Pergamon

Tetrahedron Letters 42 (2001) 2043–2044

TETRAHEDRON
LETTERS

A novel multicomponent reaction of dimethoxycarbene and DMAD with aldehydes and quinones: facile synthesis of dihydrofuran derivatives[†]

Vijay Nair,* S. Bindu and Lakshmi Balagopal

Organic Chemistry Division, Regional Research Laboratory (CSIR), Trivandrum 695019, India

Received 4 December 2000; revised 3 January 2001; accepted 10 January 2001

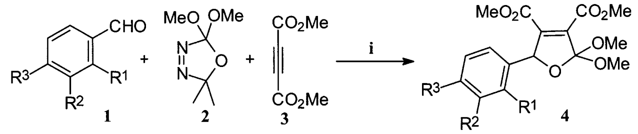
Abstract—The zwitterionic species generated by the addition of dimethoxy carbene to dimethyl acetylenedicarboxylate (DMAD) is trapped by aldehydes and quinones to yield dihydrofuran derivatives in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

The chemistry of nucleophilic carbenes, such as dimethoxy carbene, has been the subject of intense investigations by Hoffmann,[1] and more recently by Warkentin,[2] who has devised a very convenient method for generating the carbene. A reaction of dimethoxy carbene that has received much attention is its addition to activated triple bonds, e.g. DMAD leading to a zwitterionic species. Although the latter has been shown to undergo further reaction with excess DMAD,[1] no attempt has been made to trap it with other electrophiles. In the context of our recent observation that a facile multicomponent reaction (MCR) occurs with isocyanides, DMAD and aldehydes,[3] we surmised that a similar reaction would readily occur between the zwitterionic species derived from dimethoxy carbene, DMAD and aldehydes leading to dihydrofuran derivatives. The preliminary results of our investigations validating this assumption are presented here.

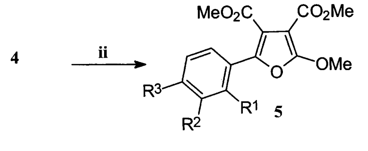
In our initial experiment, we exposed *p*-tolualdehyde to the zwitterionic species, resulting from DMAD and dimethoxycarbene, the latter being generated in situ by the thermolysis of **2** in refluxing toluene following the Warkentin protocol.[2] A facile reaction leading to the dihydrofuran derivative **4a**[4] in 85% yield occurred (Scheme 1). The product was characterised by spectroscopic analysis.

The reaction appears to be general as illustrated by its application to a number of aldehydes; moderate to excellent yields[‡] of the furan derivatives were obtained.

It is interesting to note that **4** on standing at rt for several hours lost methanol slowly to afford the furan derivative **5**. Subsequently it was found that microwave irradiation of **4** accelerated its aromatisation dramatically (Scheme 2).



Scheme 1. *Reagents and conditions*: (i) toluene, reflux, 15 h, argon; **4a**: R^1, $R^2=H$, $R^3=CH_3$, 85%; **4b**: R^1, $R^3=H$, $R^2=NO_2$, 77%; **4c**: R^1, $R^2=H$, $R^3=Cl$, 66%; **4d**: R^1, $R^3=H$, $R^2=Cl$, 75%; **4e**: R^1, $R^2=H$, $R^3=OMe$, 43%; **4f**: R^1, R^2, $R^3=H$, 45%; **4g**: R^1, $R^2=H$, $R^3=OCH_2Ph$, 69%; **4h**: R^1, $R^2=$benzo, $R^3=H$, 90%.



Scheme 2. *Reagents and conditions*: (ii) microwave (800 W), silica gel, 5 min, 90%; R^1, $R^2=H$, $R^3=CH_3$.

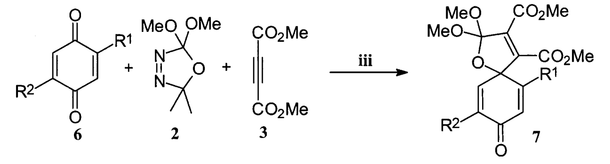
Keywords: dimethoxycarbene; acetylenedicarboxylate; aldehydes; quinones; dihydrofuran.

* Corresponding author. Fax: +91-471-491712; e-mail: gvn@csrrltrd.ren.nic.in

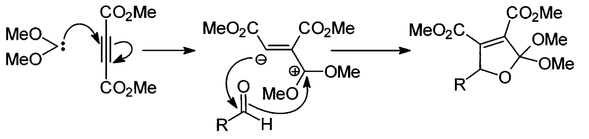
[†] This paper is dedicated with best wishes to Professor Alfred Hassner, on the occasion of his retirement.

[‡] All yields are for isolated compounds. Yield given in parenthesis is based on the recovered *p*-benzoquinone.

PII: S0040-4039(01)00070-3



Scheme 3. *Reagents and conditions*: (iii) toluene, sealed tube, 15 h, argon; **7a**: R^1, R^2=H, 75%; **7b**: R^1, R^2=CH_3, 65%; **7c**: R^1=H, R^2=Ph, 59%[§] (82).



Scheme 4.

In view of the encouraging results obtained with aldehydes and in the context of our interest in the addition of zwitterionic species to quinones,[5] it was obligatory to extend the present reaction to quinones also. An illustrative example involving *p*-benzoquinone leading to a spiro dihydrofuran derivative is presented in Scheme 3. The reaction appears to be general and applicable to other *p*-benzoquinones.[‡]

Similar reactions were observed with anthraquinone and 1,4-naphthoquinone and the spirodihydrofurans were obtained in 31 and 52% yields, respectively.

Mechanistically, the reaction may be considered to involve the cycloaddition of a zwitterion to the carbonyl group (Scheme 4).

In conclusion, we have devised a facile method for the synthesis of substituted dihydrofuran derivatives by the one pot reaction of dimethoxycarbene, generated in situ from 2,2-dimethoxy Δ^3-1,3,4-oxadiazoline, and DMAD with aldehydes and quinones. Further investigations in this area are in progress.

Acknowledgements

S.B. and L.B. thank CSIR, New Delhi for research fellowships. Thanks are also due to Mr. A. U. Vinod for useful discussion, Ms. Soumini Mathew for recording high resolution NMR spectra and Mrs. S. Viji for elemental analysis.

References

1. (a) Hoffmann, R. W.; Lilienblum, W.; Dittrich, B. *Chem. Ber.* **1974**, *107*, 3395–3407; (b) Hoffmann, R. W.; Steinbach, K.; Lilienblum, W. *Chem. Ber.* **1976**, *109*, 1759–1768; (c) Hoffmann, R. W.; Reiffen, M. *Chem. Ber.* **1976**, *109*, 2565–2571; (d) Hoffmann, R. W.; Steinbach, K.; Dittrich, B. *Chem. Ber.* **1973**, *106*, 2174–2184.
2. (a) Warkentin, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2161–2169 and references cited therein; (b) Pezacki, J. P.; Loncke, P. G.; Ross, J. P.; Warkentin, J.; Gadosy, T. A. *Org. Lett.* **2000**, *2*, 2733; (c) Lu, X.; Warkentin, J. *Org. Lett.* **2000**, *2*, 3501–3503.
3. Nair, V.; Vinod, A. U. *J. Chem. Soc., Chem. Commun.* **2000**, 1019–1020.
4. All new compounds were fully characterised.

   Typical experimental procedure and selected data for compound **4a**:

   A mixture of *p*-tolualdehyde **1** (0.100 g, 0.83 mmol), DMAD **3** (0.177 g, 1.25 mmol) and 2,2 dimethoxy Δ^3-1,3,4-oxadiazoline **2** were refluxed in dry toluene under an argon atmosphere for 15 h. The solvent was then removed under vacuum and the residue on chromatographic separation on silica gel using hexane–ethyl acetate (90:10) gave the dihydrofuran **4a** as a colourless viscous liquid (0.24 g, 85%).

   Compound **4a**: Colourless viscous liquid. IR (neat) ν_{max}: 3012, 2949, 2843, 1738, 1725, 1676, 1607, 1513, 1445, 1333, 1251, 1102, 983 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CCl_4, *v*/*v*, 3:1): 2.34 (s, 3H, CH_3), 3.40 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.84 (s, 1H, CH), 7.26–7.13 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4, *v*/*v*, 3:1): 20.03, 21.18, 50.99, 51.01, 51.42, 52.27, 52.41, 52.61, 58.38, 83.97, 123.97, 125.43, 125.57, 129.28, 127.5, 129.2, 133.81, 135.21, 138.65, 141.07, 161.61, 162.38.

   Compound **5**: Colourless solid, recrystallised from dichloromethane–hexane mixture, mp 112–113°C. IR (KBr) ν_{max}: 3012, 2956, 1732, 1723, 1601, 1457, 1264, 1095, 952 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CCl_4, *v*/*v*, 3:1): 2.36 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.19 (s, 3H, OCH_3), 7.47–7.16, (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4, *v*/*v*, 3:1): 21.38, 51.56, 52.55, 58.44, 125.51, 125.86, 128.89, 129.39, 138.60, 142.51, 162.22, 164.93. Elemental analysis calcd: C, 63.15, H, 5.30. Found: C, 63.09, H, 5.29.

   Compound **7a**: Yellow amorphous solid. IR (KBr) ν_{max}: 3055, 3005, 2949, 2837, 1743, 1727, 1673, 1632, 1444, 1394, 1332, 1276, 1119, 976, 914 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CCl_4, *v*/*v*, 3:1): 3.48 (s, 6H, OCH_3), 3.71 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.32 (d, 2H, J=9.9 Hz), 6.69 (d, 2H, J=9.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4, *v*/*v*, 3:1): 51.44, 52.70, 52.97, 80.01, 116.03, 123.81, 130.52, 138.47, 139.44, 143.72, 160.38, 161.60, 184.13.
5. Nair, V.; Vinod, A. U.; Nair, J. S.; Sreekanth, A. R.; Rath, N. P. *Tetrahedron Lett.* **2000**, *41*, 6675–6679.

[§] The product in the case of **7c** was a mixture of regioisomers in a 2:1 ratio.