Pergamon

*Tetrahedron Letters*, Vol. 38, No. 27, pp. 4873-4876, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01016-2

# An Expeditious Procedure for the Generation of Pyrimidine *Ortho*-Quinodimethanes

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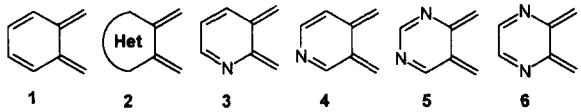
***Abstract:*** The one step synthesis of 2,4-dialkyl and 2,4-diaryl substituted 5,6-dihydrocyclobuta[*d*]pyrimidines (**12a,b**) as new precursors for pyrimidine *ortho*-quinodimethanes and their trapping with different dienophiles and $C_{60}$ is reported. © 1997 Elsevier Science Ltd.

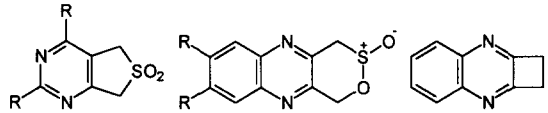
*o*-Quinodimethane (*o*-QDM) **1**, firstly reported by Cava and Napier,[1] are valuable species in organic synthesis and have been widely used for synthetic applications as highly reactive dienes in cycloaddition reactions.[2] In contrast, heterocyclic *o*-quinodimethanes **2** have received less attention despite their potential synthetic interest,[3] and only very recently this chemistry has attracted a great deal of attention.[4]

A variety of synthetic alternatives for the generation of different nitrogen containing heterocyclic *o*-quinodimethanes permit to access to this class of reactive intermediates. In this regard, pyridine derived *o*-quinodimethanes **3** and **4** are available from *o*-bis(cloromethyl)pyridines and subsequent 1,4-elimination.[5] The pyrimidine nucleus occurs widely in compounds with biological and pharmaceutical activity and therefore, pyrimidine *o*-quinodimethanes and adducts derived from them are of particular interest. It has also been recently described that pyrimidine *ortho*-quinodimethanes **5** can be generated in a multistep synthetic procedure by thermal extrusion of sulfur dioxide from pyrimidine fused-3-sulfolenes **7** as precursors.[6] Sulfolenes were obtained in four steps by reaction of amidines with 3-methoxycarbonyl-4-oxotetrahydrothiophene followed by conversion into 4-chloropyrimidines, oxidation at sulfur and subsequent displacement of the chlorine atom by nucleophiles. More recently pyrimidine and pyrimidone derivatives of [60]fullerene were formed from the respective heterocyclic *o*-quinodimethanes.[7] Chung *et al.*[8] have reported the synthesis in two steps of 7,8-disubstituted quinoxalino-fused sultines **8** and their applications in Diels-Alder reactions with alkenes and

alkynes. Sultines undergo extrusion of $SO_2$ when heated in toluene (200 °C, sealed tube). The resulting pyrazine *o*-quinodimethane derivatives **6** were trapped as 1:1 adducts in good yields. In the absence of a dienophile the cyclobuta[1,2-*b*]quinoxaline **9** is formed. Diels-Alder adducts were also formed in excellent yields when the cyclobutene **9** was heated in the presence of dienophiles, thus indicating that heterocyclic cyclobutenes could be appropriate precursors.



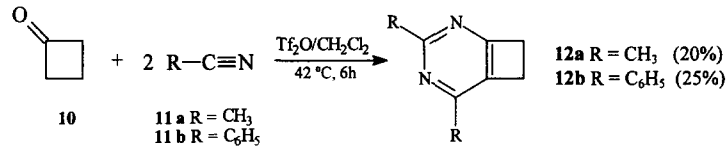

**1** **2** **3** **4** **5** **6**



**7** **8** **9**

We wish now to describe here a new and direct route for the one-step synthesis of cyclobutapyrimidines, the thermal generation of pyrimidine *o*-quinodimethanes **5** and their trapping *in situ* with various dienophiles.

The reaction of aliphatic or alicyclic ketones, aliphatic or aromatic nitriles and triflic anhydride ($Tf_2O$) leads to the formation of pyrimidines under mild conditions.[9] According to this procedure we have carried out the reaction of cyclobutanone **10** with nitriles **11a,b**. 2,4-Disubstituted alkyl or aryl pyrimidines **12a,b**[10] were directly obtained in one step in moderate yield.



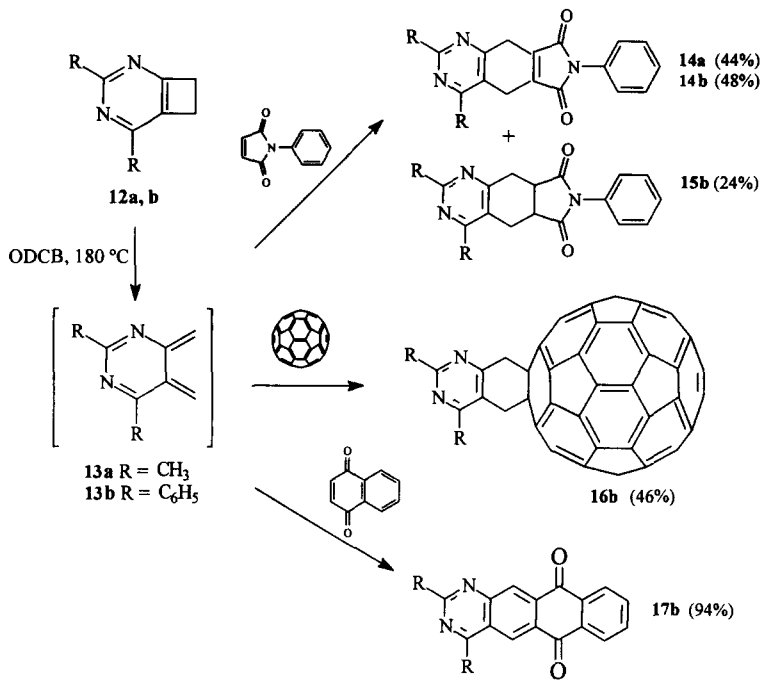

**10**

**11 a** R = $CH_3$
**11 b** R = $C_6H_5$

**12a** R = $CH_3$ (20%)
**12b** R = $C_6H_5$ (25%)

Cyclobutapyrimidines **12a,b** are excellent precursors for the *"in situ"* generation of the extremely reactive pyrimidine dienes and lead to **13a,b** which were trapped as 1:1 adducts when heated in *o*-dichlorobenzene (ODCB) at 180°C in the presence of different dienophiles.

Thermolysis of **12a** in the presence of *N*-phenylmaleinimide (NPM) gave a 1:1 adduct **14a** in 44% yield in which loss of $H_2$ occurs. Homoallylic coupling observed in the $^1H$ NMR spectrum shows structural characteristic very large $^5J$ values (6.95, 7.40 Hz for **14a,b** respectively). From diaryl compound **12b**, a 2:1 mixture of adducts **14b** and **15b** was obtained. In this paper we report the [4+2]cycloaddition of pyrimidine *o*-quinodimethanes to [60]fullerene which leads also to a 1:1 adduct in 46% yield. Diels-Alder cycloadditions to $C_{60}$ are well documented in the literature and afford to the thermally stable [6,6] monoadducts.[7,11] Thus, **16b** showed in the $^1H$ NMR spectrum the aromatic signals (8.60-7.60 ppm) as well as the methylene signals (5.10-4.90 ppm) broaded as a consequence of a restricted conformational inversion of the ring at room temperature. The $^{13}C$ NMR spectrum shows 38 lines, consistent with the $C_s$ symmetry for the molecule.




This result offers an elegant and direct method for the derivatization of $C_{60}$ with this important naturally heterocycle. Trapping of **13b** with naphthoquinone allows the isolation of an insoluble 1:1 adduct **17b** under similar experimental conditions in very high yield (94%).

In summary, we have reported for the first time an expeditious one-step procedure for the preparation of alkyl or aryl substituted cyclobutapyrimidines. These compounds are suitable precursors for the favorable "*in situ*" generation of the important pyrimidine *ortho*-quinodimethane which has been trapped with different dienophiles, including [60]fullerene. This result opens up the way to novel organofullerenes bearing biologically active organic addends containing the pyrimidine moiety. Work is in progress to prepare such compounds.

**Acknowledgements:** We are gratefully acknowledged to the DGICYT (Spain, Grant PB 95-0911 and PB95-0428-CO2) for financial support. We thank "Centro de Espectroscopía de la UCM" for determining NMR and mass spectra.

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10. Satisfactory spectral data were obtained for all products. Selected data **12b**: white solid , mp (hexane) 118-119 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 3.53, 3.61 (AA`BB`, 4H, $2CH_2$), 7.85 (m, 10H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 28.18 ($CH_2$), 36.29 ($CH_2$), 127.94, 128.17, 128.56, 128.97, 130.36, 131.12, 132.17, 135.86, 138.77, 155.00, 164.42, 174.37; **14a**: mp (hexane) 112-113 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 2.78 (t, *J*=6.95 Hz, 2H, $CH_2$), 2.81 (s, 3H, $CH_3$), 2.91 (s, 3H, $CH_3$), 3.49 (t, *J*=6.95 Hz, 2H, $CH_2$), 7.40 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 17.42 ($CH_3$), 21.15 ($CH_3$), 22.97 ($CH_2$), 53.55 ($CH_2$), 118.53, 120.76, 126.71, 127.31, 128.65, 129.33, 131.16, 136.73, 155.97, 165.00, 166.94; **16b**: IR (KBr) $\nu_{max}$ ($cm^{-1}$) 2950, 2900, 1525, 1380, 525; UV ($CHCl_3$) $\lambda_{max}$(nm) 434, 702; $^1$H NMR (300 MHz, $CS_2/CDCl_3$) δ 4.90 (bs, 2H, $CH_2$), 4.98 (bs, 2H, $CH_2$), 7.60 (m, 6H), 7.90 (m, 2H), 8.60 (m, 2H); $^{13}$C NMR (300 MHz, $CS_2/CDCl_3$) δ 40.70 ($CH_2$), 47.32 ($CH_2$), 64.81 [$sp^3$ ($C_{60}$)], 65.33 [$Csp^3$ ($C_{60}$)], 128.60, 128.73, 128.78, 129.62, 129.78, 130.85, 137.35, 137.66, 140.32, 140.45, 141.77, 141.86, 142.11, 142.13, 142.16, 142.22, 142.70, 142.74, 143.21, 144.68, 144.80, 145.56, 145.57, 145.82, 145.83, 146.35, 146.39, 146.61, 147.76, 147.79, 155.80, 163.31, 163.68, 167.66; MS (FAB, m/z) 978 ($M^+$, $C_{78}H_{14}N_2$, 12), 825 (M-153, 100), 720 ($C_{60}$, 27); **17b** yellow solid, mp (toluene) 336-338 °C; IR (KBr) $\nu_{max}$ ($cm^{-1}$) 1680, 1550, 1280; $^1$H NMR (300 MHz, $CDCl_3$) δ 9.09 (s, 1H), 9.17 (s, 1H). MS (m/z) 412 ($M^+$, 98), 355 (12), 150(72), 75(100)
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(*Received in UK* 8 *May* 1997; *accepted* 23 *May* 1997)