ORGANIC LETTERS
2001
Vol. 3, No. 22
3495−3497

Novel Pyridine-Catalyzed Reaction of Dimethyl Acetylenedicarboxylate with Aldehydes: Formal [2 + 2] Cycloaddition Leading to 2-Oxo-3-benzylidinesuccinates†

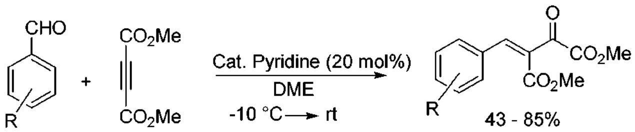
Vijay Nair,* A. Ramachandran Sreekanth, and A. Unni Vinod

Organic Chemistry Division, Regional Research Laboratory, CSIR,
Trivandrum 695 019, India

gvn@csrrltrd.ren.nic.in

Received August 9, 2001

ABSTRACT



The 1,4-zwitterionic intermediate generated from pyridine and DMAD adds to aldehydes in a formal [2 + 2] manner, resulting in the facile synthesis of 2-oxo-3-benzylidinesuccinates.

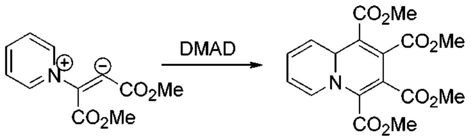
The carbon−carbon bond-forming reaction involving the addition of nucleophiles to acetylenes is of great significance in organic synthesis.[1] The conceptual framework of a 1,4-dipolar cycloaddition provided by Huisgen [2] has been realized in the reaction of pyridine with dimethyl acetylenedicarboxylate (DMAD), leading to the quinazoline derivative, via the 1,4-zwitterionic intermediate (Scheme 1).

This reaction has been studied in detail by Acheson,[3,4] who has further established the existence of the 1,4-zwitterionic intermediate by trapping it with carbon dioxide.[5] In another study it was shown that the interception of the intermediate can be effected by phenyl isocyanate.[6] An isolated example of the intramolecular addition of the 1,4-zwitterionic intermediate to a carbonyl group is also known.[7]

In the context of our general interest in the construction of heterocyclic systems via dipolar intermediates,[8] we were intrigued by the possibility of intermolecular trapping of the 1,4-zwitterionic intermediate generated from pyridine and DMAD with carbonyl compounds. The preliminary results of our investigation validating the usefulness of this process, leading to a novel formal [2 + 2] cycloaddition, are presented in this Letter.

In our initial experiment, the reaction of DMAD with 3-nitrobenzaldehyde in the presence of pyridine (20 mol %)

Scheme 1



---

† Dedicated with affection, respect, and best wishes to Prof. Gilbert Stork, whose pathbreaking discoveries have profoundly changed the course of organic synthesis, on the occasion of his 80th birthday.

(1) (a) Dickstein, J. I.; Miller, S. I. *The Chemistry of Functional Groups. The Chemistry of Carbon−Carbon Triple Bond Part 2*, Chapter 19; Patai, S., Ed.; Wiley: Chichester, 1978; pp 813−955. (b) Winterfeldt, E. *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Dekker: New York, 1969; p 267. (c) Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 423.

(2) (a) Huisgen, R.; Grashey; Sauer, J. *The Chemistry of Alkenes*; Patai, S., Ed.; Wiley- Interscience: New York, 1964; p 739. (b) Huisgen, R.; Herbig, K. *Liebigs Ann. Chem.* **1965**, *688*, 98.

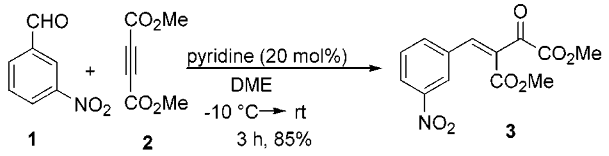
(3) Acheson, R. M. *Adv. Heterocycl. Chem.* **1963**, *1*, 125.

(4) (a) Acheson, R. M.; Taylor, G. A. *Proc. Chem. Soc.* **1959**, 186. (b) Acheson, R. M.; Taylor, G. A. *J. Chem. Soc.* **1960**, 1691.

(5) Acheson, R. M.; Plunkett, A. O. *J. Chem. Soc.* **1964**, 2676.

10.1021/ol016550z CCC: $20.00

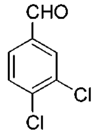
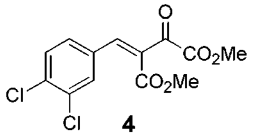
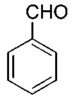
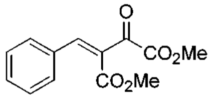
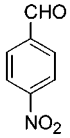
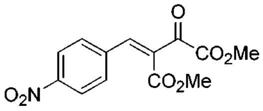
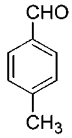
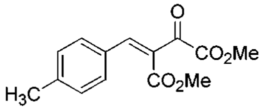
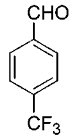
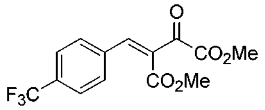
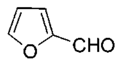
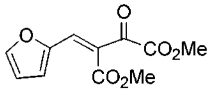
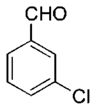
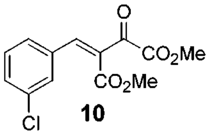
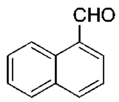
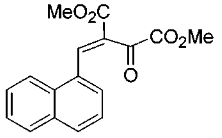
Scheme 2



in DME at −10 °C to room temperature afforded 2-oxo-3-benzylidenesuccinate **3** in 85% yield (Scheme 2).

The product was characterized on the basis of spectroscopic data. In the ^{1}H NMR spectrum, the two methoxycarbonyl groups were observed at δ 3.68 and 3.81 as two singlets, supporting the IR absorption at 1719 cm^{-1}. The olefinic proton resonated at δ 7.14. The ^{13}C signals for the two carbomethoxy groups were seen at δ 162.8 and 164.0.

Table 1. Reaction of Aldehydes with DMAD in the Presence of a Catalytic Amount of Pyridine[a]

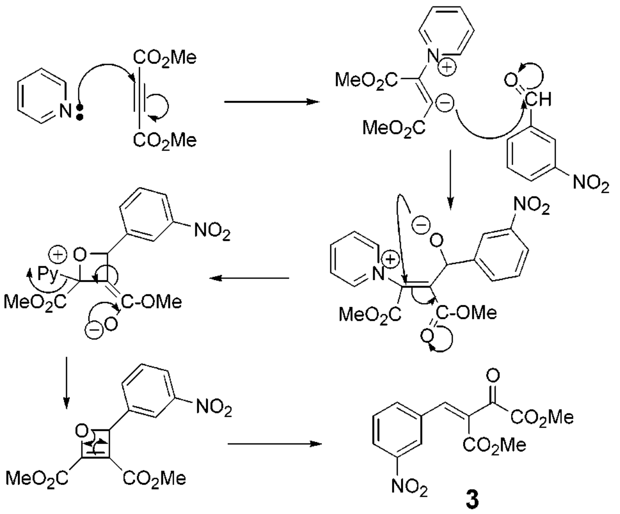
Entry	Aldehyde	Product	Yield (%)[b]
1		 **4**	84
2		 **5**	44
3		 **6**	72
4		 **7**	43
5		 **8**	84
6		 **9**	61
7		 **10**	66
8		 **11**	43

[a] See ref 9 for general experimental procedure. [b] Isolated yield.

The reaction appears to be general with a number of aldehydes, affording the 2-oxo-3-benzylidenesuccinates in moderate to excellent yields.[9] The results are summarized in Table 1.

Mechanistically, the reaction may be rationalized to involve [2 + 2] cycloaddition of the 1,4-zwitterion generated from pyridine and DMAD to the carbonyl group of the aldehyde to give an unstable oxetene, which undergoes stereospecific ring opening to give the *Z*-isomer (Scheme 3).[10,11]

Scheme 3



In this context it is interesting to note that only few reports involving thermal [2 + 2] cycloaddition between activated alkynes and carbonyl compounds are available in the literature.[12] In conclusion, we have devised a novel method for formal [2 + 2] cycloaddition of dimethyl acetylenedicarboxylate with aldehydes resulting in the facile synthesis of 2-oxo-3-benzylidenesuccinates. Further investigations with other activated alkynes and dipolarophiles are in progress.

---

(6) Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem Ber*. **1967**, *100*, 1094.

(7) Winterfeldt, E. *Chem Ber*. **1965**, *98*, 3537.

(8) (a) Nair, V.; Vinod, A. U. *Chem. Commun*. **2000**, 1019. (b) Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem*. **2001**, *66*, 4427. (c) Nair, V.; Bindu, S.; Balagopal, L. *Tetrahedron Lett*. **2001**, *42*, 2043.

(9) **General experimental procedure:** A solution of dimethyl acetylenedicarboxylate (1 equiv) and aldehyde (1 equiv) under an argon atmosphere in dry DME (10 mL) was cooled to −10 °C. To this, pyridine (20 mol %) was added, and the reaction mixture was stirred for 3 h at room temperature. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel using hexanes−ethyl acetate (80:20) gave 2-oxo-3-benzylidenesuccinates. Compound **3**: mp 97−99 °C; IR (KBr) 2959, 1719, 1686, 1533, 1440, 1261, 1202, 1016 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.63 (s, 1H), 8.45 (d, J = 8.1 Hz, 1H), 8.21 (d, J = 7.74 Hz, 1H), 7.72 (t, J = 7.92 Hz, 1H), 7.14 (s, 1H), 3.81 (s, 3H), 3.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.9, 164.0, 162.8, 148.5, 144.2, 136.9, 133.8, 131.3, 130.0, 127.8, 123.3, 53.3, 52.6. Anal. Calcd for $C_{13}H_{11}NO_7$: C, 53.25; H, 3.78; N, 4.78. Found: C, 53.40; H, 3.79; N, 4.91.

Acknowledgment. A.R.S. and A.U.V. thank CSIR, New Delhi, for research fellowships. The authors also thank Ms. Saumini Mathew for high-resolution NMR spectra and Mrs. S. Viji for CHN analysis.

Supporting Information Available: Spectroscopic data (^{1}H, ^{13}C, and IR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016550Z

---

(10) Recently Shindo et al. have proposed the mechanism for the [2 + 2] cycloaddition reactions of alkynoates with carbonyl compounds involving an oxetene intermediate, see: (a) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **1998**, *39*, 4857. (b) Shindo, M.; Sato, Y.; Shishido, K. *J. Am. Chem. Soc*. **1999**, *121*, 6507. (c) Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem*. **2000**, *65*, 5443.

(11) For a similar electrocyclic ring opening of oxetene, see: Friedrich, L. E.; Bower J. D. *J. Am. Chem. Soc*. **1973**, *95*, 6869.

(12) (a) Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 767. (b) Ficini, J. *Tetrahedron* **1976**, *32*, 1449. (c) Schollkopf, U.; Hoppe, I. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 765. (d) Schollkopf, U.; Hoppe, I. *Liebigs Ann. Chem.* **1979**, 219.