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Novel Synthesis of Highly Functionalized Pyrazolines and Pyrazoles by Triphenylphosphine-Mediated Reaction of Dialkyl Azodicarboxylate with Allenic Esters[†]

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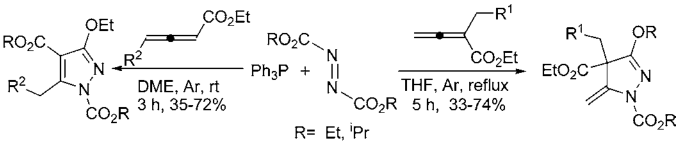
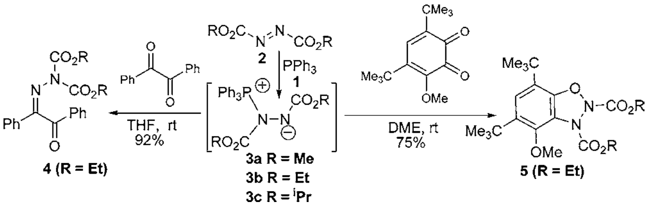
ABSTRACT



Reaction of the Huisgen zwitterion, derived from triphenylphosphine and dialkyl azodicarboxylate, with allenic esters affords highly functionalized pyrazolines and pyrazoles. The crystal structure of pyrazoline derivative 7a showed extensive C–H···O interactions. Pyrazole formation proceeds via a novel nitrogen to carbon migration of the carboalkoxy group.

The reaction of triphenylphosphine and dimethyl azodicarboxylate leading to the formation of the zwitterion **3a** has been known from the work of Huisgen.[1] Apart from its pivotal role in the well-known Mitsunobu inversion,[2] the synthetic utility of this zwitterion has received only very limited attention.[3] We have recently reported on the interception of the Huisgen zwitterion **3b** with diaryl-1,2-diones leading to *N*,*N*-dicarboethoxy monohydrazones **4** via a novel rearrangement; with *o*-benzoquinones as electrophiles, the reaction afforded dihydro-1,2,3-benzoxadiazoles **5** (Scheme 1).[4]

Scheme 1. Reaction of Huisgen Zwitterion with Cyclic and Acyclic 1,2-Diones



In this context, it was of interest to investigate the reaction of the zwitterion with allenoates because it was perceived

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[†] Dedicated with best regards to Professor Victor Snieckus.

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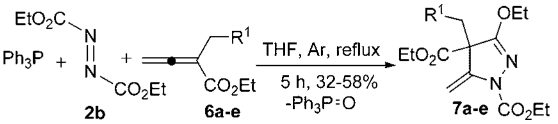
that such a process would offer a convenient route to pyrazole derivatives. Although such reactions involving allenoates are not known, a lone example of the addition of **3a** to dimethyl acetylene dicarboxylate (DMAD) leading to a pyrazole was reported by Cookson[5] and Huisgen.[6] It is noteworthy in this context that phosphine-catalyzed reactions of allenoates and butynoates is an area of topical interest in synthetic organic chemistry.[7] It is also worthy of note that pyrazoles constitute an important class of heterocycles by virtue of their biological properties relevant to the pharmaceutical and agrochemical industries.[8]

Against the literature background given above, the present studies were initiated by treating a THF solution of diethyl azodicarboxylate (DEAD) **2b** and ethyl-2-(4-nitrobenzyl)-2,3-butadienoate **6a** with a stoichiometric quantity of triphenylphosphine at reflux temperature for 5 h. Purification of the reaction mixture by SiO_2 column chromatography afforded the functionalized pyrazoline derivative **7a**[9] as colorless crystals in 58% yield (entry 1,Table 1).

Table 1. Formation of Functionalized Pyrazoline by Reaction of PPh_3-DEAD Zwitterion with **6**



entry	allene ester	R^1	product	yield[a] (%)
1	**6a**	4-NO_2-C_6H_4	**7a**	58
2	**6b**	4-Cl-C_6H_4	**7b**	49
3	**6c**	4-F-C_6H_4	**7c**	40 (73)
4	**6d**	4-OMe-C_6H_4	**7d**	30 (71)
5	**6e**	C_6H_5	**7e**	52

[a] Isolated yield; yield based on recovered **6** in parentheses.

The product was assigned the structure **7a** on the basis of spectroscopic analysis. In the IR spectrum, the ester carbonyl absorptions were seen at 1738 and 1712 cm^{-1}. In the 300 MHz ^1H NMR spectrum ($CDCl_3$), the benzylic protons displayed doublets at δ 3.30 and 3.45. The exocyclic methylene protons appeared at δ 4.77 as a sharp singlet and 5.73 as a broad singlet. This may be due to the intermolecular C−H···O interactions between the exocyclic C−H bond and the ester group. The ester carbonyls were discernible at δ 160.9 and 167.5 in the ^{13}C NMR spectrum. Finally, the structure was established unequivocally by single-crystal X-ray analysis (Figure 1).[10]

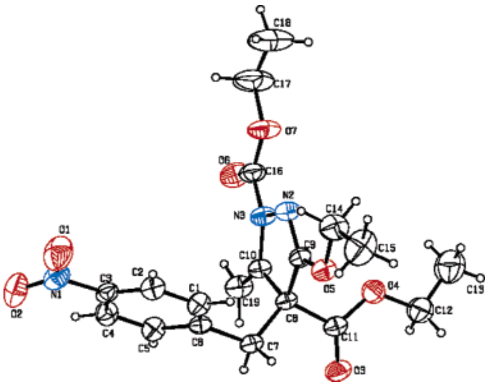


Figure 1. Single-crystal X-ray structure of **7a**.

The reaction was found to be general with respect to various allenic esters, and the functionalized pyrazoline derivatives were obtained in moderate yields (Table 1).

The packing diagram[11] of **7a** showed extensive C−H···O interactions creating a two-hydrogen-bonded two-dimensional network. It is interesting to note that the packing diagram viewed down the *b*-axis showed that oxygen atoms of the carboethoxy group that is attached to the five-membered ring are involved in strong intermolecular H-bonding interactions with the methylene hydrogen along the *c*-axis and the methyl hydrogen along the *a*-axis, creating a two-dimensional hydrogen-bonded supramolecular network along the *ac*-plane. A close-up view of this H-bonded

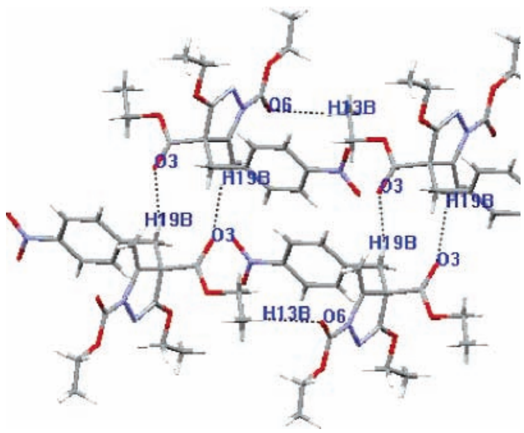


Figure 2. Close-up view of hydrogen bonding pattern in **7a**.

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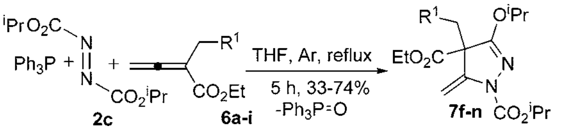
(9) For experimental details, see Supporting Information.

assembly, involving four molecules engaged in the H-bonding network, is depicted in Figure 2.

Analogous to the above-mentioned reaction, when DEAD was replaced by diisopropyl azodicarboxylate (DIAD), functionalized pyrazoline derivatives were formed. An illustrative example is the reaction of ethyl-2-(2-naphthylmethyl)-2,3-butadienoate **6f** with DIAD in the presence of triphenylphosphine in THF under reflux, affording the functionalized pyrazoline derivative **7k** in 56% yield (entry 6, Table 2).

Table 2. Formation of Functionalized Pyrazoline by Reaction of PPh$_3$-DIAD Zwitterion with **6**



entry	allene ester	R^1	product	yield^a (%)
1	**6a**	4-NO$_2$-C$_6$H$_4$	**7f**	68 (81)
2	**6b**	4-Cl-C$_6$H$_4$	**7g**	49
3	**6c**	4-F-C$_6$H$_4$	**7h**	74 (76)
4	**6d**	4-OMe-C$_6$H$_4$	**7i**	33 (74)
5	**6e**	C$_6$H$_5$	**7j**	54 (75)
6	**6f**	2-C$_{10}$H$_7$	**7k**	56
7	**6g**	4-Br-C$_6$H$_4$	**7l**	55
8	**6h**	3-NO$_2$-C$_6$H$_4$	**7m**	34 (65)
9	**6i**	3,4-Cl$_2$-C$_6$H$_3$	**7n**	60

^{a} Isolated yield; yield based on recovered **6** in parentheses.

The product was assigned structure **7k** by spectroscopic analysis. In the IR spectrum, the ester carbonyl absorptions were observed at 1734 and 1708 cm^{-1}. In the 300 MHz ^{1}H NMR spectrum (CDCl$_3$), the benzylic protons were discernible as doublets at δ 3.37 and 3.47. The exocyclic methylene protons were seen at δ 4.81 as a sharp singlet and 5.72 as a broad singlet. The ester carbonyls resonated at δ 161.7 and 167.6, respectively, in the 75 MHz ^{13}C NMR spectrum (CDCl$_3$). Finally, the structure was unambiguously established by single-crystal X-ray analysis (Figure 3).[12]

The reaction was found to be general and to occur with variously substituted allenic esters; the functionalized pyrazoline derivatives were obtained in moderate to good yields. The results are summarized in Table 2.

The following mechanistic postulate may be invoked to rationalize the reaction. It is conceivable that the phosphine reacts with the azoester in preference to the allenoate to form the zwitterion **3** and the latter then adds to the electron-deficient double bond of the allene ester to give a tetrahedral intermediate **8**, which gives the functionalized pyrazole derivative **7** presumably by the elimination of triphenylphosphine oxide via a process resembling the Wittig reaction (Scheme 2).

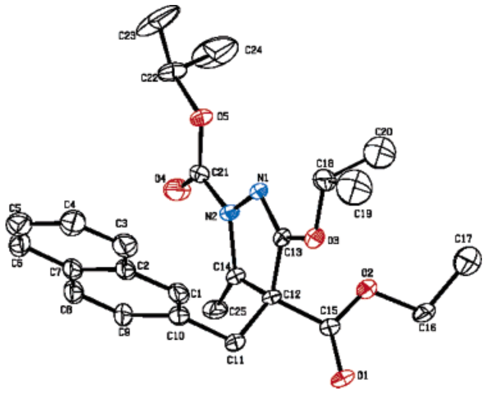


Figure 3. Single-crystal X-ray structure of **7k**.

In view of the interesting results obtained from the reaction of **3** with **6**, we extended our studies to 3-substituted allenoates. In a prototype experiment, treatment of ethyl-4-phenyl-2,3-butadienoate **11a** with DIAD in the presence of a stoichiometric amount of triphenylphosphine resulted in the formation of fully substituted pyrazole derivative **12a** as

Scheme 2. Proposed Mechanism for the Reaction

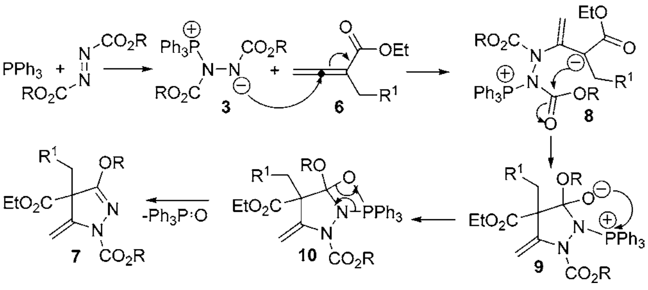
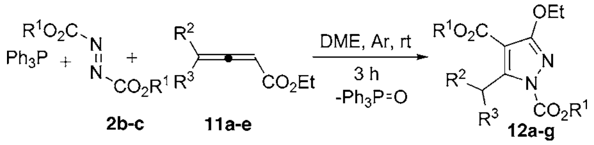


Table 3. Synthesis of Fully Substituted Pyrazoles



entry	R^1	R^2	R^3	product	yield (%)
1	isopropyl	C$_6$H$_5$	H	**12a**	56
2	ethyl	C$_6$H$_5$	H	**12b**	54
3	ethyl	CH$_3$	H	**12c**	72
4	ethyl	4-OMe-C$_6$H$_4$	H	**12d**	35
5	isopropyl	CH$_3$	H	**12e**	62
6	isopropyl	4-Cl-C$_6$H$_4$	H	**12f**	44
7	isopropyl	C$_6$H$_5$	C$_6$H$_5$	**12g**	41

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(10) Crystal structure of compound **7a** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. 298290.

(11) For packing diagram, see Supporting Information.

(12) Crystal structure of compound **7k** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 298292. The H atoms and disordered positions of C19 and C20 are omitted for clarity.

colorless crystals in 56% yield (entry 1, Table 3). The reaction proceeds via an unusual nitrogen to carbon migration of the ester group.

The structure of **12a** was established by spectroscopic analysis. In the IR spectrum, the ester carbonyls were seen at 1753 and 1702 cm^{-1}. In the 300 MHz ^1H NMR spectrum ($CDCl_3$), the benzylic protons resonated at δ 4.74 as a sharp singlet. The methine protons were discernible in the range δ 5.07−5.18 as a multiplet. The ester carbonyls were discernible at δ 161.9 and 162.3 in the 75 MHz ^{13}C NMR spectrum ($CDCl_3$). Finally, the structure was unequivocally confirmed by single-crystal X-ray analysis (Figure 4).[13]

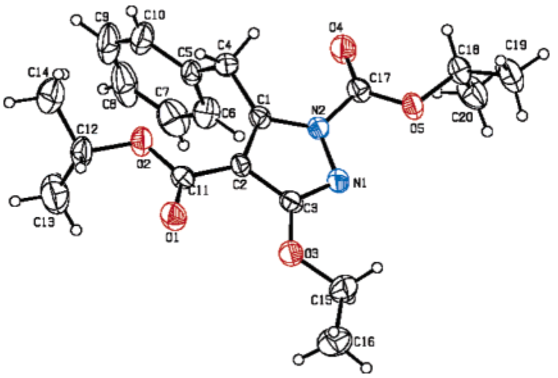
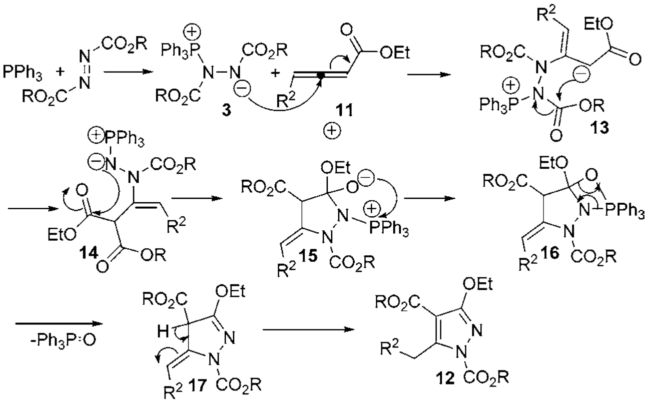


Figure 4. Single-crystal X-ray structure of **12a**.

The reaction was found to be general with respect to various allenic esters, and the fully substituted pyrazole derivatives were obtained in moderate to good yields. The results are summarized in Table 3.

The following rationalization may be advanced to explain the product formation. The zwitterion **3** adds to the electron-deficient double bond of allene ester to give the intermediate **13**, which undergoes a nucleophilic attack on the ester group of the azoester to deliver the ylide **14**. The net result is the nitrogen to carbon migration of the ester group.[14] Ring closure of the ylide **14**, followed by elimination of triphenylphosphine oxide and double bond isomerization leads to the pyrazole derivative **12** (Scheme 3).

Scheme 3. Proposed Mechanism for the Reaction



In conclusion, we have uncovered a novel synthesis of functionalized pyrazolines and pyrazoles by triphenylphosphine-mediated reaction of dialkyl azodicarboxylates with allenic esters. The fully substituted pyrazoles are formed via novel nitrogen to carbon migration of the ester group. It is noteworthy that pyrazole derivatives are often found useful as pharmaceuticals and agrochemicals.

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Supporting Information Available: General experimental procedure and spectroscopic data for all compounds and crystallographic data for **7a**, **7k**, and **12a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Crystal structure of compound **12a** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 298291.

(14) It is interesting to note that such a migration is not observed in the reaction involving 2-substituted 2,3-butadienoates. This may be attributed to the relative stability of the secondary enolate **13** versus the tertiary enolate **8**.