ORGANIC
LETTERS

2005
Vol. 7, No. 23
5139−5142

Reaction of Huisgen Zwitterion with 1,2-Benzoquinones and Isatins: Expeditious Synthesis of Dihydro-1,2,3-benzoxadiazoles and Spirooxadiazolines[†]

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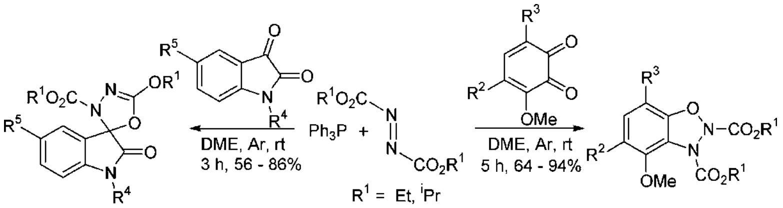
Received August 12, 2005

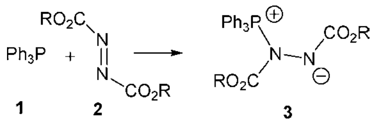
ABSTRACT



The zwitterionic intermediate generated from dialkyl azodicarboxylate and triphenylphosphine on reaction with 3-methoxy-1,2-benzoquinones afforded dihydro-1,2,3-benzoxadiazoles. N-Substituted isatins furnished spirooxadiazolines under similar conditions.

The facile reaction of triphenylphosphine with azodicarboxylate leading to the formation of zwitterion **3** and the nucleophilic reactivity of the latter was established by Huisgen and co-workers (Scheme 1).[1,2] This zwitterion is the nucleophilic trigger in the Mitsunobu reaction,[3] used widely for the stereochemical inversion of hydroxyl group. Apart from this, the chemistry of Huisgen zwitterion **3** has received only limited attention. In the attempted Mitsunobu reaction of α-hydroxy esters, unexpected transformations were observed by Kolasa and Miller,[4] and the conversion of ketones to vinyl hydrazine dicarboxylate was reported by Liu.[5] Very recent work on the reaction of **3** with various carbonyl compounds by Lee[6] as well as the unexpected formation of hydrazones from salicylaldehyde reported by Girard[7] is especially noteworthy in this context.

Scheme 1. Zwitterion Formation from Triphenylphosphine and Dialkyl Azodicarboxylate



We have recently reported the interception of **3** with diaryl-1,2-diones resulting in a facile synthesis of *N*,*N*-dicarboet-

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[†] This paper is dedicated with best wishes to Professor S. Chandrasekaran on the occasion of his 60th 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) Cookson, R. C.; Locke, J. M. *J. Chem. Soc.* **1963**, 6062. The reaction of triphenylphosphine and DEAD with dimethyl acetylenedicarboxylate affording pyrazoles is mentioned; rationalization of this reaction as occurring via the zwitterion **3** was provided by Huisgen (ref 1.)

(3) Mitsunobu, O. *Synthesis* **1981**, 1.

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

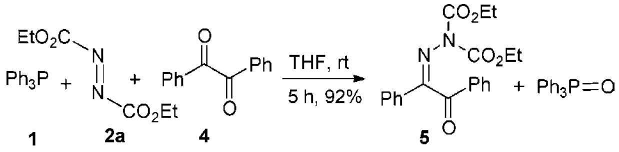
(5) Liu, Y.; Xu, C.; Liu, L. *Synthesis* **2003**, 1335.

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

10.1021/ol051956n CCC: $30.25

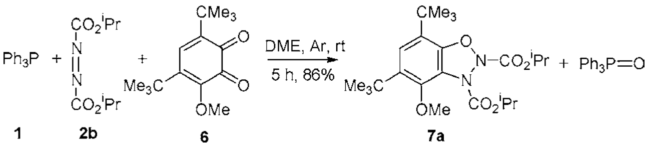
hoxy monohydrazones via a novel rearrangement (Scheme 2).[8] In this context, and in view of our general interest in the reactivity profile of *o*-benzoquinones,[9] we have explored the reaction of **3** with substituted 3-methoxy-1,2-benzoquinones and *N*-substituted isatins. The preliminary results of our investigations which expose some novel reactivity patterns of the zwitterion form the subject of this letter.

Scheme 2. Phosphine-Mediated Reaction of DEAD with Benzil



In a pilot experiment, a solution of 3-methoxy-4,6-di-*tert*-butyl-1,2-benzoquinone and diisopropyl azodicarboxylate (DIAD) in dry DME under argon atmosphere was treated with stoichiometric amount of triphenylphosphine at room temperature. The reaction mixture on usual processing afforded the dihydro-1,2,3-benzoxadiazole derivative **7a**[10] in 86% yield as a very pale brown amorphous solid (Scheme 3).[11]

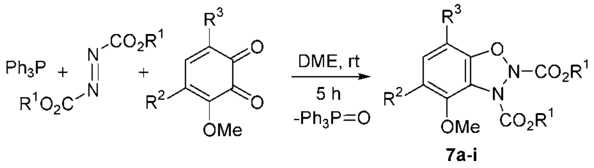
Scheme 3. Reaction of 1,2-Benzoquinone with DIAD and Ph_3P



The product was characterized by spectroscopic analysis. In the IR spectrum, the ester carbonyl absorption was seen at 1753 and 1769 cm^{-1}. In the ^{1}H NMR spectrum, the methoxy protons resonated at δ 3.86 and the methine protons were discernible at δ 4.93 and 5.21, respectively, as multiplets. The aromatic proton signal was visible at δ 7.53.

The reaction was found to be general with respect to various 1,2-benzoquinones, and the dihydro benzoxadiazoles were obtained in high yields. The results are summarized in Table 1.

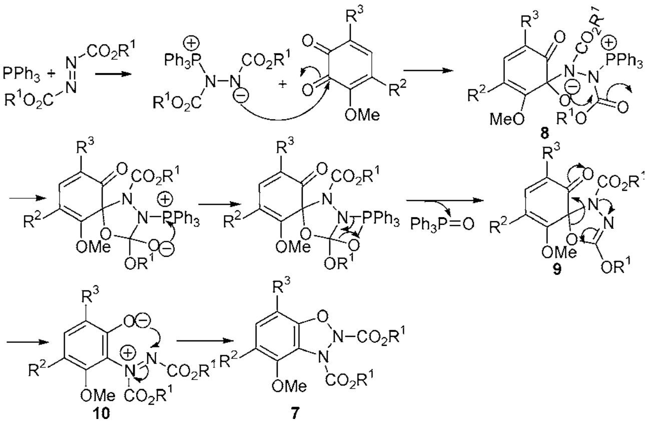
Table 1. Reaction of 1,2-Benzoquinones with Ph_3P and Dialkyl Azodicarboxylate



entry	R^1	R^2	R^3	product	yield (%)
1	ethyl	*tert*-butyl	*tert*-butyl	**7b**	75
2	ethyl	diphenylmethyl	diphenylmethyl	**7c**	78
3	ethyl	*tert*-butyl	H	**7d**	91
4	ethyl	4,4′-dichlorodiphenylmethyl	4,4′-dichlorodiphenylmethyl	**7e**	73
5	isopropyl	*tert*-butyl	H	**7f**	94
6	isopropyl	diphenylmethyl	diphenylmethyl	**7g**	85
7	isopropyl	4,4′-dichlorodiphenylmethyl	4,4′-dichlorodiphenylmethyl	**7h**	64
8	isopropyl	dimethylphenylmethyl	dimethylphenylmethyl	**7i**	85

The following mechanistic postulate may be invoked to rationalize the reaction. The Huisgen zwitterion **3** formed from triphenylphosphine and azoester adds to quinone carbonyl to give a tetrahedral intermediate **8** which gives the spirooxadiazoline **9** presumably by the elimination of triphenylphosphine oxide via a process resembling the Wittig reaction. The spirooxadiazoline undergoes aromatization by ring fragmentation to deliver **10**. The latter undergoes another ring closure to give the final product (Scheme 4).

Scheme 4. Proposed Mechanism for the Reaction



In all cases only one of the carbonyls participated in the reaction. This selectivity of the reaction may be attributed

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(7) Girard, M.; Murphy, P.; Tsou, N. N. *Tetrahedron Lett.* **2005**, *46*, 2449.

(8) Nair, V.; Biju, A. T.; Abhilash, K. G.; Menon, R. S.; Suresh, E. *Org. Lett.* **2005**, *7*, 2121.

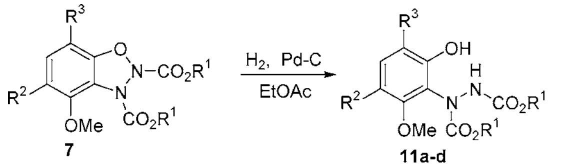
(9) (a) Nair, V.; Kumar, S. *Synlett* **1996**, 1143. (b) Nair, V.; Nair, J. S.; Vinod, A. U.; Rath, N.; P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3129. (c) Nair, V.; Nair, J. S.; Vinod, A. U. *Synthesis* **2000**, 1713. (d) Nair, V.; Vinod, A. U.; Nair, J. S.; Sreekanth, A. R.; Rath, N. P. *Tetrahedron Lett.* **2000**, *41*, 6673. (e) Nair, V.; Bindu, S.; Balagopal, L. *Tetrahedron Lett.* **2001**, *42*, 2043. (f) Nair, V.; Sreekanth, A. R.; Biju, A. T.; Rath, N. P. *Tetrahedron Lett.* **2003**, *44*, 729.

(10) To a stirred solution of the 1,2-benzoquinone **6** (133 mg, 0.53 mmol) in anhydrous DME (10 mL), under argon atmosphere, was added DIAD (0.13 mL, 0.64 mmol) followed by triphenylphosphine (167 mg, 0.64 mmol).The reaction mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure, and the residue on the silica gel column chromatography using 3% ethyl acetate−hexane afforded **7a** as a very pale brown amorphous solid (198 mg. 86%). IR (Film) ν_{max}: 2964, 1769, 1753, 1475, 1367, 1259, 1166, 1104 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.37−1.43 (m, 30H), 3.86 (s, 3H), 4.93 (m, J = 6.30 Hz, 1H), 5.21 (m, J = 6.30 Hz, 1H), 7.53 (s, 1H). ^{13}C NMR (75 MHz $CDCl_3$) δ: 21.9, 30.6, 35.4, 64.6, 72.4, 73.1, 130.0, 136.1, 137.4, 138.4, 140.5, 152.2, 157.9, 160.9. HRMS for $C_{23}H_{36}N_2O_6$: calcd (M + 1$^+$) 437.2605, found 437.2648.

(11) On exposure to air the product developed a brown color, presumably due to air oxidation. The extent of oxidation, however, is insignificant as no detectable change was observed in the ^{1}H NMR spectra of the compound after exposure to air.

to both electronic and steric factors. Interestingly, hydrogenolysis of the dihydro-1,2,3-benzoxadiazoles **7** using Pd−C in ethyl acetate afforded 2-(*N*,*N′*-dicarbethoxyhydrazino)phenol **11**, thus constituting in principle the monoamination of a catechol/*o*-quinone (Table 2).

Table 2. Hydrogenolysis of Dihydro-1,2,3-benzoxadiazoles



entry	substrate	product	yield (%)
1	**7a**	**11a**	79
2	**7b**	**11b**	88
3	**7e**	**11c**	65
4	**7h**	**11d**	73

The structure of **11a** was assigned by spectroscopic analysis. The ^{1}H NMR spectrum exhibited singlets at δ 8.51 and 7.15 (exchangeable by D_2O) supporting the IR absorption at 3278 cm^{-1}. The ester carbonyls resonated at δ 158.8 and 155.4 in the ^{13}C NMR spectrum. Finally, the structure was unequivocally established by single-crystal X-ray analysis (Figure 1).[12]

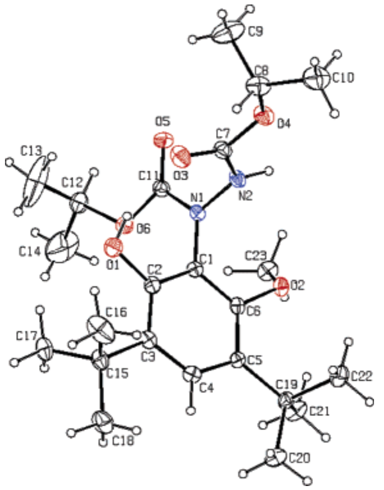
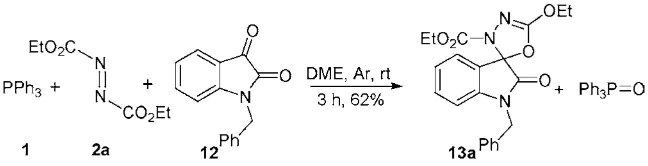


Figure 1. Single-crystal X-ray structure of **11a**.

Encouraged by the interesting results obtained in the reaction of **3** with 1,2-benzoquinones, and in anticipation of the formation of spirooxadiazoles, we extended our studies to *N*-substituted isatins. It is noteworthy that 1,3,4-oxadiazolines are known to have anticonvulsant activity.[13] In an illustrative experiment, treatment of *N*-benzyl isatin with diethyl azodicarboxylate and triphenylphosphine in dry DME under argon atmosphere resulted in the formation of spirooxadiazoline **13a** in 62% yield as colorless crystals (Scheme 5).[14]

Scheme 5. Reaction of *N*-Substituted Isatin with Ph_3P and Diethyl Azodicarboxylate



The structure of **13a** was established by spectroscopic analysis. In the IR spectrum, the ester carbonyl was seen at 1743 cm^{-1} and the amide carbonyl at 1681 cm^{-1}. The ^{1}H NMR spectrum showed different sets of signals for carboethoxy and ethoxy protons. The methylene protons resonated at δ 4.23 and 4.45. In the ^{13}C NMR spectrum, the amide carbonyl resonated at δ 168.5 and ester carbonyl at δ 157.9. The spiro carbon was discernible at δ 68.7. Finally, the structure was confirmed by single-crystal X-ray analysis (Figure 2).[15]

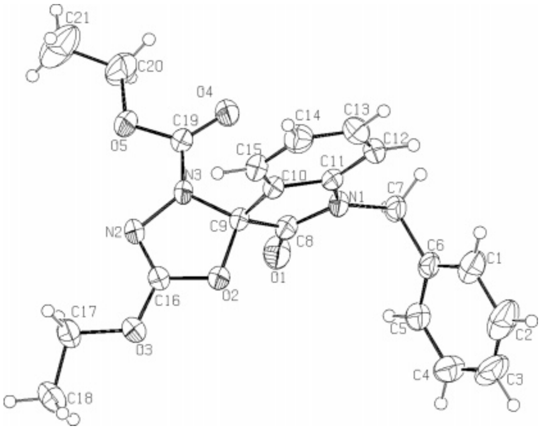


Figure 2. Single-crystal X-ray structure of **13a**.

The reaction was found to be general with various *N*-substituted isatins and the spirooxadiazolines were obtained in good yield. The results are summarized in Table 3.

A mechanistic postulate analogous to the one suggested for the reaction of 1,2-benzoquinone with triphenylphosphine and azoester may be invoked here also. Interestingly,

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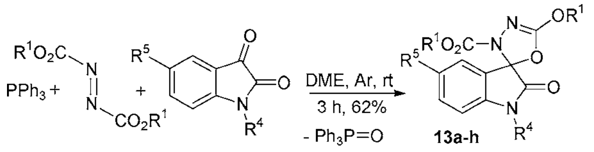
[12] Crystal structure of compound **11a** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 280314.

[13] Dogan, H. N.; Duran, A.; Rollas, S.; Sener, G.; Armutak, Y.; Keyer Uysal, M. *Med. Sci. Res.* **1998**, *26*, 755

[14] See the Supporting Information for experimental details.

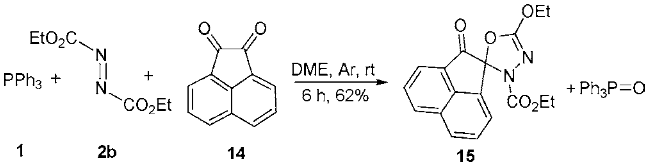
[15] The crystal structure of compound **13a** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 279798.

Table 3. Reaction of Isatins with Ph_3P and Dialkyl Azodicarboxylate



entry	R^1	R^4	R^5	product	yield (%)
1	ethyl	allyl	Br	**13b**	65
2	ethyl	methyl	H	**13c**	61
3	ethyl	ethyl	Br	**13d**	56
4	ethyl	propyl	Br	**13e**	62
5	isopropyl	propyl	Br	**13f**	65
6	isopropyl	methyl	Br	**13g**	86
7	isopropyl	allyl	Br	**13h**	60
8	isopropyl	benzyl	H	**13i**	61
9	isopropyl	ethyl	H	**13j**	66

Scheme 6. Reaction of Acenaphthenequinone with DEAD and Ph_3P



acenaphthenequinone also on treatment with triphenylphosphine and DEAD gave the spirooxadiazoline **15** in 62% yield (Scheme 6).

In conclusion, we have uncovered a novel synthesis of dihydro-1,2,3-benzoxadiazole by triphenylphosphine-mediated reaction of 1,2-benzoquinones with dialkyl azodicarboxylate. This reaction will be useful for the conversion of catechols to hydrazino phenols. Also a novel synthesis of spirooxadiazoline was established by treating *N*-substituted isatin with triphenylphosphine and azoesters.

Acknowledgment. Financial assistance from Council of Scientific and Industrial Research (CSIR), New Delhi, is acknowledged. We thank Thirumalai Kumaran and S. Viji for recording NMR and mass spectra, respectively.

Supporting Information Available: General experimental procedure and spectroscopic data for all compounds and crystallographic data for **11a** and **13a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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