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Substituent controlled reactivity switch: selective synthesis of α-diazoalkylphosphonates or vinylphosphonates *via* nucleophilic substitution of alkyl bromides with Bestmann–Ohira reagent†

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We report a substituent controlled nucleophilic displacement of alkyl bromides with Bestmann–Ohira reagent yielding either dimethyl diazoalkylphosphonates or (*E*)-vinylphosphonates. The dimethyl diazoalkylphosphonates could be readily converted into corresponding (*E*)-vinylphosphonates in the presence of Cu following nitrogen elimination in quantitative yields.

The chemistry of organophosphorus compounds has witnessed enormous advancement in recent times.[1] Vinylphosphonates are small molecules known for their interesting properties spanning across chemistry as well as biology.[2] They are suitable substrates for various name reactions[3] and are regularly used in polymer industry[4] and medicinal chemistry.[5] Despite plenty of methods available for the synthesis of vinylphosphonates,[6,7] their synthesis from readily available precursors remains a highly desirable and ever appealing prospect.

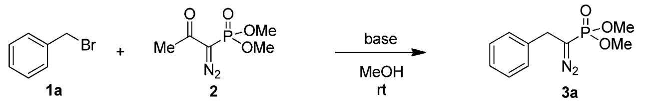
On the other hand, α-diazoethylphosphonates are rare compounds[8] and to the best of our knowledge there are very few literature reports mentioning α-diazo-arylethylphosphonates.[8d,e,g,j,k] The rare occurrence combined with the expectation that under suitable conditions α-diazo-arylethylphosphonates could be converted into *cis*- and *trans*-β-aryl vinylphosphonates selectively[8a,g,9] prompted us to delineate a suitable method for their synthesis. We envisaged that the nucleophilic substitution of benzyl halides with dimethyl (diazomethyl) phosphonate (DAMP) anion could afford the desired α-diazo-arylethylphosphonates in a single step. The DAMP anion can conveniently be generated *in situ* from Bestmann–Ohira reagent (BOR) **2**.[10] The BOR is commonly used for the aldehyde to alkyne homologation[11] or as a dipole in the 1,3-dipolar cycloaddition reactions for the synthesis of phosphonylated heterocycles.[12] However, to the best of our knowledge BOR has never been utilized in nucleophilic substitution reactions. Herein, we report our observations on the reaction of alkyl/benzyl bromides with BOR affording α-diazoethylphosphonates or vinylphosphonates depending on the substituent on the bromide.

We started our investigation with commercially available benzyl bromide **1a** and the DAMP anion was generated *in situ* by treating BOR **2** with various bases in methanol (Table 1). While the desired product **3a** was obtained with all the bases screened, 1 equivalent of KOH in MeOH appeared to be the best condition in terms of yield and reaction time (entry 4).

Furthermore, other substrates **1b** and **1c**, under optimized conditions, afforded styrylphosphonates **4b** and **4c**, respectively, as a result of nitrogen expulsion from initial diazo-arylethylphosphonates (Table 2, entries 2 and 3).[13] However, such nitrogen elimination did not take place in the case of *m*-nitro benzyl bromide **1d** providing the diazo product **3d** exclusively (entry 4). At this stage, we carefully selected benzyl bromides bearing substituents with diverse electronic character at various positions for a systematic examination of substituent effects on the reactivity of benzyl bromide towards BOR.

The results summarized in Table 2 revealed that the β-aryl vinylphosphonates **4** were obtained exclusively when the benzyl bromide carried electron withdrawing substituents at *ortho*- or

Table 1 Screening of bases for the reaction of benzyl bromide **1a** with BOR **2**[a]



Entry	Base	Time (min)	Yield of **3a**[b] (%)
1	K_2CO_3	30	60
2	KO^t-Bu	30	55
3	NaOMe	20	85
4	KOH	15	87

[a] All reactions were performed with 1 mmol of **1a**, 1.2 mmol of **2** and 1.2 mmol of base in 5 mL of MeOH. [b] Isolated yields.

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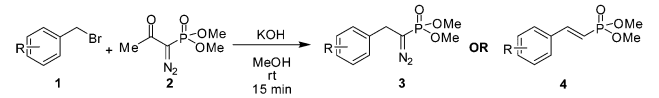
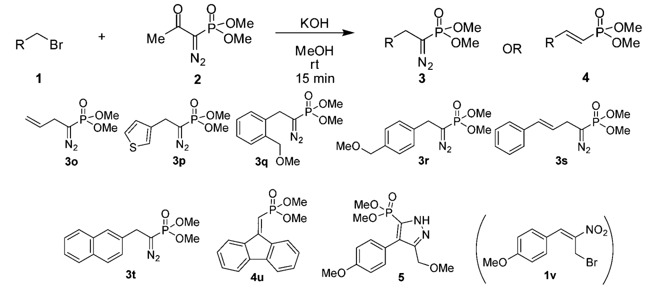
Table 2 Reaction of benzyl bromides **1** with BOR **2** under optimized conditions



Entry	1	R	Product	Yield of 3/4[a] (%)
1	**a**	H	**3a**	87 (85)[b]
2	**b**	4-NO_2	**4b**	85 (80)[b]
3	**c**	2-NO_2	**4c**	88
4	**d**	3-NO_2	**3d**	80
5	**e**	4-Me	**3e**	78
6	**f**	3-OMe	**3f**	79
7	**g**	2-Br	**3g**	76
8	**h**	3-Br	**3h**	75
9	**i**	4-F	**3i**	78
10	**j**	2-CN	**4j**	86
11	**k**	4-CN	**4k**	83
12	**l**	2-NO_2-3,4-(−OCH_2O−)	**4l**	78
13	**m**	2-NO_2-5-Cl	**4m**	80
14	**n**	2-NO_2-3-OMe	**4n**	79

[a] Isolated yields. [b] Yield for reaction at 1 gram scale.

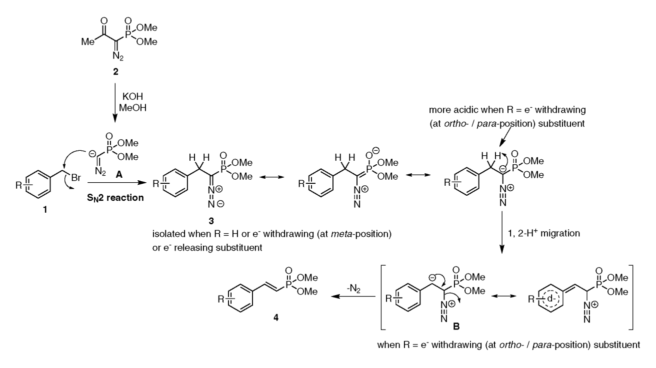
Table 3 Reaction of alkyl bromides **1** with BOR **2** under optimized conditions



Entry	1	R	Product	Yield of 3/4[a] (%)
1	**o**	Vinyl	**3o**	76
2	**p**	3-Thienyl	**3p**	78
3	**q**	2-CH_2Br-Ph	**3q**	86
4	**r**	4-CH_2Br-Ph	**3r**	88
5	**s**	Cinnamyl	**3s**	79
6	**t**	2-Naphthyl	**3t**	87
7	**u**	9-*H*-Fluorene	**4u**	85
8	**v**	(*E*)-1-(2-Nitroethene)-4-methoxybenzene	**5**	65

[a] Isolated yields.

para-positions (entries 2, 3, 10–14). The presence of an electron withdrawing substituent at the *meta*-position did not cause nitrogen elimination and afforded the α-diazo arylethylphosphonate **3** as the only product (entry 4). With benzyl bromides bearing either no substituent (entry 1) or electron releasing substituent (entries 5–9) at any position of the aryl ring, the diazo arylethylphosphonates remained the preferred product. In the case of benzyl bromides bearing two substituents with different electronic properties, the effect of electron withdrawing substituent dominated over the electron releasing one (entries 13 and 14). Here it is noteworthy that the transformation of **1** to **3**/**4** could be carried out in small as well as on gram scale with comparable yields (entries 1 and 2). The plausible mechanism compatible with these observations is depicted in Scheme 1. The benzyl bromide undergoes S_N2 substitution with the DAMP anion **A** generated *in situ* by basic methanol promoted deacylation of the BOR **2**. The resultant resonance stabilized diazomethyl arylethylphosphonate **3** can be isolated in the case of unsubstituted benzyl bromides or benzyl bromides bearing substituents other than *ortho*- and *para*-electron withdrawing ones. However, when benzyl bromide bears electron withdrawing substituents at *ortho*- or *para*-positions, the benzylic proton, which is sufficiently acidic due to the −M mesomeric effect of the *o*-/*p*-substituent, undergoes 1,2-migration furnishing zwitterion **B**. Zwitterion **B** following nitrogen elimination leads to the β-aryl vinylphosphonate product **4**.



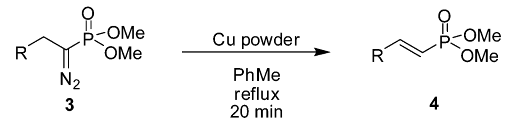
Scheme 1 Plausible mechanism for the formation of **3** and **4**.

Furthermore, in order to explore the potentialities of the protocol, diverse substrates such as allyl bromide **1o**, heteroaryl bromide **1p**, bis-bromomethyl benzenes **1q**–**1r**, alkyl bromides with extended conjugation **1s**–**1t** and secondary bromide **1u** were studied (Table 3). We also used the allylic bromide **1v** derived from the Morita–Baylis–Hillman (MBH) alcohol of (*E*)-4-methoxy nitrostyrene[14] since this substrate can react with BOR in different capacities *i.e.* substitution and/or cycloaddition.

The reaction proceeded well with allyl bromide **1o** as well as with 3-(bromomethyl)thiophene **1p**, furnishing the diazo products **3o** and **3p**, respectively, in high yields (entries 1 and 2). In the case of 1,2- and 1,4-bis-bromomethyl benzenes **1q** and **1r** only one bromide underwent substitution with the diazomethylphosphonate group while the other bromide was replaced by the methoxide anion from the solvent (entries 3 and 4). In both these cases, the excess BOR suffered decomposition within 15 min. The extended conjugation in **1s** and **1t** appears to exert a negligible effect on the acidity of β-hydrogen, leading to the isolation of diazo products in both the cases (entries 5 and 6). However, **1u** possessing secondary bromide afforded the vinylphosphonate product **4u** as expected, due to the enhanced stability of the secondary carbanion generated during the reaction leading to nitrogen expulsion (entry 7). It was interesting to note that the MBH product derived allyl bromide **1v** preferred dipolar cycloaddition over nucleophilic substitution of bromide with the DAMP anion. However, the bromide group was replaced with the methoxide anion from the solvent yielding product **5** (entry 8).

Finally, in order to convert the dimethyl diazoethylphosphonate products **3** into corresponding vinylphosphonates **4** stereoselectively, we analyzed the possibility of nitrogen elimination

Table 4 Conversion of dimethyl diazoethylphosphonates **3** into vinylphosphonates **4**[a]



Entry	3	R	Product	Yield of **4**[b] (%)
1	**a**	Ph	**4a**	98
2	**d**	3-NO_2-Ph	**4d**	88
3	**e**	4-Me-Ph	**4e**	98
4	**f**	3-OMe-Ph	**4f**	96
5	**g**	2-Br-Ph	**4g**	95
6	**h**	3-Br-Ph	**4h**	91
7	**i**	4-F-Ph	**4i**	98
8	**o**	Vinyl	**4o**	85
9	**p**	3-Thienyl	**4p**	95
10	**q**	2-CH_2OMe-Ph	**4q**	96
11	**r**	4-CH_2OMe-Ph	**4r**	96
12	**t**	2-Naphthyl	**4t**	96

[a] All reactions were performed with 1 mmol of **3** and 10 mol% of Cu powder in 5 mL of toluene. [b] Isolated yields.

under base catalyzed,[9] acid catalyzed[9] as well as metal catalyzed[8a,9] conditions (see ESI,† Table S1). The copper catalyzed decomposition of **3a** which is likely to proceed *via* a carbenoid intermediate and therefore expected to provide a *cis–trans* mixture of the corresponding vinylphosphonate[8a,9,15] provided the *trans* isomer **4a** in excellent yield in toluene (see ESI,† Table S1). Thus other dimethyl diazoethylphosphonates **3d–i**, **3o–r** and **3t** were converted into corresponding vinylphosphonates under the optimized reaction conditions (Table 4). However, dimethyl-α-diazo-4-phenylbut-3-enylphosphonate **3s** under these conditions led to a complex mixture of products.

In summary, we devised an efficient method for the selective synthesis of substituted dimethyl diazoethylphosphonates and (*E*)-vinylphosphonates *via* a nucleophilic substitution reaction of commercially available and inexpensive bromides with Bestmann–Ohira reagent. The diazoethylphosphonates obtained were smoothly transformed into corresponding (*E*)-vinylphosphonates by copper mediated nitrogen expulsion.

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