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Pyridine-Catalyzed Addition of Diaryl-1,2-diones to Dimethyl Butynedioate Leading to the Formation of 1,2-Diaroyl Dimethyl Maleates via an Unprecedented Rearrangement[†]

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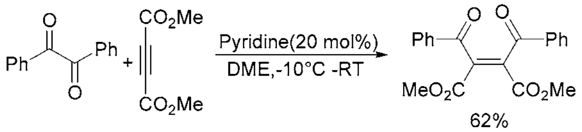
ABSTRACT



Pyridine catalyzes the reaction of 1,2-diaryl diones with dimethyl butynedioate to afford diaroyl maleates. This unprecedented rearrangement involves a unique benzoyl migration and proceeds with complete stereoselectivity.

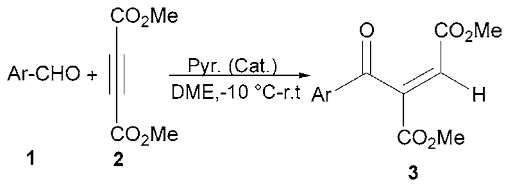
In the course of our recent explorations of the reactivity of zwitterions derived from nucleophilic species and activated acetylenes,[1] we happened upon a fascinating reaction that is tantamount to the trans addition of aldehydes to the triple bond of dimethyl butynedioate leading to 1-aroyl fumarates (Scheme 1).[2]

Mechanistically, the reaction was viewed as occurring by the addition of the zwitterion derived from pyridine and dimethyl butynedioate[3] to the aldehyde to form a tetrahedral intermediate that undergoes a [1,3]-*H* shift, σ-bond rotation, and eventual ejection of pyridine to deliver the product. Irreversibility of the key steps in the sequence provides the driving force for the reaction (Scheme 2).

We speculated that the zwitterion was likely to add to 1,2-dicarbonyl compounds such as benzil, and that the tetrahedral intermediate stood a good chance to undergo cleavage of the relatively weak 1,2 C−C bond (BE ≈ 70 kcal) and concomitant acyl migration to produce a new zwitterion, which would stabilize (neutralize) itself by the ejection of pyridine. The results of our work validating the concept outlined above are presented here.

Our studies were initiated by the addition of a catalytic amount of pyridine (20 mol %) to a solution of benzil and

Scheme 1. Pyridine-Catalyzed Addition of Aldehydes to Dimethyl Butynedioate



[†] This paper is dedicated to Professor Gilbert Stork, in honor of his phenomenal contributions to organic synthesis.

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(1) (a) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (b) Nair, V.; Remadevi, B.; Vidya, N.; Menon, R. S.; Abhilash, N.; Rath, N. P.; *Tetrahedron Lett.* **2004**, *45*, 3203.

(2) Nair, V.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T.; Remadevi, B.; Menon, R. S.; Rath, N. P.; Srinivas, R. *Synthesis* **2003**, 1895.

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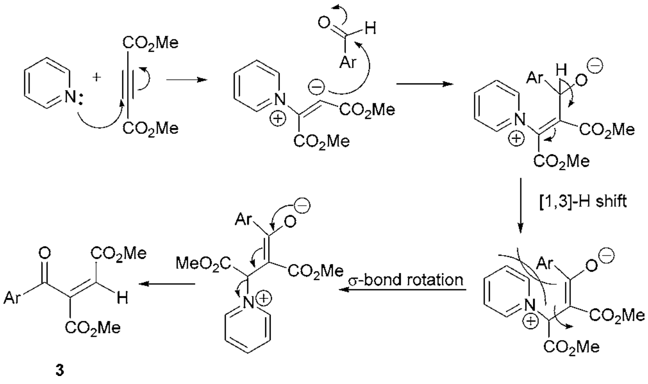
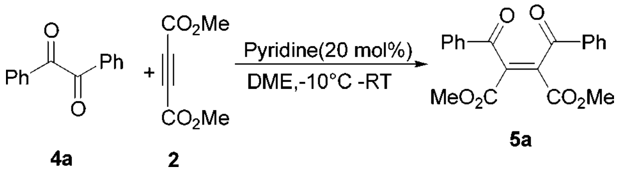
Scheme 2. Proposed Mechanism for Reaction in Scheme 1



dimethyl butynedioate in anhydrous dimethoxy ethane (DME) at −10 °C.

The mixture was allowed to warm to rt (29 °C) and allowed to stir for 8 h. The usual processing of the reaction mixture followed by column chromatography afforded dibenzoyl maleate **5a** in 62% yield[4] along with unreacted benzil (33%) as shown in Scheme 3.

Scheme 3. Pyridine-Catalyzed Reaction of Benzil and Dimethyl Butynedioate



Product **5a** was characterized on the basis of spectroscopic data. The IR spectrum showed characteristic absorptions at 1754 cm^{-1}, indicating the presence of ester carbonyl, and at 1666 cm^{-1}, which corresponds to the benzoyl group. In the ^{1}H NMR, the carbomethoxy groups gave a singlet at δ 3.81. The ^{13}C resonance signals for the two carbomethoxy groups were seen at δ 163.7 and those of the benzoyl carbonyl groups at δ 189.9. Unambiguous evidence for the structure and stereochemistry of **5a** was obtained by single-crystal X-ray analysis (Figure 1).[5] The reaction appears to be general with the analogues of benzil, and the results are presented in Table 1.

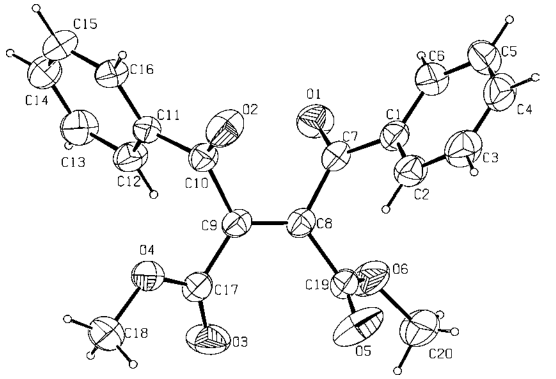


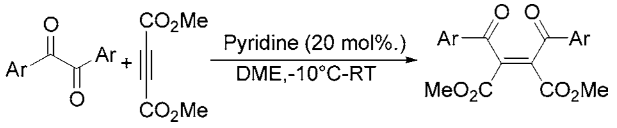
Figure 1. X-ray crystal structure of **5a**.

Two probable mechanistic pathways for the formal insertion of butynedioate to benzil are depicted in Scheme 4. The initially formed pyridine-butynedioate zwitterion adds to benzil, furnishing the alkoxide intermediate **A** (refer to Scheme 2). In path 1, a 1,2-migration of the benzoyl group with its pair of electrons to afford the pyridinium ylide **B** and subsequent generation of a cyclopropane intermediate **C** is conceived. Elimination of pyridine from **C** furnishes the product. Alternatively, as shown in path 2, alkoxide **A** can transform to an epoxy derivative **D**, which then collapses to the pyridinium ylide **E**. An intramolecular benzoyl transfer followed by elimination of pyridine affords the final product via **F**. Involvement of epoxy intermediates in the nucleophilic addition to 1,2-diones is precedented in the work of Schowen.[6] Though less likely, an alternate mechanism involving a 1,3-benzoyl migration, σ-bond rotation, and ejection of pyridine may also be invoked.

The possibility of generation of a pyridinium ylide by the addition of pyridine to benzil and subsequent rearrangement was discounted on the basis of blank experiments carried out in the absence of butynedioate.

Although superficially this reaction is reminiscent of the Liebig benzilic acid rearrangement,[7,8] it is important to recognize that mechanistically it is quite distinct from the

Table 1. Reaction with Various 1,2-Diones



entry	Ar		time (h)	yield (%)
1	4-trifluoromethylphenyl	**5b**	7	64[a] (91)[b]
2	4-methylphenyl	**5c**	10	53[a] (69)[b]
3	4-chlorophenyl	**5d**	8	58[a] (74)[b]
4	3-chlorophenyl	**5e**	8	60[a] (80)[b]
5	4-bromophenyl	**5f**	8	59[a] (76)[b]
6	4-methoxyphenyl	**5g**	10	51[a] (64)[b]
7	3,4-dichlorophenyl	**5h**	8	61[a] (84)[b]
8	2-thienyl	**5i**	8	52[a] (88)[b]

[a] Isolated yield. [b] Yield based on recovered starting material.

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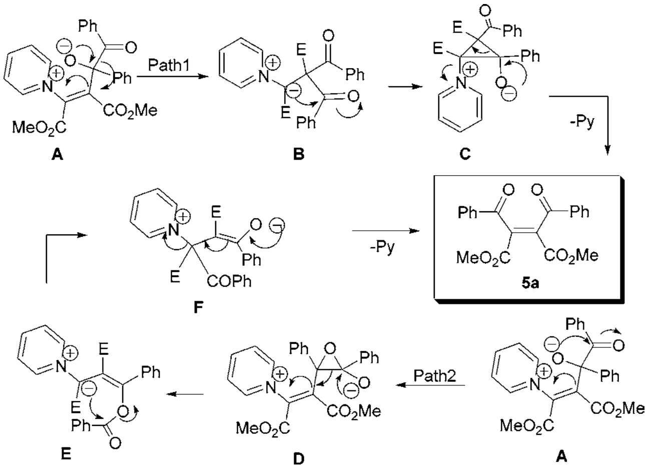
(3) (a) Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1932**, *16*, 498. (b) Acheson, R. M.; Taylor, G. A. *Proc. Chem. Soc.* **1959**, 186. (c) Acheson, R. M.; Taylor, G. A. *J. Chem. Soc.* **1960**, 1691. (d) Acheson, R. M.; Gagan, J. M. F.; Taylor, G. A. *J. Chem. Soc.* **1963**, 1903. (e) Acheson, R. M. *Adv. Heterocycl. Chem.* **1963**, *1*, 125. (f) Winterfeldt, E.; Naumann, A. *Chem. Ber.* **1965**, *98*, 3537. (g) Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem. Ber.* **1967**, *100*, 1094. (h) Acheson, R. M.; Plunkett, A. O. *J. Chem. Soc., Perkin Trans. 1* **1975**, 438.

(4) Yield based on recovered benzil is 92%.

(5) CCDC file no. 250731 contains the supplementary crystallographic data for this paper. See Supporting Information for details.

Scheme 4. Proposed Mechanistic Pathways for the Reaction



latter. Furthermore, the system is predisposed against undergoing a benzilic acid rearrangement because that would produce an energetically untenable species, with the carbonyl group conjugated to a highly electrophilic pyridinium fumarate system. For the record, acyl transfer in benzilic acid rearrangement occurs *only* in reactions involving 1,2,3-tricarbonyl compounds that have no other options available.[9]

Interestingly, the *trans*-diethyl ester corresponding to **5a** is related to a class of natural products known as lignans that are endowed with a broad range of pharmacological activities.[10,11] The trans isomer of **5g**, viz., dimethyl 1,2-(4-methoxybenzoyl)fumarate, was synthesized very recently by the electrolytic oxidative dimerization of methyl 3-(4-methoxyphenyl)propynoate in a $CF_3COOH{-}CH_2Cl_2{-}PbO_2$ system.[12]

In a preliminary screening of catalysts, we have found that the reaction works well with 4-dimethylamino pyridine (DMAP) but less efficiently with triphenylphosphine and not at all with *N*-methyl imidazole and triethylamine.

In conclusion, we have uncovered a novel reaction of the zwitterion derived from pyridine and dimethyl butynedioate with acyclic 1,2-diones. In addition to the mechanistic importance, this reaction offers an easy route for the synthesis of 1,2-diaroyl maleates that may function as useful dienophiles in Diels−Alder cycloadditions. Further investigations aimed at defining the scope and limitations of the reaction are in progress.

Acknowledgment. Financial assistance from Council of Scientific and Industrial Research (CSIR), Government of India, is acknowledged.

Supporting Information Available: Experimental procedure and spectroscopic data for all compounds and crystallographic data for **5a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Kuevrich, J. P.; Schowen, R. L. *J. Am. Chem. Soc*. **1971**, *93*, 1220.

(7) von Liebig, J. *Annalen* **1838**, *25*, 27. It is appropriate to refer to the benzilic acid rearrangement discovered at the dawn of Organic Chemistry by Justus von Liebig, one of the founding fathers of the discipline, as Liebig benzilic acid rearrangement or Liebig rearrangement.

(8) For reviews on benzilic acid rearrangements, see: (a) Selman, S.; Eastham, J. F. *Quart. Rev. Chem. Soc.* **1960**, *14*, 221. (b) Gill, G. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 3, p 821.

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(11) **5a** has been previously reported as a minor byproduct (3%) formed in the thermal rearrangement of the corresponding furan endoperoxide (Graziano, M, L.; Iesce, M. R.; Scrapati, R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2007. It should be noted that no evidence for its structure is provided in this paper).

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