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One-Pot, Two-Step Conversion of Aldehydes to Phosphonyl- and Sulfonylpyrazoles Using Bestmann–Ohira Reagent

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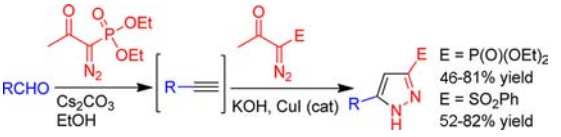
ABSTRACT



A one-pot, two-step, three-component method for the conversion of commercially available aldehydes to phosphonylpyrazoles has been developed, demonstrating, for the first time, the dual reactivity of the Bestmann–Ohira reagent (BOR) in a single-pot transformation. This method, extended to the synthesis of sulfonylpyrazoles by employing BOR in the first step and a diazomethyl sulfone in the second step, is complementary, with regard to regioselectivity, to the previous methods for the synthesis of such functionalized pyrazoles.

Bioactive heterocycles constitute the backbone of medicinal chemistry, and prominent among them is pyrazole, which is present in natural products and designed molecules.[1] The analgesic and CNS depressant alkaloid Withasomnine,[2,3] the antiarthritic drug Celecoxib, and the phosphodiesterase inhibitor Viagra are among the numerous pyrazole-based compounds that exhibit a wide range of therapeutic properties. Introduction of functional groups such as phosphonate or sulfone, especially in a regioselective fashion, could dramatically enhance or alter the pharmacophoric profile of pyrazole. This is because of the proven ability of phosphonate to mimic the carboxylate moiety in the peptide bond cleavage[4] and the presence of a key sulfonyl group in many drug molecules, for instance, the antiprostate cancer drug Bicalutamide and the antileprosy drug Dapsone. Besides the biological properties, the tautomerism exhibited by pyrazoles[5] and their role as ligands in synthesis[6] and as precursors to N-heterocyclic carbenes (NHC)[7] received considerable attention.

The general methods for the synthesis of pyrazoles[8] are 1,3-dipolar cycloaddition of diazo compounds with alkenes

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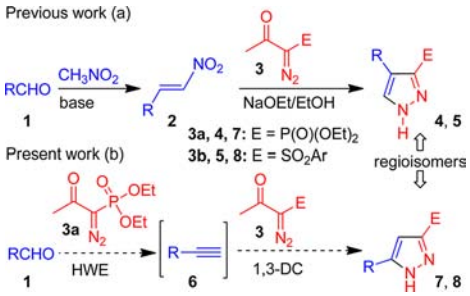
or alkynes (Pechmann synthesis)[9] and the cyclocondensation between hydrazines and 1,3-difunctional compounds (Knorr synthesis).[10] These approaches were employed for the synthesis of various functionalized phosphonyl- and sulfonylpyrazoles as well.[11−14] Recently, we[15] and Smietana et al.[16] have employed α-diazo-β-ketophosphonate (Bestmann−Ohira reagent, BOR) **3a**[17] as a diazomethyl phosphonate precursor in the 1,3-dipolar cycloaddition with various electron-deficient alkenes (e.g., **2**, Scheme 1a) for the regioselective synthesis of phosphonylpyrazoles (e.g., **4**). We also extended this strategy to the synthesis of sulfonylpyrazoles **5** using α-diazo-β-ketosulfone **3b** as a 1,3-dipole precursor.[3]

The new role played by BOR **3a** as a 1,3-dipole precursor, besides its traditional role as a Horner−Wadsworth−Emmons (HWE) reagent in the one-pot conversion of aldehydes **1** to acetylenes **6**,[18] appeared to have further

Scheme 1



scope in the development of novel synthetic methods. Interestingly, in both reactions, the proposed species is diethyl diazomethylphosphonate (Seyferth−Colvin−Gilbert reagent)[19] anion, which is generated in situ by a nucleophilic base. Therefore, we embarked on the idea of exploiting the dual reactivity of BOR **3a** in the single-pot transformation of aldehydes **1** to phosphonylpyrazoles **7** (Scheme 1b). Although the first step is well established,[18] the transformation of acetylenes **6** to phosphonylpyrazoles **7**, using BOR **3a** as a cycloaddition partner, is unreported hitherto.[20] More importantly, we realized that such a transformation of aldehyde **1** to pyrazole **7** (whose R group is analogous to that in antiarthritic drug Celecoxib) would provide the regioisomer of **4**, which is otherwise difficult to synthesize. A new dimension to this strategy would emerge with a different diazo compound, e.g., diazosulfone **3b**, in the second step, which would give rise to sulfonylpyrazole **8**, the regioisomer of **5**.

Our initial attempts to convert *p*-nitrobenzaldehyde **1a** to pyrazole **7a** in one pot using 2 equiv of BOR **3a** in the presence of 2 equiv of bases such as KOH, K_2CO_3, and Cs_2CO_3 were unsuccessful due to incomplete conversion of aldehyde **1a** to alkyne **6a** even after 24 h (Table 1). However, in the presence of excess BOR **3a** and 2.5 equiv of Cs_2CO_3, complete conversion of aldehyde **1a** to alkyne **6a** was achieved (TLC analysis, entry 1). But since further transformation of alkyne **6a** to pyrazole **7a** in the same pot did not take place, it became necessary to activate the in situ generated alkyne **6a** for further reaction as a dipolarophile. To this end, 20 mol % of CuI was added to the reaction mixture after the alkyne formation was complete (entry 2). Since this too did not yield the desired pyrazole **7a**, we added BOR **3a** in batches, i.e., 2.5 equiv before the first step and 1.5 equiv on completion of the first step. This strategy worked well, and the reaction was complete in 5 h to afford the product **7a** in 65% yield (entry 3). Further attempts to improve the yield using CuBr instead of CuI (entry 4), NaOEt, and LiOH

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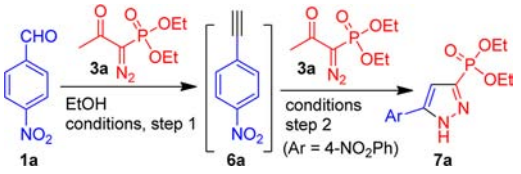
Table 1. Optimization of the Reaction Conditions



entry	step 1	step 2	time (h)	% yield[a]
1	Cs_2CO_3(2.5 equiv), BOR (3.5 equiv)		24	[b]
2	Cs_2CO_3 (5 equiv), BOR (3.5 equiv)	CuI (20 mol %)	24	[b]
3	Cs_2CO_3 (5 equiv), BOR (2.5 equiv)	BOR (1.5 equiv), CuI (20 mol %)	5	65
4	Cs_2CO_3 (5 equiv), BOR (2.5 equiv)	BOR (1.5 equiv), CuBr (20 mol %)	24	33
5	NaOEt (5 equiv), BOR (2.5 equiv)	BOR (1.5 equiv), CuI (20 mol %)	8	55
6	LiOH.H_2O, BOR (2.5 equiv), 4 Å MS	BOR (1.5 equiv), CuI (20 mol %)	6	63
7	Cs_2CO_3 (3 equiv), BOR (2.5 equiv)	KOH (2 equiv), BOR (1.5 equiv), CuI (20 mol %)	6	81

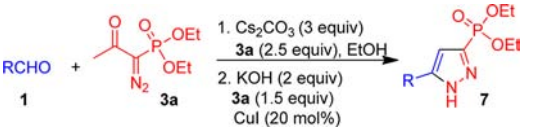
[a] Isolated yield after purification by silica gel chromatography. [b] Only alkyne was formed.

instead of Cs_2CO_3 as bases (entries 5 and 6) provided unsatisfactory results. This prompted us to employ a stronger base for the second step in which the reactive dipolarophile copper acetylide had to be generated. Thus, addition of 2 equiv of KOH, besides 1.5 equiv of BOR **3a** and 20 mol % of CuI, led to dramatic improvement in the yield of **7a** to 81% (entry 7).

The above optimized conditions were employed to investigate the scope of the reaction (Table 2). As expected, aromatic aldehydes **1a**−**e** possessing electron withdrawing substituents such as NO_2, CF_3, F, Cl and Br at the para position of the aromatic ring afforded the products **7a**−**e** in good to excellent yield (70−81%, entries 1−5). Marginally lower yields were encountered when the substituent was at the meta position (68%, entry 6) and in the case of unsubstituted aromatic aldehydes **1g** and **1h** (58−67%, entries 7 and 8). While aldehyde **1i** afforded the product **7i** in good yield (71%, entry 9), other aldehydes **1j**−**k** and **1s**, possessing strongly electron-donating substituents, gave the corresponding pyrazoles **7j**,**k**,**s** in much lower yield (46−55%, entries 10−11 and 19). Aromatic aldehydes **1l**, **m** with weakly electron donating substituents and heteroaromatic aldehydes **1n**−**p** reacted with BOR **3a** to furnish pyrazoles **7l**−**p** in satisfactory yield (62−66%, entries 12−16). The desired products were not isolated in the case of aliphatic and α,β-unsaturated aldehydes **1q** and **1r**, respectively. Since both steps involve nucleophilic attack of diazomethyl phosphonate anion, electron-deficient aldehydes/acetylenes that possess low-lying LUMOs are, in general, found to be more reactive. The structure and regiochemistry of pyrazoles **7a**−**p** were confirmed by NMR and further unambiguously established by single-crystal X-ray analysis of a representative compound **7g** (see the Supporting Information).[21]

The proposed mechanism involves initial alkyne **6** formation from aldehyde **1** and BOR **3a** under HWE conditions[18] and subsequent Cu(I)-catalyzed 1,3-dipolar cycloaddition of alkyne **6** with in situ generated diazomethyl phosphonate anion **III** (Scheme 2). While the first step that involves the

Table 2. One-Pot Synthesis of Phosphonylpyrazoles **7** from Aldehydes **1** and BOR **3a**

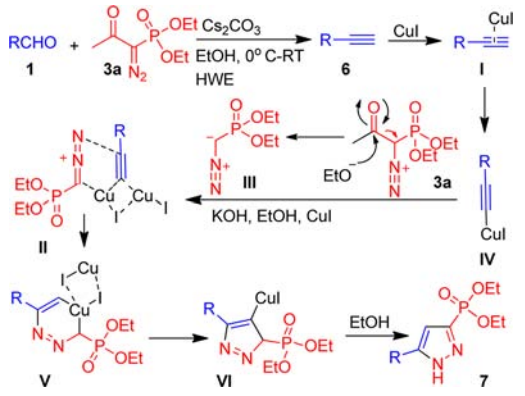


entry	R	time[a] (h)	7	% yield[b]
1	4-$NO_2C_6H_4$	6	**7a**	81
2	4-$CF_3C_6H_4$	26	**7b**	75
3	4-FC_6H_4	24	**7c**	70
4	4-ClC_6H_4	26	**7d**	75
5	4-BrC_6H_4	28	**7e**	72
6	3-BrC_6H_4	24	**7f**	68
7	C_6H_5	30	**7g**	67[c]
8	1-naphthyl	29	**7h**	58
9	benzo[*d*][1,3]dioxole	28	**7i**	71
10	3,4-$(OMe)_2C_6H_3$	36	**7j**	51
11	4-$OMeC_6H_4$	36	**7k**	55
12	4-$CH_3C_6H_4$	30	**7l**	64
13	4-*i*-Pr-C_6H_4	30	**7m**	65
14	2-furyl	28	**7n**	60
15	2-thienyl	26	**7o**	62
16	3-thienyl	32	**7p**	66
17	isovaleryl	48	**7q**	[d]
18	PhCH=CH	48	**7r**	[d,e]
19	2-$OMeC_6H_4$	40	**7s**	46

[a] Time needed for 1,3-DC (second step) is ~0.5 h in all the cases. [b] Isolated yield after purification by silica gel chromatography. [c] Control reaction between phenylacetylene and BOR under step 2 conditions afforded **7g** in 70% yield. [d] No desired product other than aliphatic alkyne. [e] Michael addition of ethoxide preceded alkyne formation.

(21) The pyrazole proton in **7** appeared either as a singlet or as a doublet in the range δ 6.90−7.40 with a *J* value of 2.0−2.2 Hz due to coupling with P. In stark contrast, the pyrazole proton in regioisomers **4** appeared in the range δ 7.30−8.30 (ref 15a,15b). The X-ray structure of **7g** confirms that the preferred tautomer of **7** in solid state is pyrazole 3-phosphonate (P-3-P) as in the case of its regioisomer **4**. Moreover, the room-temperature ^1H and ^{31}P NMR solution spectra do not indicate the existence of another tautomer except in the case of **7a** and **7i**. The tautomerism in **7a** and **7i**, observed clearly by ^{31}P NMR, could be blocked by N-alkylation (see the Supporting Information).

Scheme 2. Proposed Mechanism for the One-Pot Synthesis of Phosphonylpyrazoles **7** from Aldehydes **1** and BOR **3a**



intermediacy of a vinylidenecarbene and its rearrangement to alkyne **6** is well established,[18] the second step, i.e., the reaction between alkyne **6** and diazophosphonate anion **III**, is unreported, to our knowledge, especially the one involving generation of **III** from a stable precursor such as BOR **3**. However, the mechanism of this step is analogous to the Cu(I)-catalyzed 1,3-dipolar cycloaddition of alkyne with azide (click chemistry).[22] Thus, Cu(I) reacts with alkyne **6** to form the π-complex **I**, which undergoes proton abstraction by the base to form copper acetylide **IV**. This activated acetylide reacts smoothly in a 1,3-dipolar fashion with diazophosphonate anion **III**, generated in situ from BOR **3a**, by alkoxide mediated deacylation. The resulting intermediate **II**, in which copper is weakly coordinated to both dipole and dipolarophile, gets transformed to intermediate **V** which further dissociates to intermediate **VI**. Protonation of **VI** followed by isomerization completes the reaction to deliver pyrazole **7** as a single regioisomer.

Having demonstrated the dual role of BOR **3a**, viz. as HWE reagent and as a cycloaddition partner, in the one-pot transformation of aldehydes **1** to phosphonylpyrazoles **7**, we desired to extend our methodology to the synthesis of sulfonylpyrazoles **8**. The fact that BOR **3a** had to be added in batches (2.5 equiv for the first step and 1.5 equiv for the second step) in our approach to synthesize phosphonylpyrazoles **7** became handy in the one-pot conversion of aldehydes **1** to sulfonylpyrazoles **8** because we could simply replace the second batch of BOR **3a** with sulfone **3b** (Table 3). This idea worked very well to afford a variety of 5-substituted 3-sulfonylpyrazoles **8**. Thus, as in the previous case, the electron poor aromatic aldehydes **1a**,**c**−**e**,**t**−**u** provided the products **8a**,**c**−**e**,**t**−**u** in high yields (73−82%, entries 1−4, 9, and 10, Table 3). Relatively electron-rich aromatic aldehydes **1i** and **1l** as well as heteroaromatic aldehydes **1n**,**o**,**v** also took part in the transformation in a satisfactory

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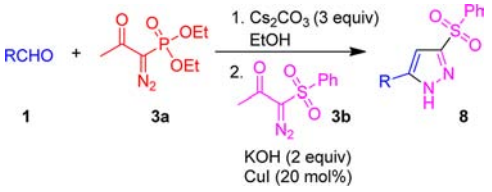
Table 3. One-Pot, Three-Component Synthesis of Sulfonylpyrazoles **8** from Aldehydes **1**, BOR **3a**, and Diazosulfone **3b**



entry	R	**8**	time (h)	% yield[a]
1	4-$NO_2C_6H_4$	**8a**	6	81
2	4-FC_6H_4	**8c**	24	77
3	4-ClC_6H_4	**8d**	23	73
4	4-BrC_6H_4	**8e**	24	76
5	benzo[d][1,3]dioxole	**8i**	18	77
6	4-$CH_3C_6H_4$	**8l**	26	69
7	2-furyl	**8n**	22	71
8	2-thienyl	**8o**	22	74
9	3-$NO_2C_6H_4$	**8t**	15	75
10	4-CNC_6H_4	**8u**	9	82
11	3-pyridyl	**8v**	26	52

[a] Isolated yield after purification by silica gel chromatography.

fashion to furnish the sulfonylpyrazoles **8i**, **l**, **n**, **o**, **v** in moderate to good yield (52−77%, entries 5−8 and 11).[23]

In conclusion, the Bestmann−Ohira reagent (BOR) has been employed as a HWE reagent and as a cycloaddition partner in the same reaction vessel for the first time. The method involves reaction of BOR with aldehydes to generate terminal acetylenes and subsequent reaction of BOR with the in situ generated acetylenes under simple Cu(I) catalyzed conditions to generate phosphonylpyrazoles. Application of a diazomethyl sulfone instead of BOR as the cycloaddition partner in the second step provides sulfonylpyrazoles. Quite remarkably, this strategy enables us to synthesize a variety of 5-substituted 3-phosphonylpyrazoles that are regioisomeric to the pyrazoles (4-substituted 3-phosphonyl) synthesized previously from nitroalkenes and Bestmann−Ohira reagent.

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Supporting Information Available. Complete characterization data and copies of NMR spectra for all new compounds as well as X-ray data for compound **7g** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org. The authors declare no competing financial interest.

(23) The pyrazole proton in **8** appeared as a singlet in the range δ 6.90−7.60, whereas in its regioisomer **5** (ref 3) it appeared as a singlet in most cases in the range δ 7.60−8.40 (see the Supporting Information).

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