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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 4843–4845

Synthesis of polycyclic pyrazoles through formation of the first fused heterocyclic *o*-quinodimethane intermediate

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Received 11 March 2005; revised 10 May 2005; accepted 18 May 2005

Abstract—1-Benzoyl-4,6-dibromo-3-methyl-1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole (**2**) was used as a precursor for *o*-quinodimethane **3**, which was trapped by in situ reactions with dienophiles to give bridged pyrazole derivatives.

o-Quinodimethane (*o*-QDM) derivatives are reactive dienes and can be generated in situ by a number of methods. The inter- and intramolecular Diels–Alder reactions of these compounds form the basis of the synthesis of a wide range of target molecules.[1] Traditionally, heterocyclic *o*-QDMs have received much less attention. However, the generation and synthetic applications of these materials have been recently reviewed[2] and interest in them is growing rapidly. Pyrazoles have long been of pharmacological interest[3] as antianxiety,[4,5] antipyretic, analgesic and antiinflammatory drugs,[6–8] as well as antimicrobials.[9–13] Agrotechnical and analytical applications have also been reported for some pyrazole derivatives.[14] Certain hydroxy phenylpyrazoles can act as ultraviolet stabilizers[15] and as analytical reagents in the complexation of transition metal ions.[16] 3-Benzoylpyrazoles can act as precursors of other important heterocyclic compounds (e.g., in the preparation of cizolirtine, a potent analgesic).[17,18] This highlights the potential applications of benzoylpyrazoles and has stimulated the study of their synthesis.

In continuation of our work on the synthesis of pyrazole derivatives[19] and on heterocyclic *o*-QDMs,[20] we herein describe the bromination of the cyclopentapyrazole **1**, the generation of the corresponding fused pyrazole *o*-quinodimethane **3** and the in situ trapping of this reactive intermediate in Diels–Alder reactions with dienophiles.

The bromination of 1-benzoylcyclopentapyrazole **1** was initially attempted with NBS under reflux in carbon tetrachloride solution irradiated with a 200 W light bulb, whereupon the formation of several products was observed. However, the use of NBS (2.2 equiv) in the presence of either dibenzoyl peroxide or 2,2′-azoisobutyronitrile (AIBN) resulted, after selective bromination, in the formation of a mixture of *syn–anti* dibromocyclopentapyrazoles **2**. The reaction was followed by TLC until almost complete disappearance of the starting pyrazole **1** (~10 min). Unfortunately, all attempts to separate the bisbromides **2** by chromatography failed, because of their instability and partial decomposition. However, by studying the ^{1}H NMR spectrum of the crude reaction mixture, we concluded that a 1:1 mixture of the *syn–anti* isomers had been formed.[21]

In the next step, the crude bromide mixture **2** was used for the formation of the *o*-QDM intermediate **3** through the action of sodium iodide in dry DMF at 80 °C for 45 min, whereupon in the presence of *N*-methylmaleimide a single cycloadduct **4*endo*** was obtained in 31% overall yield (Scheme 1). The *endo* stereochemistry was established by the coupling constants (Table 1) between protons 1 and 12 (4.60 Hz) and protons 7 and 8 (4.70 Hz) and also on the basis of the NOESY H–H spectrum, where a correlation signal between the 8 and 12 protons and the 13-*syn* proton was observed. This result is in agreement with the results obtained for the addition of *N*-methylmaleimide to isoindene.[22] In

Keywords: Pyrazoles; *o*-Quinodimethanes; Diels–Alder reactions.
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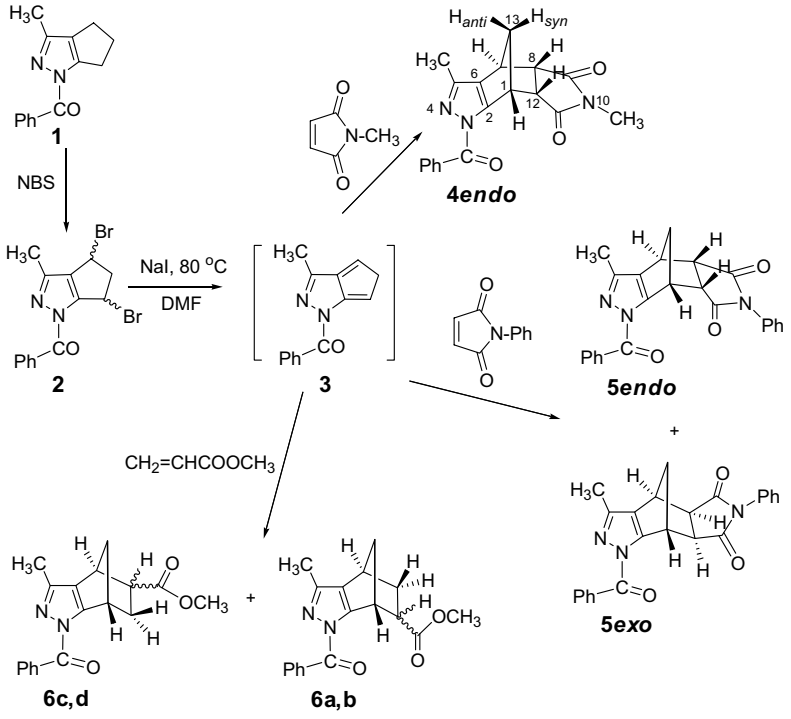
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.05.079



Scheme 1. Formation of the heterocyclic *o*-QDM **3** and its reaction with some dienophiles.

contrast, *N*-phenylmaleimide reacted with **3** to afford a ***5endo*–5*exo*** (1:1) mixture in 30% overall yield. However, by successive recrystallizations from ethanol a pure sample of the ***5endo*** isomer was isolated, hence the NMR spectral data of the ***5exo*** isomer was also established.[23] Finally, in the case of the less reactive dienophile methyl acrylate, neither regio- nor stereo-selectivity was observed and a mixture of all four isomers (2:2:1:1) was isolated in 18% overall yield (Table 1).

In summary, a route leading to a fused *N*-benzoyl-cyclopentanopyrazole quinodimethane **3** and its reaction in situ with dienophiles yielding bridged polycyclic benzoylpyrazole derivatives has been described.

To our knowledge, this is the first example of the formation of a heterocyclic quinodimethane formed through bromination of fused methylene groups. Further appli-

Table 1. NMR data[a] (^{1}H, ^{13}C and COLOC C–H) for compound ***4endo***

Position[b]	C	H	COLOC[c]
1	45.05	4.38 (1H, dddd, *J* = 4.60, 1.61, 1.53, 1.10)[d]	129.66, 40.88
2	152.13		
5	147.67		
5-CH_3	12.68	2.22	152.13, 147.67, 129.66
6	129.66		
7	40.88	3.83 (1H, dddd, *J* = 4.70, 1.63, 1.54, 1.10)	152.13, 45.05
8	47.33	3.55 (1H, dd, *J* = 7.52, 4.70)	175.47, 129.66
9	176.70		
10-CH_3	24.04	2.53	176.70, 175.47
11	175.47		
12	47.70	3.50 (1H, dd, *J* = 7.52, 4.60)	176.70, 152.13
13	54.24	*syn*-2.05 (1H, ddd, *J* = 9.36, 1.63, 1.61)	152.13, 129.66
		anti-2.38 (1H, ddd, *J* = 9.36, 1.54, 1.53)	
N3–CO	165.28		
1′	131.62		
2′,6′	131.41	8.04–8.08 (2H, m)	165.28, 132.88
3′,5′	128.08	7.40–7.50 (2H, m)	131.62
4′	132.88	7.56–7.62 (1H, m)	131.41

[a] Chemical shifts in ppm relative to TMS in $CDCl_3$ solution; coupling constants *J* in hertz.
[b] Primed numbers referred to the C-atoms of the Ph group.
[c] Long range correlations (^2J and ^3J) between the H-atom on the left column and the C-atoms stated in this column.
[d] The spin system consisting of protons H1–H7–H8–H12–H13$_{syn}$–H13$_{anti}$ has been studied also by simulation (SpinWorks ver. 2.2.0).

cations of these intermediates in cycloaddition reactions are being studied.

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21. Selected data for the crude mixture of the two enantiomeric pairs of **2** are given: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.35 (s, 3H), 3.27–3.36 (m, 1H), 3.61–3.69 (m, 2H), 3.79–3.89 (m, 1H), 5.19–5.23 (m, 1H), 5.34–5.41 (m, 1H), 5.58–5.66 (m, 2H), 7.45–7.55 (m, 4H), 7.60–7.66 (m, 2H), 8.15–8.25 (m, 4H); MS (EI) *m/z* (rel. int.) 382, 384, 386 ($M^{+\cdot}$, 40), 303, 305 (74), 224 (54), 105 (100).
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23. Selected data for the new compounds **5*endo*** and **5*exo***:
Compound **5*endo***: mp 240–242 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.13 (ddd, 1H, J = 9.35, 1.5, 1.5 Hz, H-13$_{anti}$), 2.29 (s, 3H, CH_3), 2.46 (ddd, 1H, J = 9.35, 1.5, 1.5 Hz, H-13$_{syn}$), 3.69 (dd, 1H, J = 7.9, 4.6 Hz, H-8), 3.74 (dd, 1H, J = 7.9, 4.6 Hz, H-12), 3.94 (dddd, 1H, J = 4.6, 1.5, 1.5, 0.8 Hz, H-7), 4.48 (dddd, 1H, J = 4.6, 1.5, 1.5, 0.8 Hz, H-1), 6.81–6.85 (m, 2H, *o-N*–Ph), 7.31–7.36 (m, 3H, *m*, *p-N*–Ph), 7.35–7.40 (m, 2H, *m-CO*–Ph), 7.50–7.57 (m, 1H, *p-CO*–Ph), 7.91–7.94 (m, 2H, *o-CO*–Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.86 (CH_3), 41.28 (C-7), 45.35 (C-1), 47.70 (C-8), 47.98 (C-12), 54.91 (C-13), 126.41 (*o-N*–Ph), 128.00 (*m-CO*–Ph), 128.69 (*p-N*–Ph), 129.12 (*m-N*–Ph), 130.00 (C-6), 131.35 (*o-CO*–Ph), 131.43 (*i-N*–Ph), 131.48 (*i*-CO–Ph), 132.83 (*p*-CO–Ph), 147.78 (C-5), 152.52 (C-2), 165.50 (*N*–CO), 174.49 (C-11), 175.75 (C-9).
Compound **5*exo***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (dd, 1H, J = 8.6, 1.5 Hz, H-13), 2.10 (s, 3H, CH_3), 2.70 (dd, 1H, J = 8.6, 1.5 Hz, H-13), 3.75 (dd, 1H, J = 8.3, 5.1 Hz, H-8), 3.92 (dd, 1H, J = 5.1, 1.5 Hz, H-7), 4.43 (d, 1H, J = 8.3 Hz, H-12), 6.25 (d, 1H, J = 3.2 Hz, H-1), 7.07–7.10 (m, 2H, *o-N*–Ph), 7.31–7.52 (m, 6H), 7.89–7.92 (m, 2H, *o-CO*–Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.78, 41.42, 43.54, 50.78, 64.27, 80.00, 122.30, 126.25, 127.75, 128.60, 129.03, 129.31, 129.96, 131.37, 133.65, 147.70, 151.30, 167.19, 173.94, 175.55.