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Base-Mediated Reaction of the Bestmann–Ohira Reagent with Nitroalkenes for the Regioselective Synthesis of Phosphonylpyrazoles

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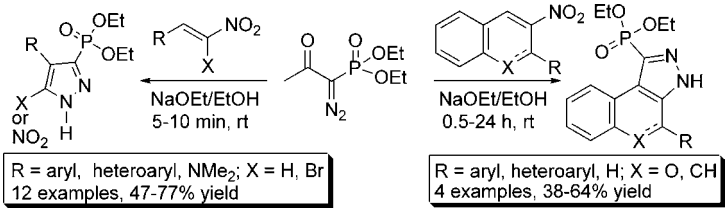
ABSTRACT



1,3-Dipolar cycloaddition of the anion of diethyl 1-diazomethylphosphonate, generated in situ from diethyl 1-diazo-2-oxopropylphosphonate (Bestmann–Ohira reagent), with conjugated nitroalkenes provides regioisomerically pure phosphonylpyrazoles in moderate to good yield. These pyrazoles are formed in one pot via spontaneous elimination of the nitro group. However, nitropyrazoles could be synthesized by the same strategy using α-bromonitroalkenes. The methodology works for the synthesis of phosphonylpyrazoles fused to other carbo- and heterocycles as well.

Organophosphorus compounds, including natural products, are remarkable for their diverse and potent biological activities.[1] Their efficacy is often enhanced by their association with various heterocycles which in their own right are biologically active.[2] Prominent among such bioactive heterocycles is the pyrazole moiety which is present in a plethora of natural and synthetic compounds.[3] Pyrazoles are also efficient coordinating ligands in synthesis.[4] Although a variety of methods are known in the literature for the synthesis of pyrazoles,[3] which include reaction between hydrazines and β-difunctional compounds[5] and 1,3-dipolar cycloaddition (1,3-DC) of diazo compounds to alkenes and alkynes,[6,7] methods for the synthesis of pyrazole directly substituted with phosphorus-containing functional groups are scarce and involve multistep reaction sequences.[8]

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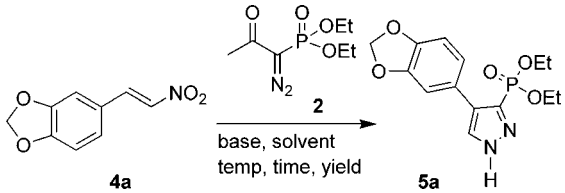
In this context, we envisaged that cycloaddition of diethyl 1-diazomethylphosphonate (Seyferth−Colvin−Gilbert reagent) **1**[9] or its corresponding anion, conveniently generated in situ using a suitable base from diethyl 1-diazo-2-oxopropylphosphonate (Bestmann−Ohira reagent, BOR) **2**,[10] with suitable alkenes or alkynes would provide phosphonylated pyrazoles **3a** and/or **3b**. Surprisingly, although these reagents have been extensively used for the transformation of aldehydes to one-carbon homologated acetylenes,[11] their application as cycloaddition partners remains largely unexplored.[12,13] In particular, BOR **2** has not been used, to our knowledge, as a substrate per se or as a precursor to **1** in cycloadditions.[13]

In view of our continued interest in the chemistry of conjugated nitroalkenes[14] together with the possibility of achieving high regioselectivity in cycloadditions involving nitroalkenes, we embarked on the idea of using nitroalkenes as cycloaddition partners with BOR **2** under suitable experimental conditions. To this end, BOR **2** was prepared in one step from commercially available 2-oxopropylphosphonate[15] and was then reacted with nitroalkene **4a** in the presence of K_2CO_3 in EtOH at room temperature (Table 1, entry 1). This provided a colorless solid whose spectral data

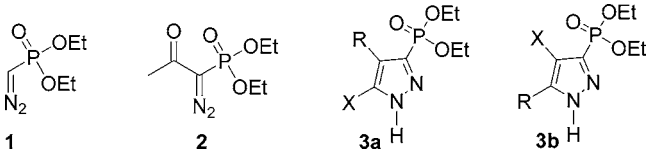
Table 1. Optimization of the Reaction Conditions for the 1,3-DC Reaction of Nitroalkenes **4** with BOR **2**



entry	base	solvent	temp	time	yield (%)[a] of **5a**
1	K_2CO_3	EtOH	rt	7 h	65
2	–	EtOH	rt	5 days	no reaction
3	–	EtOH	reflux	15 h	no reaction
4	Et_3N	EtOH	rt	24 h	5[b]
5	DABCO	EtOH	rt	24 h	traces[b]
6	DBU	EtOH	rt	15 h	63
7	**NaOEt**	**EtOH**	**rt**	**15 min**	**77**
8	NaOMe	MeOH	rt	15 min	64
9	DBU	CH_3CN	rt	24 h	complex
10	DBU	1,4-dioxane	rt	24 h	no reaction
11	DBU	DMF	rt	24 h	no reaction
12	DBU	THF	rt	24 h	no reaction
13	NaOEt	THF	rt	24 h	32[b]

[a] Isolated yield after purification by silica gel column chromatography. [b] **4a** polymerized.

suggested it to be an isomerically pure pyrazole (see the Supporting Information). The structure was subsequently



confirmed to be **5a** by $^1H-^1H$ NOESY (NOE between C5-H and aromatic protons) and was further unambiguously established by single-crystal X-ray analysis (Figure 1, see also the Supporting Information).[16] Our detailed optimization experiments confirmed the requirement of a nucleophilic base and protic solvent (Table 1). Under the optimized conditions,

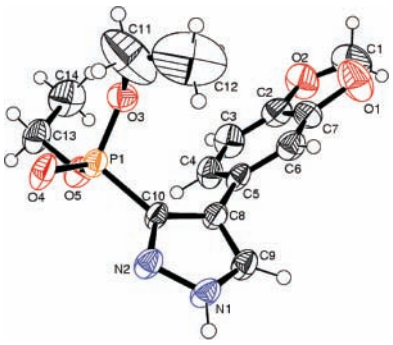


Figure 1. ORTEP diagram of **5a**.

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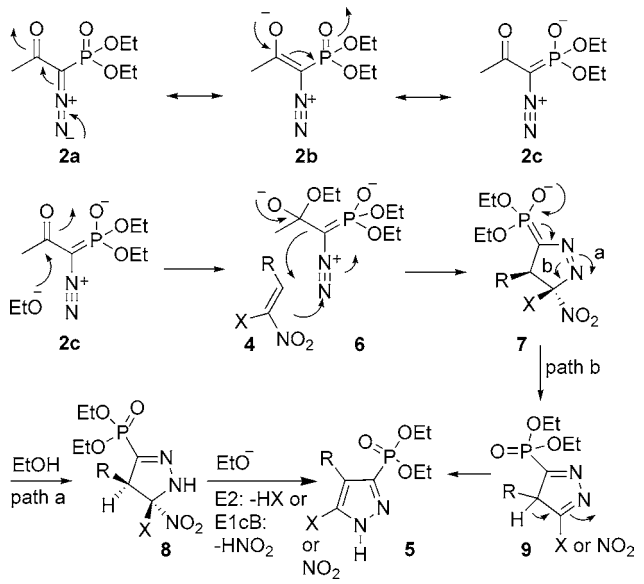
i.e., in the presence of NaOEt in EtOH at room temperature, **5a** was isolated in 77% yield. The results suggested that the alkoxide ion[17] played the role of a nucleophilic base in these reactions, and the base-mediated acyl cleavage of BOR **2** was taking place prior to cycloaddition with nitroalkene **4** (X = H, Scheme 1). Thus, the 1,3-dipolar cycloaddition of

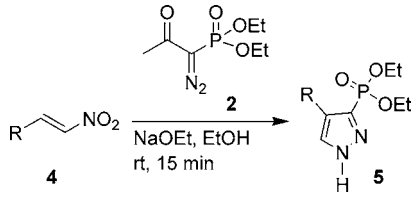
Scheme 1. Proposed Mechanism for the Formation of Phosphonyl Pyrazoles **5** from BOR **2** and Nitroalkene **4**



the in situ generated anion of **1** with nitroalkene **4** would provide the initial cycloadduct **7**. Protonation of **7** followed by base-assisted elimination of HNO_2 (path a, E1cB) or elimination of the NO_2 group followed by intramolecular proton transfer (path b) would furnish phosphonylpyrazole **5**.[18]

Under the above optimized conditions, we reacted a variety of aromatic, heteroaromatic, and other nitroalkenes **4b**−**j** with BOR **2** to afford the phosphonylpyrazoles **5b**−**j** as single regioisomers in moderate to good yields (Table 2). Entries 1−7 (Table 2) show that aromatic nitroalkenes with both electron-donating and electron-withdrawing substituents

Table 2. 1,3-DC Reaction of Nitroalkenes **4** with BOR **2** in the Presence of NaOEt in EtOH at Room Temperature



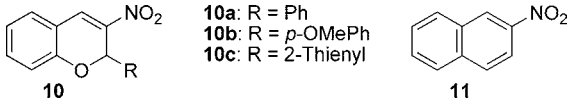
entry	4	R	yield (%)[a] of 5
1	**4a**	benzo[*d*][1,3]dioxole	77
2	**4b**	*p*-$OMeC_6H_4$	66
3	**4c**	*p*-ClC_6H_4	61
4	**4d**	*p*-$NO_2C_6H_4$	64
5	**4e**	*m*-$NO_2C_6H_4$	61
6	**4f**	*o*-$NO_2C_6H_4$	67
7	**4g**	C_6H_5	62
8	**4h**	2-furyl	55[b]
9	**4i**	2-thienyl	49[b]
10	**4j**	NMe_2	64

[a] Isolated yield after purification by silica gel column chromatography. [b] Part of **4** polymerized.

4a−**f** and parent nitrostyrene **4g** provided the cycloadducts **5a**−**g** in good yields (61−77%). The yields were moderate, 55% and 49%, respectively, with heteroaromatic nitroalkenes **4h** and **4i** (entries 8 and 9). Enamino-nitroalkene **4j** furnished *N*,*N*-dimethylaminophosphonylpyrazole **5j** in good yield (64%, Table 2, entry 10).

Having succeeded in synthesizing phosphonylpyrazoles **5**, possessing an aryl, heteroaryl, or amino group vicinal to the phosphonate moiety, from *β*-substituted nitroethylenes **4** and BOR **2** under base-mediated conditions, we turned our attention to the possible synthesis of pyrazoles fused to other carbo- or heterocycles. This objective appeared achievable using cyclic nitroalkenes, e.g., **10**[19] and **11**.

Although reaction of BOR **2** with nitroalkenes **10a**−**c** required longer reaction times, we were pleased to observe the formation of pyrazoles fused to the benzopyran ring as single regioisomers **12a**−**c** in good yield (Table 3, entries 1−3). Under these conditions, phosphonylpyrazole fused to napthalene ring **13** could also be synthesized, albeit in low yield (Table 3, entry 4).



Nitroalkenes **4**, **10**, and **11** were the cycloaddition partners with BOR **2** in the above cases. However, the pyrazole formation involved elimination of the nitro group, a synthetically and biologically useful functionality. Therefore, it was felt that the nitro group could be retained in the pyrazole

(16) Selected X-ray crystallographic data for **5a**, $C_{14}H_{17}N_2O_5P$: M = 324.27, monoclinic $P2_1/c$, a = 13.2560 (11) Å, b = 8.1070 (9) Å, c = 15.4750 (15) Å, β = 113.411(7), V = 1526.1 (3) Å^3, Z = 4, D_{calcd} = 1.411 g cm^{-3}, μ = 0.205 mm^{-1}. Reflections collected: unique 2802/2680 [R(int) = 0.0875]. Final R indices [$I > 2\sigma(I)$], R1 = 0.0664, wR2 = 0.1516, R indices (all data), R1 = 0.1773, wR2 = 0.1879.

(17) This appears to be the case in K_2CO_3- and DBU-catalyzed reactions as well. In the case of K_2CO_3, it is known that K_2CO_3 is partially soluble in methanol and generates potassium methoxide. See: Platonov, A. Y.; Evdokimov, A. N.; Kurzin, A. V.; Maiyorova, H. D. *J. Chem. Eng. Data* **2002**, *47*, 1175.

(18) Formation of pyrazole from pyrazoline by an elimination reaction. For elimination of H_2O: (a) Flores, A. F. C.; Martins, H. A. P.; Rosa, A.; Flores, D. C.; Zannatta, N.; Bonacorso, H. G. *Synth. Commun.* **2002**, *32*, 1585. (b) Singh, S. P.; Kumar, D.; Jones, B. G.; Threadgill, M. D. *J. Fluorine Chem.* **1999**, *94*, 199. For elimination of HBr: (c) Chandrasekhar, S.; Rajaiah, G.; Srihari, P. *Tetrahedron Lett.* **2001**, *42*, 6599. (d) Jiang, B.; Xu, Y. Y. *J. Fluorine Chem.* **1994**, *67*, 83. For elimination of *p*-TsOH: (e) Midura, W. H.; Krysiak, J. A.; Mikolajczyk, M. *Tetrahedron* **1999**, *55*, 14791. For elimination of HNO_2: (f) Mancera, M.; Rodriguez, E.; Yang, J.; Roffe, I.; Galbis, J. A. *Carbohydr. Res.* **1994**, *253*, 307.

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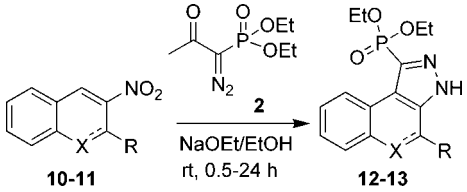
Table 3. 1,3-DC Reaction of Nitroalkenes **10** and **11** with BOR **2** in the Presence of NaOEt in EtOH at Room Temperature

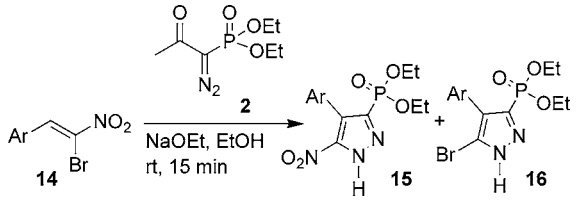


entry	**10**−**11**	time	pyrazole **12**−**13**	yield (%)[a] of **12**−**13**
1	**10a**	0.5 h	**12a**	64
2	**10b**	1 h	**12b**	57
3	**10c**	12 h	**12c**	59
4	**11**	24 h	**13**	38[b]

[a] Isolated yield after purification by silica gel column chromatography. [b] 22% of **11** was recovered.

moiety, provided the nitroalkene possesses an α-substituent which is a better leaving group than the nitro group. This was realized by taking α-bromonitroalkenes **14** as cycloaddition partners with BOR **2** (Table 4). Thus, although

Table 4. 1,3-DC Reaction of 1-Bromo-1-nitrostyrene **14** with BOR **2** in the Presence of NaOEt in EtOH



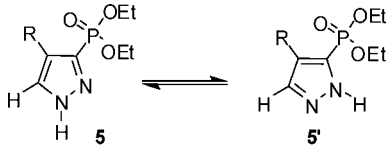
entry	**14**	Ar	yield (%)[a] of **15** + **16**	**15**/**16** ratio
1	**14a**	C_6H_5	47[b]	100:0
2	**14b**	*p*-$OMeC_6H_4$	54[b]	61:39

[a] Isolated yield after purification by silica gel column chromatography. [b] Part of **14** polymerized.

nitropyrazole **15a** was the only product isolated when **14a** was reacted with BOR **2** (Table 4, entry 1), nitropyrazole **15b** and bromopyrazole **16b** were isolated as a ∼60:40 mixture when nitroalkene **14b** was the cycloaddition partner (entry 2).[20]

Pyrazoles **5a**−**j** and **12a**−**c** exhibited tautomerism in solution which could be monitored by ^{1}H and ^{31}P NMR. For instance, although pyrazole 3-phosphonate **5** was the only tautomer observed in the solid state (from single-crystal X-ray analysis; see Figure 1 and the Supporting Information), two tautomers, **5** and **5′**, were observed in ∼1:1 ratio in a noninteracting solvent such as $CDCl_3$ (Scheme 2). This ratio

Scheme 2. Tautomerism in Phosphonylpyrazoles **5**



medium	**5**:**5'** ratio
solid	1:0
$CDCl_3$	1:1
DMSO-d_6	major: minor

changed, presumably in favor of **5**, when the NMR spectra were recorded in a strongly hydrogen-bonding solvent such as DMSO-d_6.[21]

In conclusion, one-pot reaction of the Bestmann−Ohira reagent with conjugated nitroalkenes under the influence of a nucleophilic base at room temperature provides regioisomerically pure phosphonylpyrazoles in good yield.[22] The same strategy could be employed for the synthesis of various fused and functionalized phosphonylpyrazoles.

Acknowledgment. The authors thank DST (India) for financial support and SAIF (IIT Bombay) for selected NMR spectra. R.M. thanks IIT Bombay for a research fellowship. This paper is dedicated to Dr. N. Kalyanam on the occasion of his 57th birthday.

Supporting Information Available: X-ray data for **5a** in CIF format, experimental procedures and full characterization data, copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra for all new compounds, and a copy of the 2D-NOESY spectrum for **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Although **15** can be formed via path a (E2) or path b, **16** is expected via path a (E1cB) and by path b (Scheme 2). However, it appears that the E1cB mechanism is not operative in the case of entry 1 (Table 4).

(21) In DMSO-d_6, the major tautomer has the C-5 proton deshielded which is presumably due to stronger, unhindered H-bonding by the N−H and the C−5H with the solvent in **5** as compared to that in **5′**. Previous studies on the tautomerism in substituted pyrazoles also showed that the tautomer in the solid state predominated in solution as well: (a) Szabo, A.; Cesljevic, V. I.; Kovacs, A. *Chem. Phys.* **2001**, *270*, 67. (b) Claramunt, R. M.; Lopez, C.; Elguero, J.; Rheingold, A. L.; Zakharov, L. N.; Trofimenko, S. *ARKIVOC* **2003**, 209. Detailed investigations on the tautomerism in **5** and **12** and reaction of BOR **2** with other activated alkenes are currently underway and will be reported in the full paper.

(22) It may be noted that the reactions described in Tables 2−4 were quite clean and complete (except in Table 3, entry 4), and no side products were isolated. In cases where the yields were low to moderate, some polymerization of the nitroalkene was the only side reaction. Attempts to eliminate this problem by carrying out the reaction at 0 °C led to incomplete conversion.