
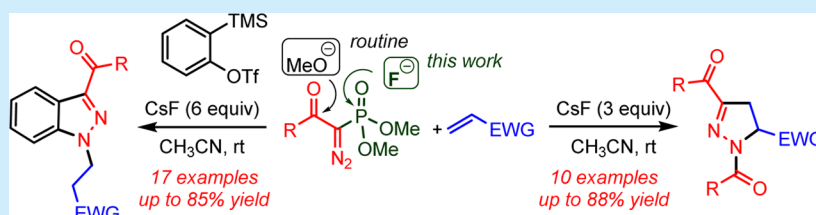


Fluoride-Mediated Dephosphonylation of α -Diazo- β -carbonyl PhosphonatesRavindra S. Phatake,^b Venkannababu Mullapudi, Vivek C. Wakchaure, and Chepuri V. Ramana*^b

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 Supporting Information

ABSTRACT: The possibility of fluoride-mediated selective dephosphonylation of α -diazo- β -carbonyl phosphonates such as the Ohira–Bestmann reagent has been proposed and executed. The resulting α -diazocarbonyl intermediates undergo a (3 + 2)-cycloaddition at room temperature with conjugated olefins and benzyne. Interestingly, under the current conditions, the resulting cycloaddition products underwent either *N*-acylation (with excess α -diazo- β -carbonyl phosphonates) or Michael addition (with conjugated olefins).

The Ohira–Bestmann reagent (dimethyl diazo-2-oxopropylphosphonate, OBR) has been developed as an improved stable alternative for the Seyferth–Gilbert reagent that has been used for the preparation of terminal alkynes from aldehydes.¹ The OBR is characterized by a fully functionalized diazomethane having pendant acyl and phosphonyl groups on the central carbon. The alkynylation of aldehydes, which includes the carbene reactivity of OB reagent, is associated with a net loss of all the three functional units around the central carbon. Besides its established and widespread utility in alkyne synthesis, the diverse functionality present in OBR provides an opportunity for its chemoselective functionalization. Thus, the selective manipulation of this reagent to retain some of these functional units in the end products is an attractive application that has only been tackled very recently.²

In 2004, Yuan and co-workers revealed the cycloaddition of the Rh-carbenoids derived from the OBR with the aryl nitriles resulting in the synthesis of oxazolyl-4-phosphonates.³ The recent seminal contributions from the Namboothiri,^{4a} Smietana,^{4b} and Mohanan^{4g} groups have revealed that the intermediate (diazomethyl)phosphonate anion can be efficiently trapped in an apparent (3 + 2)-cycloaddition process with conjugated olefins, imines, and alkynes resulting in the formation of pyrazolyl-/triazolylphosphonates.⁴ The presence of the pyrazole unit in various marketed drugs and the easy introduction of the phosphonate group has led to rapid exploration of this area.⁵ Very recently, the carbenoids derived from the OBR have been used as potential electrophiles in the metal-catalyzed directed C–H functionalization reactions for the annulation of pyridine/pyridinone units bearing a phosphonate group.⁶

Having looked at the available information on the reactions employing OBR, it was apparent that all reports comprise of

the selective loss of either the acyl or the azo groups, with the phosphonate group carried forward in the end products.⁴ However, retaining the acyl group in place of phosphonate is an attractive proposal that provides more substituent diversity and a provision for further functionalization. Remarkably, this aspect has never been explored with a preconceived dogma of considering OBR as a surrogate for the (diazomethyl)phosphonate anion. In this paper, we address this aspect by displacing the phosphonate group in place of acyl and have revealed the potential synthetic utility of this complementary functionalization of OBR.

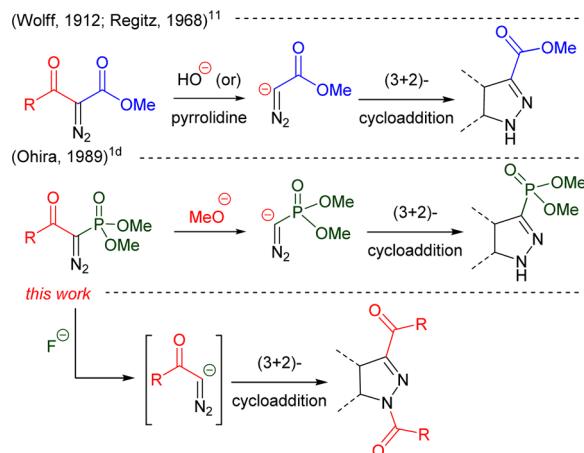
In general, treatment of OBR with either potassium carbonate or potassium *tert*-butoxide in methanol selectively forms the (diazomethyl)phosphonate anion with the removal of the acetyl unit. We reasoned that, with suitable tuning of the base, it could be made to selectively react with the phosphorus center, which should lead exclusively to the complementary (α -acyl)diazomethane anion (Scheme 1). In this context, we chose the fluoride ion because of its smaller size, weak basicity (pK_a of HF 3.5, MeOH \sim 15.5 and *t*-BuOH \sim 18), and importantly, its affinity for a phosphorus center, which we reasoned would selectively facilitate the departure of the phosphonate group from the OBR.^{7,8a} Indeed, preliminary DFT calculations of the reactions involving the fluoride ion mediated displacement of either acyl or the phosphonyl groups revealed that the latter process was an exothermic one ($\Delta E = -1.3$ kcal/mol) that would be preferred over the former ($\Delta E = +4.3$ kcal/mol).

Having this information in hand, preliminary experiments were conducted by employing stoichiometric amounts of OBR (1a), ethyl acrylate (2a), and cesium fluoride in acetonitrile at

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Scheme 1. Synthetic Strategies for 4,5-Dihydropyrazole



room temperature. Despite the reaction being sluggish, the formation of a new product in substantial amounts was observed. Chromatographic purification of this incomplete reaction led to the isolation of this new product **3a** in 34% yield (Table 1, entry 1). Analysis of the spectral data of **3a** led to the

Table 1. Optimization of Reaction Conditions^a

no.	BOR, 2a (equiv)	F [−] source (equiv)	solvent	3a yield ^b (%)
1	1.1	CsF (2.0)	CH ₃ CN	34
2	1.1	CsF (3.0)	CH ₃ CN	35
3	2.2	CsF (2.0)	CH ₃ CN	61
4	2.2	CsF (3.0)	CH ₃ CN	88
5	3.0	CsF (5.0)	CH ₃ CN	89
6 ^c	2.2	CsF (3.0)	CH ₃ CN	50
7 ^d	2.2	CsF (3.0)	THF	75
8	2.2	TBAF (3.0)	THF	39
9	2.2	TBAF (5.0)	THF	57
10	2.2	KF (3.0) and 18-crown-6 (3.0)	THF	42

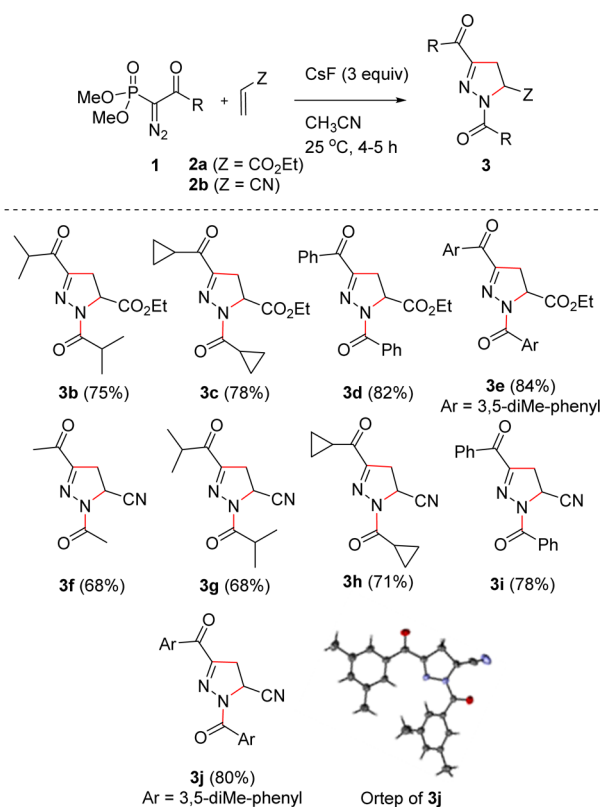
^aAll reactions were carried out on approximately a 0.3 mmol scale at a 0.08 M concentration. All reagent and substrate addition was done at room temperature (25 °C) and stirred for the next 4–5 h. ^bIsolated yields. ^cReaction addition and stirring continued at −10 °C for 10 h. ^dSubstrate addition at rt and stirred at 60 °C for 5 h.

identification of this compound as ethyl 1,3-diacetyl-4,5-dihydro-1H-pyrazole-5-carboxylate, thus endorsing the validity of our hypothesis, although the intended initial N-H pyrazole underwent further N-acylation by the OBR. The N-acylation with OBR has not yet been documented. However, it can be expected considering the basicity of the Δ²-pyrazoline (pK_a ~15),⁹ which is close to that of methanol (pK_a ~15.5), and corroborating with the N-acylation of pyrrolidine with ethyl diazoacetoacetate.^{10,11} Considering this, further optimization studies were conducted by varying the amount of OBR and CsF with respect to the acrylate **2a**.

After experimenting with several conditions, the use of 2.2 equiv of OBR and 3.0 equiv of CsF in acetonitrile as a solvent

improved the reaction outcome with the isolation of pyrazole **3a** in 88% yield (Table 1, entry 4). Control experiments revealed that the use of other fluoride sources such as tetrabutylammonium fluoride (TBAF) and KF/18-crown-6 were not beneficial (Table 1, entry 8–10), and the reactions carried out higher or lower temperature were not efficient (Table 1, entries 6 and 7). It is pertinent to mention here that during the optimization study we were unable to trap or isolate the free N-H pyrazole intermediate.

Having the optimized conditions in hand, the scope of the reaction was explored by employing a wide range of diazophosphonate-containing aliphatic (isopropyl, cyclopropyl), aromatic (phenyl, 3,5-dimethylphenyl), heteroaromatic [2-(N-methylindolyl)], and carboxyl groups (Table 2). It was

Table 2. Scope of Substituted 4,5-Dihydropyrazole Synthesis^a

^aReaction conditions: **1** (2.2 equiv), **2a/2b** (0.25 mmol), in CH₃CN (1 mL). Isolated yields are given.

found that the reaction with an aliphatic group next to carbonyl, such as -Me, -isopropyl, and -cyclopropyl, provided the corresponding products **3a–c** in good to excellent yields. In the case of aromatic systems such as simple phenyl and 3,5-dimethylphenyl, both substrates gave excellent yields. At the same time, the reactions with indole-derived and diazophosphonate having a carboxylate group were found to be sluggish and gave complex reaction mixtures. Also examined was the compatibility of acrylonitrile **2b** under the current conditions. The reactions proceeded smoothly with the aliphatic and aromatic substrates giving **3f–j** in very good yields. Additionally, the structure of **3j** was confirmed by single-crystal X-ray diffraction studies.

After this initial success in the synthesis of 1,3-disubstituted 4,5-dihydropyrazoles, we next examined the possibility of

extension to an indazole synthesis employing aryne intermediates as electrophiles.¹² Yamamoto^{12a} and Larock^{8a} had previously documented the (3 + 2)-cycloaddition of diazo compounds with in situ generated arynes. With diazomethane derivatives, either N-H or N-arylindazoles are obtained depending upon the conditions and reaction stoichiometry.^{8,12}

Interestingly, when ethyl diazoacetoacetate was employed, the resulting cycloaddition products underwent acyl migration to afford 1-acylindazole-3-carboxylate.^{8a} As observed in previous reports, the N-functionalization of the initially formed N-H indazole was a competing reaction and required another equivalent of the aryne precursor for a successful product outcome.

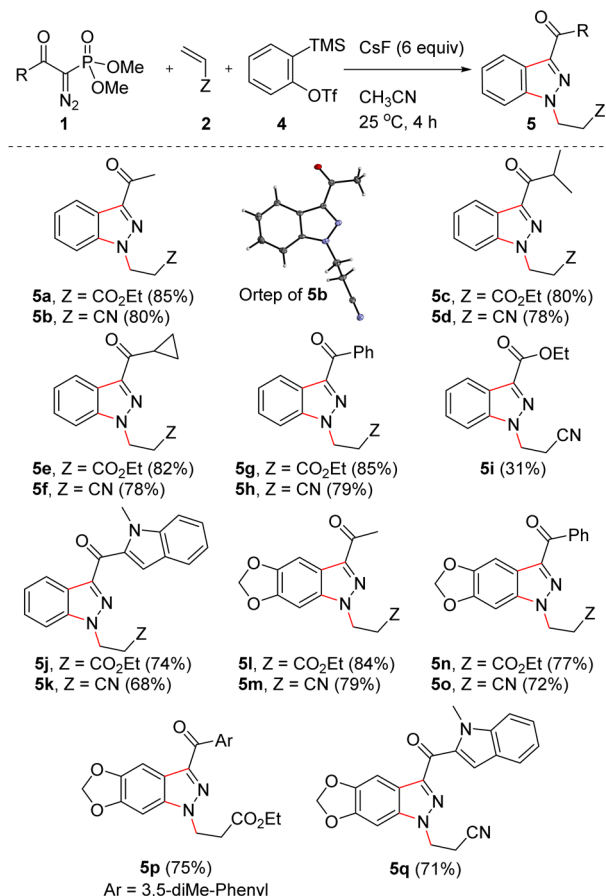
In this regard, we opted to use either acrylate or acrylonitrile to trap the intermediate N-H indazole (parent indazole: $pK_a \sim 13.86$)¹³ via an aza-Michael addition reaction.¹⁴ With this initial work, preliminary experiments were carried out by employing the benzyne precursor **4a** (1.1 equiv), OBR **1a** (1.0 equiv), and ethyl acrylate **2a** (1.1 equiv) and varied the concentration of CsF (3–6 equiv) in CH₃CN at room temperature. The results with 6 equiv of CsF were encouraging with the reaction being complete within 4 h. It gave the desired product **5a** from the expected (3 + 2) cycloaddition followed by Michael addition in 85% yield.

As observed previously, a change of fluoride source from CsF to TBAF and KF led to a large decrease in the yield of isolated **5a** from 85% to 36–57% (see Table SI-T2). With these results in hand, the scope and limitation of this (3 + 2) cycloaddition/aza-Michael addition process were examined employing various diazo phosphonates, aryne precursors, and ethyl acrylate/acrylonitrile as the Michael traps. We were pleased to observe that a wide range of diazo phosphonates containing both aliphatic and aromatic groups underwent (3 + 2)-cycloaddition followed by aza-Michael addition with aryne and acrylate/acrylonitrile very smoothly to furnish the corresponding 1,3-disubstituted indazole derivatives (**5a–h**) in good to excellent yields (Table 3). Next, various phosphonate derivatives were examined, including the indole-derived phosphonate **1h**. The reactions proceeded smoothly and provided the corresponding products in very good yields. The yields were found to be poor only with ethyl diazophosphonoacetate **1e**. Furthermore, the reaction of substituted aryne precursor **4b** under the standard conditions gave the corresponding indazoles in high yields.

Next, a series of control experiments was conducted to verify the fluoride-mediated C–P bond cleavage. As shown in Scheme 2, when the diazo phosphonate **1f** alone was stirred with CsF (3.0 equiv) for 2 h and its crude HRMS recorded, the peak corresponding to dimethyl phosphorofluoridate (**7**) [(HRMS (ESI⁺) calcd for C₂H₇O₃FP⁺ 129.0111, found 129.0113] could be seen. In addition, quenching the same reaction with water led to the isolation of 2-diazo-1-phenylethan-1-one (**6**) in 68% yield. The formation of **6** and **7** supports the proposed fluoride mediate C–P bond cleavage. Further, the reaction of two different diazo phosphonates **1f** and **1g** (1.1 equiv of each) with **2a** gave all possible crossover products (see the SI). This clearly suggested that the fluoride-mediated C–P bond cleavage is the first step, followed by the (3 + 2) cycloaddition and N-acylation of the resulting pyrazoles with OBR or the aza-Michael reaction of intermediate indazoles with conjugated olefins.

To conclude, here we have provided an answer to the puzzle of selectively attacking the phosphonate in the Ohira–Bestmann reagent and related α -diazo- β -carbonyl phosphonates. This method complements the acyl cleavage noticed with

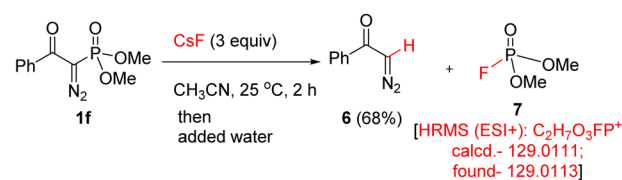
Table 3. Scope of 1,3-Disubstituted Indazole Synthesis^a



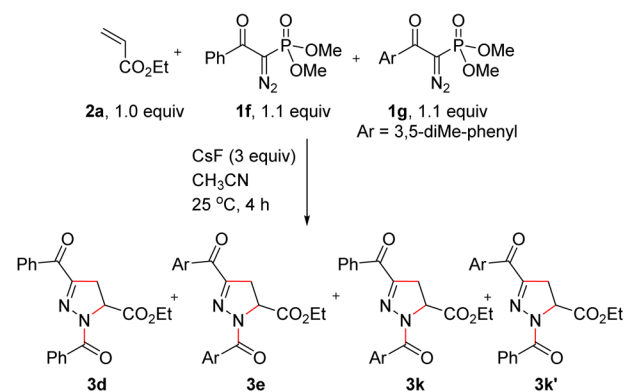
^aReaction conditions: **1** (0.25 mmol), **2** (1.1 equiv), and **4** (1.1 equiv) in CH₃CN (1 mL). Isolated yields are provided.

Scheme 2. Preliminary Mechanistic Investigation

a) Trapping of 2-diazo-1-phenylethan-1-one and characterization of dimethyl phosphorofluoridate



b) Crossover Experiment for Substituted 4,5-Dihydro-Pyrazole



both α -diazoacetoacetates and α -diazo- β -carbonyl phosphonates. The successful trapping of the intermediate α -

diazocarbonyl anions with conjugate olefins/benzyne complements the previous methods on carrying phosphonate in the end products. The isolation of 2-diazo-1-phenylethan-1-one and the tracing of the presence of intermediate dimethyl phosphorofluoridate by HRMS support our proposal of the fluoride-mediated dephosphonylation.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03573.

Experimental procedure, characterization of new compounds (^1H , ^{13}C NMR, HRMS spectra), and X-ray crystallographic data (PDF)

X-ray data for **3j** (CIF)

X-ray data for **5b** (CIF)

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Notes

The authors declare no competing financial interest.

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