(Diazomethyl)dimethylphosphine Oxide – A Diazoalkane Reagent for [3+2] Cycloadditions

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Dedicated to the people of Ukraine

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Abstract: A safe and efficient method for the in-situ preparation of (diazomethyl)dimethylphosphine oxide – a hereto unexplored diazoalkane reagent – is developed. The method is based on the diazotization of the corresponding $P(O)Me_2$-substituted amine (readily available in multigram quantities) in non-aqueous media. The protocol provides the target product as ca. 1.5 M $CHCl_3$ solution which is stable at –18 °C. The utility of the synthesized diazoalkane is illustrated by its [3+2] cycloaddition with electron-poor alkynes and alkenes providing the corresponding $P(O)Me_2$-substituted pyrazoles and pyrazolines with moderate to good efficiency. In this view, the title compound represents and an important extension of medicinally relevant phosphine oxide reagents.

Introduction

For many decades, phosphine oxides were infamous among chemists as annoying and difficult-to-separate by-products in many classical organic transformations, such as Wittig, Mitsunobu, or Appel reactions, as well as undesirable products of phosphine ligand oxidation.[1] In drug discovery and agricultural chemistry, these compounds were long overlooked and even considered unwanted,[2] despite the introduction of fosazepam, a water-soluble derivative of the well-known sedative diazepam, as early as in 1970s (Figure 1, *A*).[3] The situation changed in 2010s when several $P(O)Me_2$-substituted compounds entered clinical trials, and the anti-cancer agent brigatinib was approved by the FDA in 2017.[4,5] When introduced into a biologically active molecule, the phosphine oxide moiety can improve the compound's physicochemical properties and metabolic stability, provide additional possibilities for intermolecular non-covalent interactions, and enable isosteric replacements for a number of functional groups (Figure 1, *B*).[2]

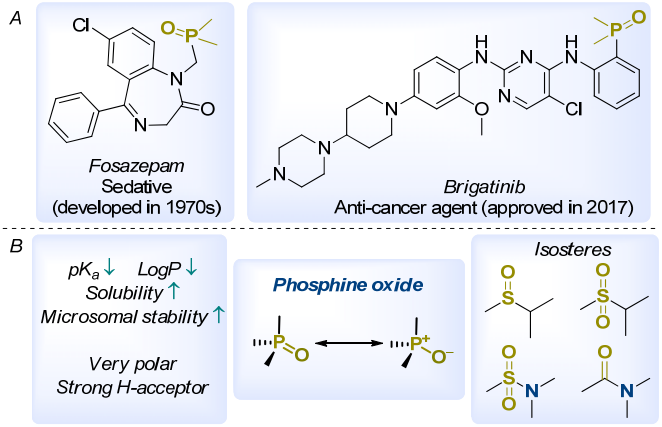
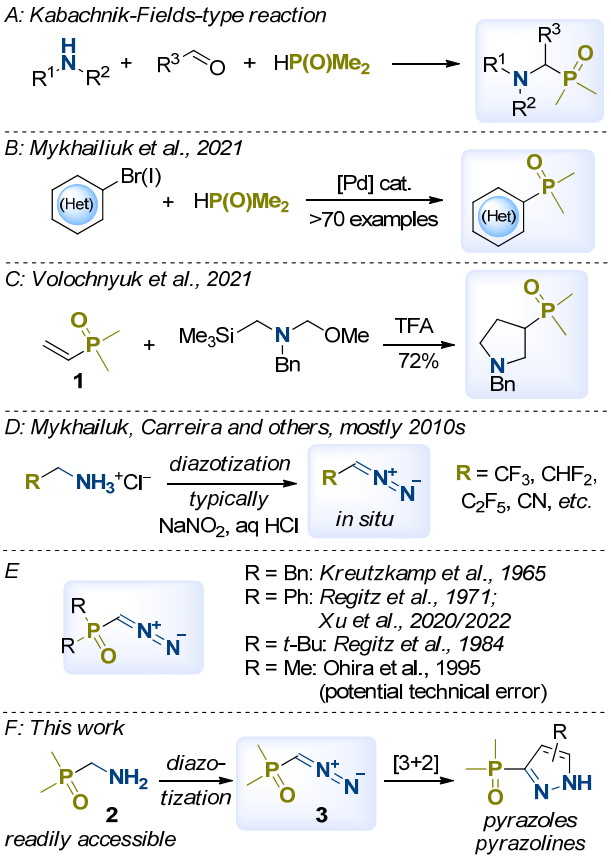


Figure 1. (*A*) Marketed drugs containing the $P(O)Me_2$ moiety. (*B*) Significance of phosphine oxides to medicinal chemistry.

Despite considerable interest to $P(O)Me_2$-substituted compounds in recent years, synthetic approaches for their preparation remain relatively scarce. A classical approach relies on the modified Kabachnik-Fields (phospha-Mannich) reaction (Scheme 1, *A*). Recently, we have applied this approach to the synthesis of $P(O)Me_2$-substituted saturated heterocyclic amines.[6] Also in 2021, Mykhailuk and co-authors reported preparation of (het)aryl-dimethylphosphine oxides through Pd-catalyzed C–P couplings (Scheme 1, *B*).[7]



Scheme 1. (*A–C*) Known approaches to $P(O)Me_2$-substituted compounds. (*D*) Recent developments in the safe preparation of diazoalkanes. (*E*) Some known α-diazo phosphine oxides. (*F*) (Diazomethyl)dimethylphosphine oxide (**3**) – key compound of this work.

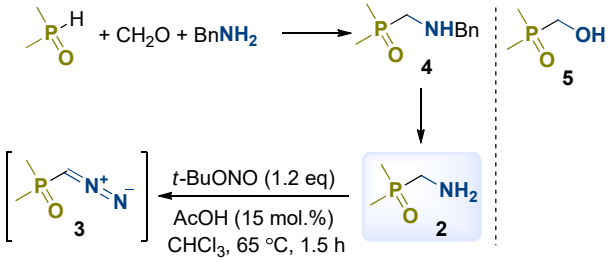
In both cases mentioned above, dimethylphosphine oxide ($HP(O)Me_2$) was used as the source of the $P(O)Me_2$ group. More sophisticated $P(O)Me_2$-substituted reagents are rare. For example, vinyldimethylphosphine oxide (**1**) was introduced into [3+2] cycloaddition with azomethine ylide (Scheme 1, *C*).[6]

Diazoalkanes are versatile reagents in organic synthesis that have become increasingly important in recent years due to the development of safe protocols for their in-situ generation.[8–12] While dialkyl diazophosphonates are widely recognized reagents in organic synthesis,[13,14] diazoalkanes with a phosphine oxide moiety are much rarer (Scheme 1, *E*),[15–18] and their reactivity is studied very scarcely. Thus, the simplest (diazomethyl)dimethylphosphine oxide (**3**) was only briefly mentioned by Ohira and co-workers in their 1995 communication.[19] No characterization or preparation details were provided by the authors. Furthermore, in the text, the compound was referred to as "dimethyl (diazomethyl)phosphonate", indicating a potential technical error in the schemes.

In this work, we have aimed at efficient in situ preparation of diazoalkane **3** via diazotization of amine **2** – a readily accessible building block (Scheme 1, *F*). Additionally, we have evaluated stability of compound **3** and its reactivity in [3+2] cycloaddition reactions with alkenes and alkynes, resulting in the formation $P(O)Me_2$-substituted pyrazoles and pyrazolines.

Results and Discussion

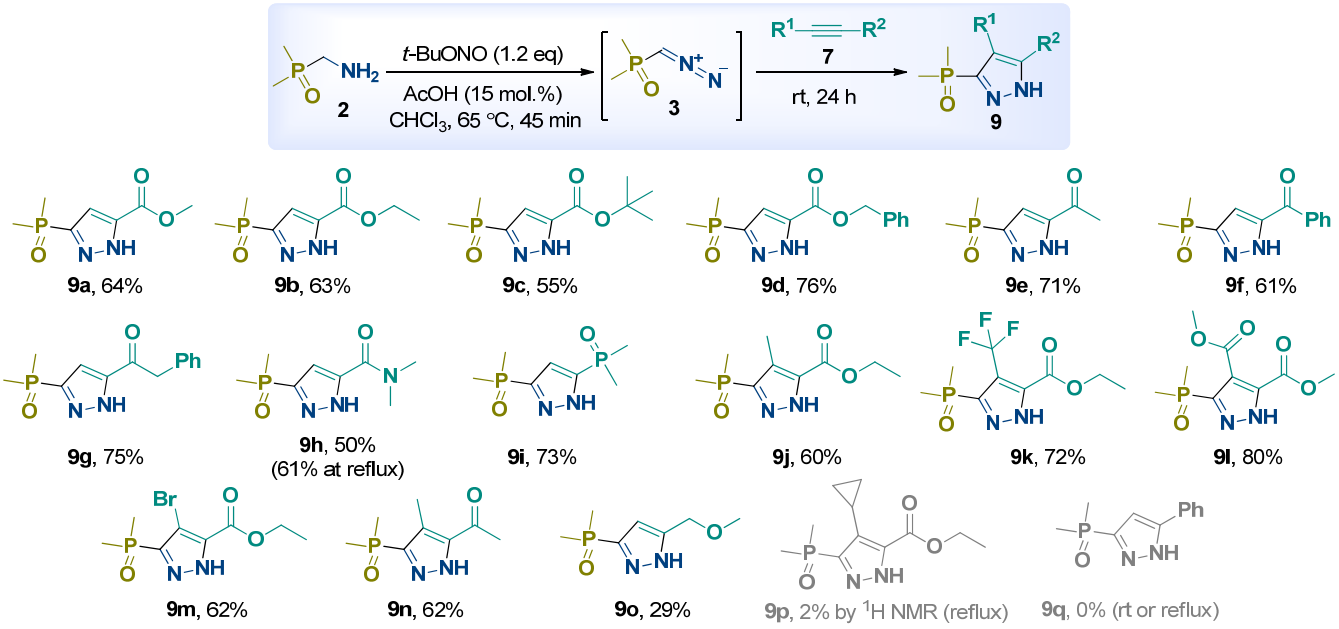
Our study commenced with preparation of amine **2** in multigram quantities. This compound was described by Mayer in 1990;[20] in our work, we have used a slightly modified reaction sequence (Scheme 2). In particular, we relied on the Kabachnik-Fields-type reaction reported by Kaukorat and co-workers for the first step (preparation of compound **4**).[21] In this way, compound **2** could be obtained on up to 50 g scale.



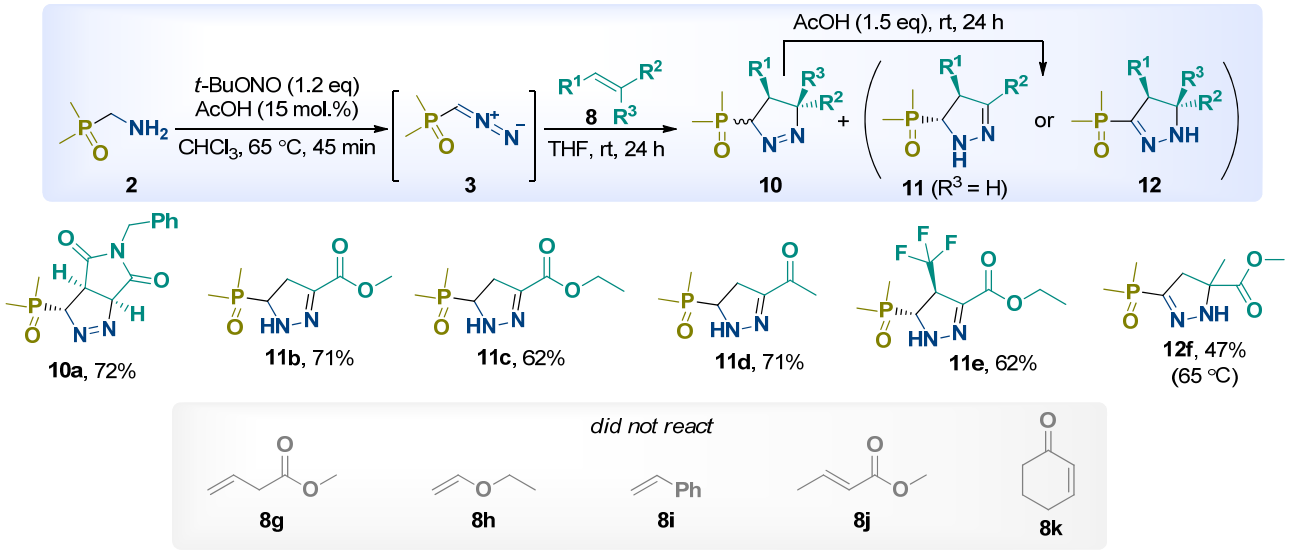
Scheme 2. Synthesis of amine **2** and its diazotization.

Initially, we have evaluated classical diazotization conditions for the compound **2** that were used for the preparation of other EWG-substituted diazoalkanes ($NaNO_2$, aq HCl). Unfortunately, no target diazoalkane **3** was detected in the reaction mixture; instead, formation of hydrolysis product **5** was observed by spectroscopic methods (Table S1 in the Supporting Information). Meanwhile, switching to anhydrous conditions (*t*-BuONO, cat. AcOH, CH_2Cl_2 or $CHCl_3$) resulted to the formation of target product **3**, which was confirmed by ^1H NMR spectroscopy. Further optimization of the reaction conditions allowed obtaining compound **3** as ca. 1.5 M solution in $CHCl_3$ in nearly quantitative yield (according to ^1H NMR spectra). Monitoring the reaction progress showed that the complete formation of diazoalkane **3** at 65 °C is observed after 1.5–2 h. Already after 3 h at this temperature, compound **5** started to form, along with other admixtures; after 17 h, no diazoalkane remained in the solution (see the Supporting Information). Slow decomposition of compound **3** was also observed at rt. Nevertheless, the solution was stable upon storage in a freezer at –18 °C for a month. After removal of the solvent, stability of the product diminished significantly: only a half of the diazoalkane remained after keeping the product at –18 °C for 40 h.

Having in hands an efficient protocol for the safe generation of diazoalkane **3** in solution, we have aimed at the demonstration of its reactivity in [3+2] cycloaddition reactions with various dipolarophiles. Thus, adding methyl propiolate (**7a**) to the solution of compound **3** at rt and keeping the reaction mixture for 24 h resulted in the formation of target pyrazole **9a** in 64% yield (Scheme 3). We have applied these conditions to a series of various alkynes **7b–q** and alkenes **8a–k**. With mono- and disubstituted alkynes bearing at least one strong electron-withdrawing group (**7a–n**), products **9a–n** were obtained in 55–75% yield. With sterically hindered alkyne **7p**, less than 2% conversion was observed by ^1H NMR spectroscopy at reflux; the corresponding product could not be isolated. In the case of phenylacetylene (**7q**) lacking a



Scheme 3. [3+2] cycloadditions of diazoalkane **3** with alkynes.



Scheme 4. [3+2] cycloadditions of diazoalkane **3** with alkenes.

strong electron-withdrawing group, no target products were observed either at rt or at reflux, and the starting dipolarophile was recovered. Intriguingly, alkyne **7o** with CH_2OMe group gave the target product in 29% yield from the reaction mixture that was kept at rt for 9 months.[22]

Reaction of diazoalkane **3** and alkenes **8** gave Δ^1-pyrazolines **10**, Δ^2-pyrazolines **11**/**12**, or mixtures thereof (Scheme 4). In the case of maleimide derivative **8a**, Δ^1-isomer **10a** precipitated from the reaction mixture and was isolated in 72% yield. With monosubstituted alkenes **8b–d**, mixtures of **10** and **11** initially formed (**11** : **10** = 70:30 to 85:15) were treated with AcOH (1.5 eq) at rt for 24 h. This manipulation led to their equilibration into **11b–d** that were isolated in 62–71% yield. In analogous manner, pyrazoline **11e** was obtained in 62% starting from *trans*-1,2-disubstituted alkene **8e**. In the case of 1,1-disubstituted alkene **8f**, product **12f** (47%) could be obtained after heating of the reactants at 65° C. Finally, alkenes **8g–k** did not react with diazoalkane **3** either at rt or at 65 °C.

Pyrazolines **10a** and **11e** were obtained as single diastereomers; their relative stereochemistry was confirmed by 2D NMR experiments (see the Supporting Information for more details).

Conclusions

In conclusion, a convenient and efficient protocol for the in-situ generation of $Me_2P(O)CHN_2$ (diazomethyl)dimethylphosphine oxide) was developed. The method relies on diazotization of the readily accessible $Me_2P(O)$-substituted amine under non-aqueous conditions (*t*-BuONO, AcOH) and provides the target diazoalkane as ca. 1.5 M solution in $CHCl_3$. The utility of this previously unexplored reagent is demonstrated by its [3+2] cycloaddition reactions with various dipolarophiles providing pyrazole/pyrazoline derivatives. It is shown that the scope of the method is limited by electron-poor alkenes and alkynes without significant steric hindrance. The reaction demonstrated high regio- and stereoselectivity. In the case of pyrazoline products, formation of Δ^1 and Δ^2 tautomers was typically observed; nevertheless, the corresponding mixtures could be easily equilibrated into pure Δ^2 isomers in the presence of AcOH. These results show that the title compound is an important addition to the scope of $Me_2P(O)$-substituted reagents, with special relevance to medicinal chemistry. We anticipate its further applications in early drug discovery projects, including a variety of other chemical transformations characteristic of diazoalkanes.

Experimental Section

The solvents were purified according to the standard procedures.[22] Compound **2** was prepared according to the reported procedures.[20,21] All other starting materials were available from Enamine Ltd. or purchased from other commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H}, ^{31}P{^{1}H} NMR spectra were recorded on a Agilent ProPulse 600 spectrometer (at 151 MHz for ^{13}C NMR), a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C{^{1}H} NMR, 470 MHz for ^{19}F{^{1}H} NMR, and 202 MHz for ^{31}P{^{1}H} NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C{^{1}H} NMR, 376 MHz for ^{19}F NMR, and 162 MHz for ^{31}P{^{1}H} NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C{^{1}H} in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C{^{1}H} in DMSO-d_6. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). High-resolution mass spectra (HRMS) were recorded on Agilent Infinity 1260 UHPLC system coupled to 6224 Accurate Mass TOF LC/MS system.

(Diazomethyl)dimethylphosphine oxide (3, ca. 1.5 M in $CHCl_3$). To a solution of (aminomethyl)dimethyphosphine oxide (**2**) (1.60 g, 15 mmol) in $CHCl_3$ (10 mL), *tert*-butyl nitrite (1.86 g, 18 mmol) and AcOH (0.11 mL, 2.25 mmol) were added at rt. The reaction mixture was stirred at this temperature for 10 min and then at 65 °C for 45 min. The resulting yellow solution contained ca. 1.5 M of the target product (nearly quantitative yield) that was used in the next step immediately without isolation. To record NMR spectra of product **3**, the reaction was performed in $CDCl_3$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (d, *J* = 13.9 Hz, 1H), 1.69 (d, *J* = 13.4 Hz, 6H). ^{31}P{^{1}H} NMR (202.4 MHz, $CDCl_3$) δ 33.6.

General procedure for the synthesis of pyrazoles 9. To a solution of diazoalkane **3** (7.0 mL, ca. 1.5 M in $CHCl_3$, ca. 10 mmol), a solution of alkyne **7** (5 mmol) in $CHCl_3$ (5 mL) was added. The resulting mixture was stirred at rt for 24 h. The precipitate formed was filtered and recrystallized from *t*-BuOMe or MeCN.

General procedure for the synthesis of pyrazolines 10–12. To a solution of diazoalkane **3** (7.0 mL, ca. 1.5 M in $CHCl_3$, ca. 10 mmol), a solution of alkene **8** (5 mmol) in THF (10 mL). was added. The resulting mixture was stirred at rt for 24 h. In the case of alkene **8a**, the precipitate formed was filtered and triturated with *t*-BuOMe (5 mL); the filtrate was evaporated in vacuo, and the residue was also triturated with *t*-BuOMe (2 mL). The solids were filtered, combined, and dried in vacuo. In other cases, AcOH (0.37 mL, 7.5 mmol) was added, and the mixture was stirred at rt for additional 24 h, then evaporated in vacuo. The residue was purified by column chromatography ($CHCl_3$ – MeOH (5:1 to 14:1) as eluent) or recrystallization from *t*-BuOMe or MeCN.

Supporting Information

The Supporting Information contains experimental details, compound characterization data, and copies of NMR spectra.

Acknowledgements

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Keywords: cycloaddition • diazoalkanes • phosphorus • pyrazoles • nitrogen heterocycles

Experimental Section

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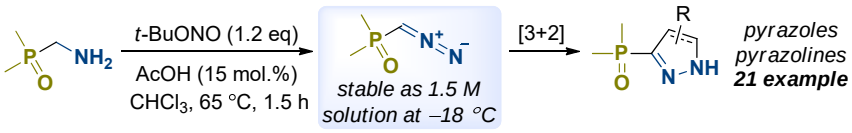
Diazoalkanes



An efficient protocol for the generation of (diazomethyl)dimethylphosphine – a novel diazoalkane reagent – based on the diazotization reaction under anhydrous conditions is described. The title compound can be prepared as ca. 1.5 M solution in chloroform and can be stored at –18 °C for at least a month. The proposed reagent readily undergoes [3+2] cycloaddition with various electron-poor alkynes and alkenes providing the corresponding $Me_2P(O)$-substituted pyrazoles and pyrazolines, respectively.

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