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Reaction of Diaryl-1,2-diones with Triphenylphosphine and Diethyl Azodicarboxylate Leading to *N*,*N*-Dicarboethoxy Monohydrazones via a Novel Rearrangement[†]

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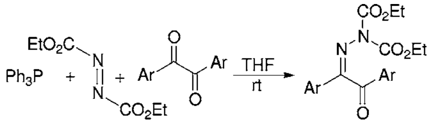
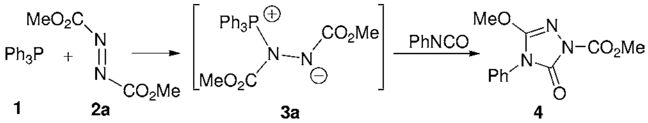
ABSTRACT



A mechanistically novel reaction of diaryl-1,2-diones with diethyl azodicarboxylate and triphenylphosphine to afford *N*,*N*-dicarboethoxy monohydrazones is described. The reaction proceeds via a nitrogen to nitrogen migration of a carboethoxy group.

In the course of his extensive investigations on azodicarboxylic esters and with a quest to discover novel 1,3-dipoles, Huisgen generated a zwitterion by the addition of triphenylphosphine to dimethyl azodicarboxylate.[1,2] In addition to establishing its structure (Scheme 1), he also demonstrated the nucleophilic reactivity of this species by its reaction with dimethyl acetylenedicarboxylate (DMAD), phenyl isocyanate, and phenyl isothiocyanate.[1c] After this work, apart from its pivotal role in the Mitsunobu reaction[3] offering the most reliable and universally accepted synthetic protocol for the stereochemical inversion of a hydroxyl group, the chemistry of Huisgen zwitterion **3** has received only scant attention. Kolasa and Miller's observation[4] of unexpected transformations in the attempted Mitsunobu reaction of hydroxy esters and the transformation of ketones to vinyl hydrazines under Mitsunobu conditions reported by Liu[5] et al. are noteworthy in this connection.

Scheme 1. Huisgen's Study of the Diazoester−Phosphine Zwitterion



[†] This paper is dedicated with best wishes to Professor Dr. Rolf Huisgen on the occasion of his 85th birthday.

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(1) (a) Huisgen, R. In *The Adventure Playground of Mechanisms and Novel Reactions: Profiles, Pathways and Dreams*; Seeman, J. I., Ed.; American Chemical Society: Washington, DC, 1994; p 62. (b) Huisgen, R.; Blaschke, H.; Brunn, E. *Tetrahedron Lett.* **1966**, 405. (c) Brunn, E.; Huisgen, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 513.

(2) Morrison, D. C. *J. Org. Chem.* **1958**, *23*, 1072. (A reaction of triphenylphosphine and DEAD resulting in the formation of *N*,*N*′-dicarboethoxy hydrazine and triphenylphosphine oxide, presumably via a zwitterion, is mentioned.)

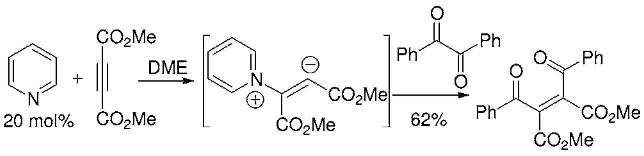
(3) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127. (c) Watanabe, T.; Gridnev, I. D.; Imamoto, T. *Chirality* **2000**, *12*, 346. (d) Tsunoda, T.; Ito, S. *J. Synth. Org. Chem. Jpn.* **1997**, *50*, 631.

(4) Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4978.

(5) Liu, Y.; Xu, C.; Liu, L. *Synthesis* **2003**, 1335.

10.1021/ol050403+ CCC: $30.25

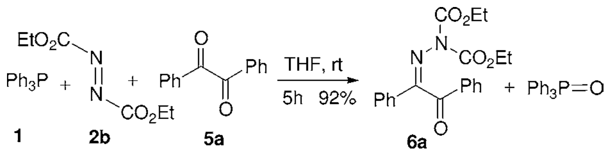
Scheme 2. Pyridine-Catalyzed Reaction of Diones and DMAD



In the context of our recent studies on the reactivity of zwitterionic species derived from DMAD and a wide range of nucleophiles,[6] viz., triphenylphosphine, isocyanides, nucleophilic carbenes, and nitrogen heterocycles, and drawing inspiration from the observation of a novel reaction involving pyridine−DMAD zwitterion and benzil[7] (Scheme 2), we ventured into an exploration of the Huisgen zwitterion **3** with diaryl-1,2-diones. The preliminary results of our experiments, which revealed an unprecedented reactivity of the zwitterion and its implications, form the subject matter of this letter.

Our studies were initiated by treating a THF solution of diethyl azodicarboxylate (DEAD) **2b** and benzil with a stoichiometric quantity of triphenylphosphine at room temperature to afford a white crystalline solid. To our surprise, in the product both the carboethoxy groups were on the same nitrogen atom (Scheme 3).

Scheme 3. Reaction of Benzil with DEAD and Ph$_3$P



The product was assigned the structure **6a** on the basis of spectroscopic analysis.[8] Triphenylphosphine oxide was also isolated from the reaction mixture. In the IR spectrum, the ketone carbonyl absorption was seen at 1680 cm^{-1}. The ^{1}H NMR spectrum of **6a** exhibited a mutually coupled pair of triplet and quartet signals centered at δ 1.26 and 4.19, respectively. The ketone carbon resonated at δ 193.2 in the ^{13}C NMR spectrum. Unambiguous evidence for the structure of **6a** was obtained from single-crystal X-ray analysis (Figure 1).[9]

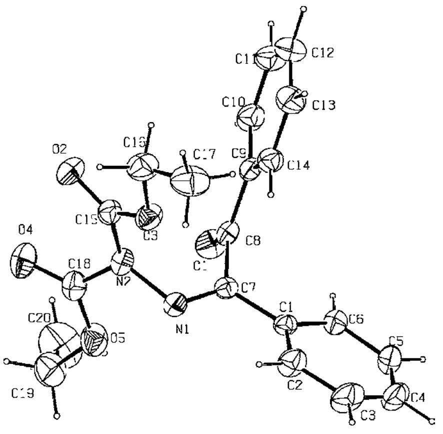
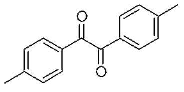
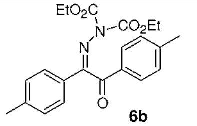
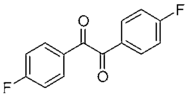
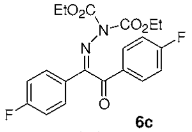
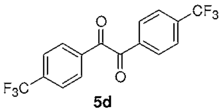
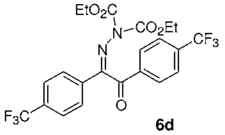
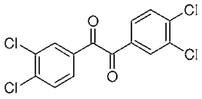
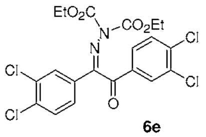
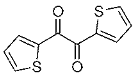
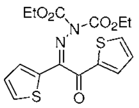
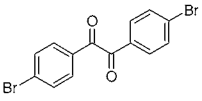
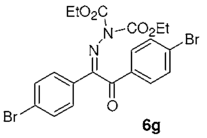
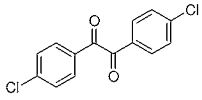
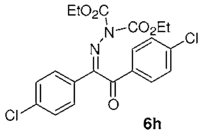
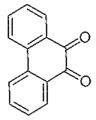
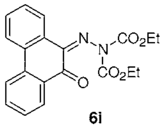


Figure 1. Single-crystal X-ray structure of **6a**.

Table 1. Reaction of Diaryl Diones with DEAD and Ph$_3$P

entry	dione	time (h)	product	yield[a] (%)
1	 **5b**	18	 **6b**	39 (89)
2	 **5c**	6	 **6c**	74 (86)
3	 **5d**	14	 **6d**	80 (94)
4	 **5e**	12	 **6e**	40 (88)
5	 **5f**	12	 **6f**	49 (73)
6	 **5g**	15	 **6g**	33 (96)
7	 **5h**	8	 **6h**	35 (66)
8	 **5i**	12	 **6i**	77

[a] Isolated yield; yield based on recovered **5** in parentheses.

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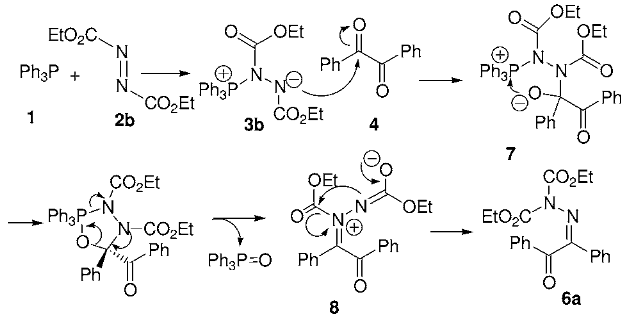
(6) Phosphines: (a) Nair, V.; Nair, J. S.; Vinod, A. U. *Synthesis* **2000**, 1713. Isocyanides: (b) Nair, V.; Vinod, A. U. *Chem. Commun.* **2000**, 1019. Nucleophilic carbenes: (c) Nair, V.; Bindu, S.; Balagopal, L. *Tetrahedron Lett.* **2001**, *42*, 2043. (d) Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5*, 665. Nitrogen heterocycles, (e) Nair, V.; Sreekanth, A. R.; Vinod, A. U. *Org. Lett.* **2001**, *3*, 3495. (f) Nair, V.; Sreekanth, A. R.; Vinod, A. U. *Org. Lett.* **2002**, *4*, 2807. For a review, see: (g) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. Also see: (h) Hoffmann, R. W.; Lilienblum, W.; Dittrich, B. *Chem. Ber.* **1974**, *107*, 3395. (i) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535 and references therein.

(7) Nair, V.; Pillai, A, N.; Menon, R. S.; Suresh, E. *Org. Lett.* **2005**, *7*, 1189.

Scheme 4. Proposed Mechanism for the Reaction

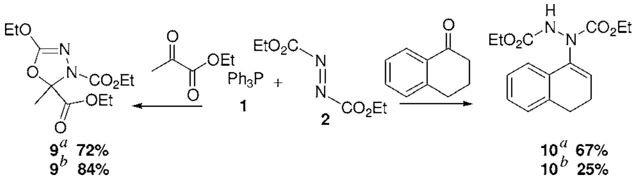


The reaction was found to be general with a number of diaryl-1,2-diones. The results are summarized in Table 1. Interestingly, a cyclic 1,2-dione (phenanthrenequinone, entry 8, Table 1) also afforded the corresponding hydrazone derivative.

Although the mechanistic underpinnings of the reaction are not clearly known, the following rationalization may be advanced to explain the product formation. Presumably, the Huisgen zwitterion **3b**[10] formed from triphenylphosphine and DEAD adds to benzil to furnish a tetrahedral intermediate **7**, which then eliminates phosphine oxide to produce **8**.[11,12] The latter rearranges to the final product by an N to N carboxyl transfer (Scheme 4).

While this manuscript was under preparation, a reaction of diazoesters, triphenylphosphine, and carbonyl compounds leading to oxadiazolines (from dicarbonyl compounds) and ene-hydrazines (from ketones) was reported by Lee (Scheme 5).[13]

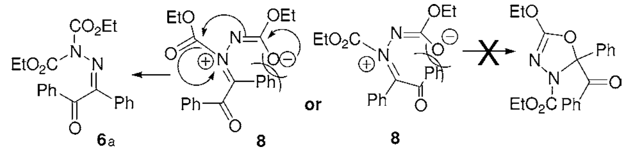
Scheme 5. Comparison with Lee's Studies



[a] Reaction in THF (1 mL) with 1.2 equiv of DEAD and 1.5 equiv of PPh_3 at room temperature (Lee's conditions). [b]Reaction in THF(10 mL) with 1.2 equiv of DEAD and 1.2 equiv of PPh_3 at room temperature.

The mechanistic dichotomy of our reaction vis-á-vis Lee's may be attributed to steric repulsion endemic to the transition state leading to the formation of oxadiazoline in the reaction involving diaryl-1,2-diones. The dipole **8** can easily assume an alternative arrangement conducive for the N to N carboethoxy transfer giving rise to the hydrazone **6a** (Scheme 6).

Scheme 6. Mechanistic Dichotomy



Any role for the alkoxy group of the diazoester in eliciting dual reactivities by the zwitterion may be excluded by the observation that, when α-tetralone was treated with diethyl azodicarboxylate and triphenylphosphine under exactly the same conditions as reported by Lee, the ene-hydrazine (corresponding to **10**, Scheme 5) was isolated as the sole product.

In conclusion, we have unraveled a novel transformation involving triphenylphosphine, DEAD, and diaryl-1,2-diones that proceeds through a nitrogen to nitrogen migration of a carboethoxy group affording dicarboethoxy monohydrazones of diaryl-1,2-diones.

Acknowledgment. Financial assistance from Council of Scientific and Industrial Research (CSIR), New Delhi, is acknowledged. The authors thank Priya A. Nair, Thirumalai Kumaran, and Sreemathi Viji for recording IR spectra, NMR spectra, and mass spectra, respectively.

Supporting Information Available: General experimental procedure and spectroscopic data for all compounds and crystallographic data for **6a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) To a stirred solution of benzil (105 mg, 0.5 mmol) and diethyl azodicarboxylate (104 mg, 0.6 mmol) in anhydrous THF (10 mL) under an atmosphere of Ar was added triphenylphosphine (157 mg, 0.6 mmol), and the reaction mixture was stirred at room temperature for 5 h. Solvent was removed on a rotavap, and the residue was column chromatographed on silica gel using 9:1 hexanes−ethyl acetate as the eluent to afford **6a** as a white solid (169 mg, 92%). Mp: 125−127 °C. IR (KBr) ν_{max}: 2991, 1798, 1710, 1680, 1592, 1449, 615 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.26 (t, $J = 7.17$ Hz, 6H), 4.19 (q, $J = 7.17$ Hz, 4H), 7.42−7.62 (m, 5H), 7.81 (d, $J = 7.44$ Hz, 2H), 7.89 (d, $J = 7.53$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 63.5, 128.4, 128.8, 129.0, 129.5, 131.9, 132.6, 133.9, 134.8, 150.8, 175.1, 193.2. Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 64.76; H, 5.02; N, 7.67.

(9) Crystal structure for compound **6a** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 262931.

(10) This zwitterion is commonly called Mitsunobu reagent.

(11) See footnote 11 in ref 13.

(12) Probability of an initial rearrangement of **3b** to a Staudinger ylide via an analogous N to N carboethoxy transfer was categorically ruled out by the observation that the corresponding ene-hydrazine product (cf. Scheme 5, compound **10**) was isolated when a stirred solution of PPh_3 and DEAD in THF was treated with 4-nitroacetophenone.

(13) Otte, R. D.; Sakata, T.; Guzei, I. A.; Lee, D. *Org. Lett.* **2005**, *7*, 495.