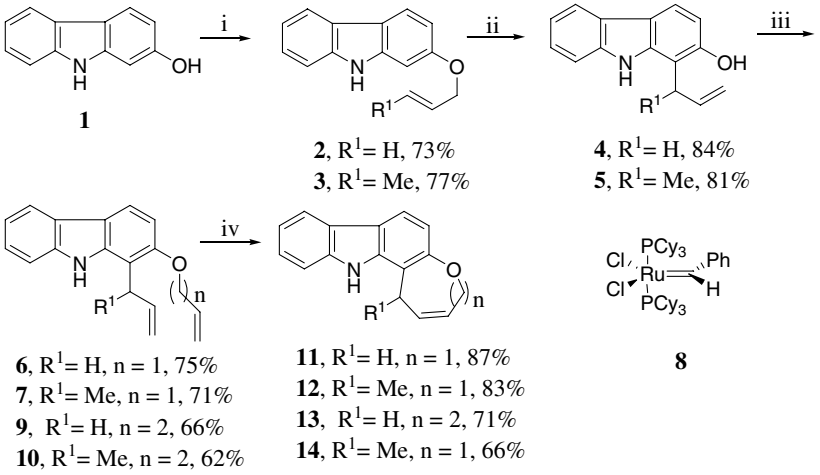
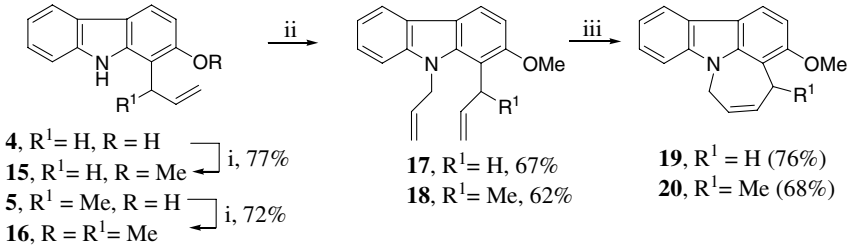


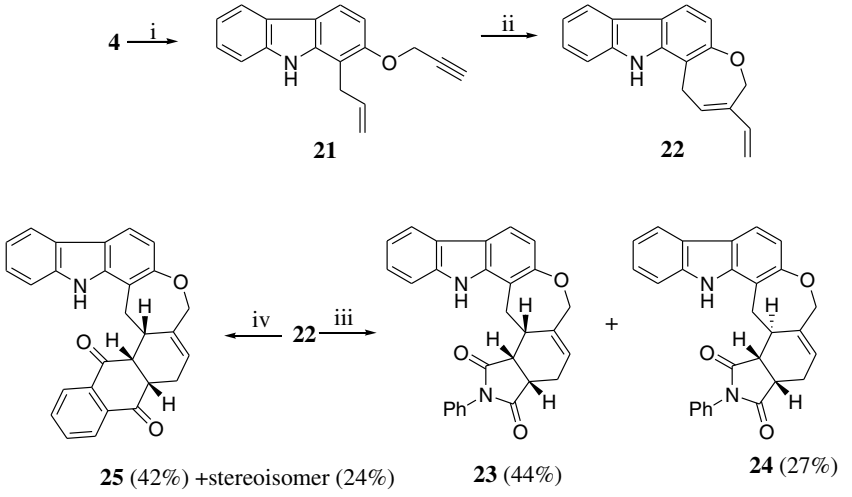
Scheme 1. Reagents and conditions: (i) allyl bromide, K_2CO_3, acetone, reflux, 18 h; (ii) $PhNEt_2$, reflux, 5 h; (iii) allyl bromide or 4-bromo-1-butene, K_2CO_3, acetone, reflux, 24 h; (iv) Grubbs' catalyst **8** (5 mol %), CH_2Cl_2, rt, 2–4 h for **11** and **12**, 24 h for **13** and **14**.

derivative **19** was secured. Similarly, the conversion **18** → **20** proceeded without difficulty thereby indicating that the carbazole ring-nitrogen atom, although not basic, is well tolerated by the Grubbs' first generation catalyst (see Scheme 2).

2,5-Pyrrolidinedione-appended polycyclic carbazole derivatives such as staurosporine, rebeccamycin, granulatimide, UCN-01 and synthetic analogues thereof are of interest[15] because of their biological activity. Development of routes to this type of ring system is therefore of significance. We prepared the enyne derivative **21** (Scheme 3) by straightforward propargylation of phenol **4**. Ring-closing enyne metathesis[16] using catalyst **8** provided diene **22** in good yield. In Diels–Alder cycloadditions of vinylcycloalkenes, *endo–exo* stereoselectivity is



Scheme 2. Reagents and conditions: (i) MeI, K_2CO_3, acetone, reflux, 12 h; (ii) NaH, allyl bromide, DMF, 0 °C to rt, 18 h; (iii) Grubbs' catalyst **8** (5 mol %), CH_2Cl_2, rt, 5 h for **17**, 11 h for **18**.



Scheme 3. Reagents and conditions: (i) propargyl bromide, K_2CO_3, acetone, reflux, 4 h, 83%; (ii) Grubbs' catalyst **8** (5 mol %), CH_2Cl_2, rt, 24 h, 67%; (iii) *N*-phenylmaleimide, toluene, 95 °C, 24 h; (iv) 1,4-naphthoquinone, toluene, 95 °C, 24 h.

highly variable. With vinylcyclohexenes, both modes of cycloaddition have been observed.[17] On the other hand, we have recently observed[6] that Diels–Alder cycloaddition with coumarin-annulated vinyloxepines led only to *endo* products. However, when diene **22** was refluxed with *N*-phenylmaleimide two products were formed in a ratio ~3:2. The major product was assigned[18] the *endo* stereochemistry, **23**, mp 120 °C, while the other product appeared to be the *exo*-adduct **24**. Similarly, cycloaddition of diene **22** with 1,4-naphthoquinone proceeded to give a separable mixture of the major product **25** and its *exo* isomer in a combined yield of 66%.

In summary, we have demonstrated that various oxepine- and azepine-annulated polycyclic carbazole frameworks[19] can be conveniently prepared by successive applications of three atom economic processes, viz. Claisen rearrangement, ring-closing diene/enyne metathesis and Diels–Alder reactions. The stereodivergence observed during the Diels–Alder reaction of diene **22** is noteworthy. The methodology developed may prove to be helpful for the preparation of other carbazole derivatives of similar complexity. The compounds prepared may prove to be useful in biological applications.

Acknowledgements

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18. The structural assignments were based on the data obtained from ^{1}H, ^{13}NMR, COSY, DEPT and HMBC experiments on compounds **23** and **24**.
19. All new compounds reported here gave satisfactory spectroscopic and/or analytical data. Data for **11**: mp 154 °C. IR (KBr) 3314, 1607, 1462, 1430, 1207, 1057, 1021 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (1H, d, $J = 7.5$), 7.95 (1H, br s), 7.86 (1H, d, $J = 8.0$), 7.43 (1H, td, $J = 8.0$, 1.1), 7.38 (1H, td, $J = 7.0$, 1.0), 7.23 (1H, td, $J = 7.0$, 1.5), 7.01 (1H, d, $J = 8.5$), 5.97–5.92 (1H, m), 5.65–5.61 (1H, m), 4.65 (2H, d, $J = 2.0$), 3.69 (2H, d, $J = 2.4$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3 (s), 139.8 (s), 138.1 (s), 128.6 (d), 125.2 (d), 124.9 (d), 123.7 (s), 120.4 (s), 120.0 (d), 119.6 (d), 118.7 (d), 117.3 (s), 113.9 (d), 110.5 (d), 71.1 (t), 25.9 (t). HRMS (EI): obs. 235.098986; calcd. 235.099714. Compound **13**: mp 116 °C. IR (KBr) 3296, 1607, 1462, 1427, 1324, 1221, 1206, 1050 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (1H, d, $J = 7.5$), 7.98 (1H, br s), 7.87 (1H, d, $J = 8.0$), 7.43 (1H, d, $J = 8.0$), 7.39 (1H, td, $J = 8.5$, 1.5), 7.22 (1H, td, $J = 8.0$, 1.1), 6.98 (1H, d, $J = 8.1$), 6.07 (1H, dt, $J = 11.0$, 7.0), 5.73–5.68 (1H, m), 4.15 (2H, t, $J = 5.0$), 3.66 (2H, d, $J = 6.5$), 2.42–2.38 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5 (s), 139.8 (s), 138.6 (s), 131.4 (d), 127.7 (d), 125.2 (d), 123.9 (s), 120.0 (s), 119.9 (d), 119.6 (d), 118.8 (d), 118.5 (s), 114.9 (d), 110.5 (d), 73.7 (t), 27.9 (t), 26.4 (t). Mass (EI, 70 eV): *m*/*z* 249 (100%), 220 (48%). Compound **19**: mp 114 °C. IR (KBr)

2930, 1624, 1598, 1460, 1350, 1243, 1217 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (1H, d, $J = 7.5$), 7.83 (1H, d, $J = 8.7$), 7.41–7.33 (2H, m), 7.16–7.13 (1H, m), 6.83 (1H, d, $J = 8.4$), 6.37 (1H, dt, $J = 10.2$, 6.9), 6.18 (1H, m), 4.93 (2H, d, $J = 6.9$), 3.89 (3H, s), 3.49 (2H, d, $J = 6.6$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6 (s), 141.4 (s), 140.8 (s), 134.4 (d), 125.3 (d), 124.9 (d), 122.4 (s), 119.5 (d), 118.6 (d), 118.3 (d), 117.9 (s), 109.6 (s), 107.7 (d), 104.6 (d), 56.7 (q), 40.8 (t), 22.1 (t). Elemental analyses: C, 81.78%, H, 6.01%, N, 5.49%; $C_{17}H_{15}NO$ requires C, 81.90%, H, 6.06%, N, 5.62%. Mass (TOF MS ES+): m/z 249 (M^+). Compound **23**: mp 120 °C. IR (KBr) 3378, 1700, 1606, 1466, 1384, 1208 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.10 (1H, s), 7.96 (1H, d, $J = 7.6$), 7.82 (1H, d, $J = 8.4$), 7.56–7.52 (2H, m), 7.48–7.43 (2H, m), 7.36–7.29 (3H, m), 7.19 (1H, dt, $J = 8.0$, 1.2), 6.82 (1H, d, $J = 8.4$), 6.19–6.18 (1H, m), 5.27 (1H, td, $J = 12.4$, 1.2), 4.70 (1H, d, $J = 12.4$), 3.88 (1H, dd, $J = 15.2$, 4.0), 3.57 (1H, dd, $J = 15.2$, 4.4 Hz), 3.04 (1H, q, $J = 9.2$), 2.92–2.89 (1H, m), 2.78–2.70 (2H, m), 2.36 (1H, ddd, $J = 14.4$, 5.6, 2.8). ^{13}C NMR (90 MHz, $CDCl_3$): δ 179.3 (s), 178.0 (s), 154.9 (s), 141.1 (s), 139.8 (s), 138.3 (s), 131.5 (d), 129.8 (s), 129.3 (d), 128.9 (d), 126.5 (d), 124.6 (d), 123.8 (s), 119.5 (s), 119.4 (s), 119.3 (d), 117.7 (d), 112.4 (d), 110.9 (d), 107.3 (d), 72.5 (t), 42.5 (t), 38.8 (d), 38.3 (d), 26.4 (d), 22.5 (t). Elemental analyses: C, 77.29%, H, 5.14%, N, 6.49%; $C_{28}H_{22}N_2O_3$ requires C, 77.40%, H, 5.10%, N, 6.45%. Mass (FAB): m/z 434 (M^+, 51%).