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A Multiheteroatom [3,3]-Sigmatropic Rearrangement: Disproportionative Entries into 2-(*N*-Heteroaryl)methyl Phosphates and α-Keto Phosphates

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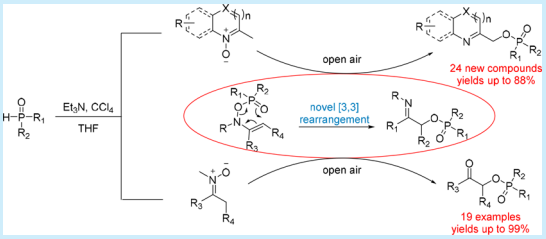
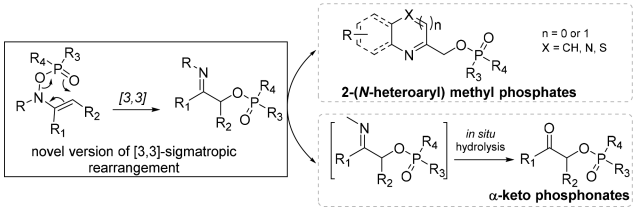
Supporting Information

ABSTRACT: A novel multiheteroatom (N, O and P) [3,3]-sigmatropic rearrangement is disclosed, based on two important types of organophosphates, 2-(*N*-heteroaryl) methyl phosphates and α-keto phosphates, being accessed smoothly and efficiently.



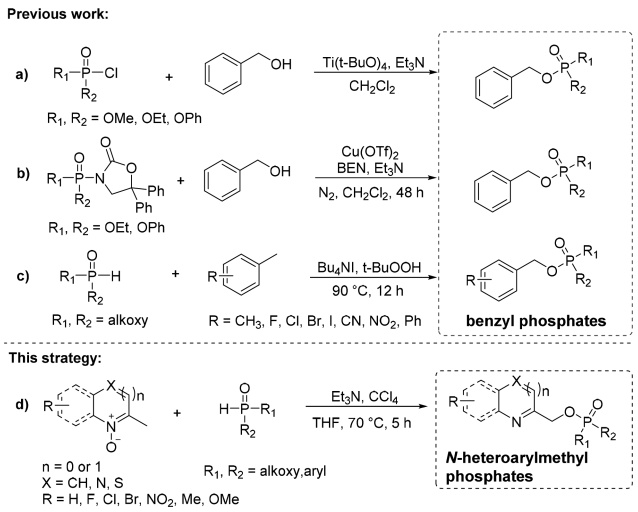
[3,3]-Sigmatropic rearrangements are among the most powerful intramolecular reactions in organic synthesis.[1] Since the discovery of the Claisen rearrangement by Rainer Ludwig Claisen in 1912, a number of different variants of [3,3]-rearrangement have been developed, including the well-known Cope rearrangement and Chen−Mapp reaction.[2] Here, we report a novel multiheteroatom (N, O, and P) variant of [3,3]-sigmatropic rearrangement, by means of which two synthetic strategies have been developed and successfully applied to the synthesis of two important types of organic compounds, 2-(*N*-heteroaryl) methyl phosphates and α-keto phosphates (Scheme 1).

Scheme 1. A [3,3]-Sigmatropic Rearrangement Route into Ketol Phosphates and Heteroarylmethyl Phosphates



Organophosphates have extensive applications in the fields of agrochemicals and pharmaceutical chemistry as well as industrial chemistry.[3] Organophosphate motifs also widely exist in a variety of biological molecules, such as DNA, RNA, ATP, lipids, etc.[4] Among numerous organophosphate derivatives, benzyl phosphates are often seen as important synthons in synthetic chemistry.[5] For example, the metal-catalyzed cross-coupling reaction of benzyl phosphates with aryl organometallics (or arylboronic acids or arylsilanes) is one of the most straightforward methods currently available for synthesizing diphenylmethanes,[6] a class of biologically and pharmaceutically important compounds.[7] Traditional approaches into benzyl phosphates use nucleophilic substitution reactions of benzyl alcohol with dialkylchlorophosphates [$(RO)_2P(O)-Cl$] in the presence of base (sometimes metal catalysis is needed) as shown in Scheme 2a.[8a,b] In 2005, the Jones group developed a similar method via copper-catalyzed phosphorylation of benzyl

Scheme 2. Comparison with Previous Work



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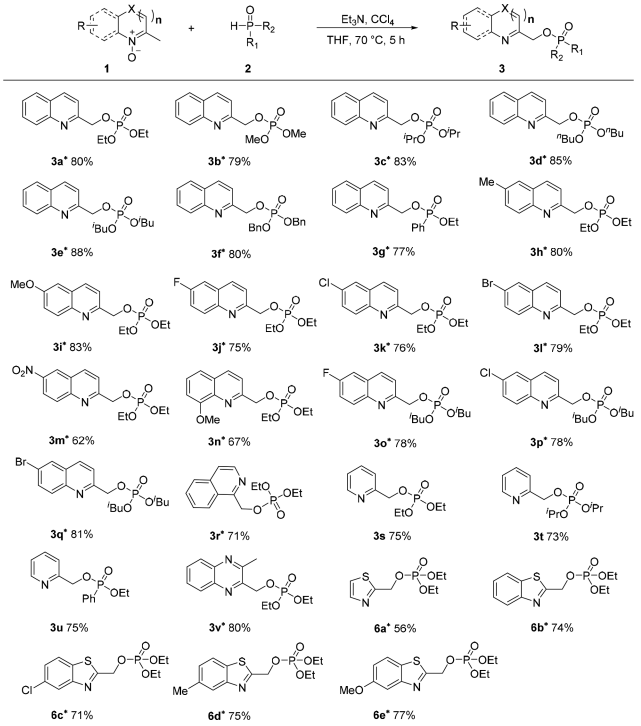
alcohol with *N*-phosphoryl oxazolidinones (Scheme 2b).[8c] In 2014, Tang's group developed a metal-free approach toward benzyl phosphates via reactions of substituted toluenes with dialkyl *H*-phosphonates in the presence of Bu_4NI and TBHP (Scheme 2c).[8d] Especially worth mentioning here is that all the above-mentioned approaches focused mainly on synthesizing benzyl phosphates. However, there are still no efficient approaches available for synthesizing heteroarylmethyl phosphates, another important class of arylmethyl phosphates. According to the literature, heterocycles are found in more than 90% of the new synthetic compounds with biological activity.[9] Quinolines, pyridines, quinoxalines, thiazoles, and benzothiazoles are among the most common heterocycles employed in medicinal and agricultural chemistry. Considerable effort has been dedicated to their synthesis and functionalization in the past.[10] Thus, facile and efficient synthetic methods toward diverse *N*-heteroarylmethyl phosphates are valuable. Here, we disclose a practical and simple synthetic method (Scheme 2d), by which a large variety of new *N*-heteroarylmethyl phosphates were prepared by the one-pot reaction of 2-methylheteroaromatic *N*-oxides with dialkyl *H*-phosphonates in the presence of CCl_4 and Et_3N.

We initiated our study by establishing optimal experimental conditions using the model reaction of 2-methylquinoline *N*-oxide (**1a**) with diethyl *H*-phosphonate (**2a**) in the presence of CCl_4 for 5 h, as summarized in Table S1. After intensive experimentation, the optimal reaction conditions were established as follows: **1a** (0.5 mmol), **2a** (5 equiv), Et_3N (4 equiv), and CCl_4 (0.5 mL) were mixed in THF at 70 °C for 5 h (yield 83%).

Having the optimal conditions in hand, we next examined the reaction scope with various 2-methylheteroaromatic *N*-oxides and organophosphorus reagents (Scheme 3). As can be seen, seven organophosphorus reagents, including diethyl-, dimethyl-, diisopropyl-, dibutyl-, diisobutyl-, and dibenzyl-*H*-phosphonates as well as ethyl phenylphosphinate, reacted smoothly with 2-methylquinoline *N*-oxide itself, giving the resulting (quinolin-2-ylmethyl) phosphates in good to satisfactory yields (**3a**−**3g**). Meanwhile, a series of substituted 2-methylquinoline *N*-oxides reacted well with diethyl *H*-phosphonate, affording the corresponding phosphates in moderate to good yields (**3h**−**3n**). Electronic effects were examined in cases of **3h**−**3m**. Electron-donating groups (Me, MeO) in the C6 position of quinoline ring resulted in relatively high yields (80% and 83%, respectively, **3h**−**3i**), whereas electron-withdrawing groups (F, Cl, Br, and NO_2) gave relatively low yields (**3j**−**3m**), with the most strongly electron-withdrawing nitro group giving the lowest yield (62%, **3m**). In comparison with diethyl *H*-phosphonate as in the cases of **3j**−**3l**, when three substituted 2-methylquinoline *N*-oxides bearing F, Cl, and Br reacted with diisobutyl *H*-phosphonate, another phosphorus reagent, relatively high yields were obtained (**3o**−**3q**). The method also worked well with 1-methylisoquinoline *N*-oxide (**3r**). To our surprise, this chemistry also proceeded well with many other 2-methylheteroaromatic *N*-oxides. For example, 2-methylpyridine *N*-oxide was capable of reacting with all the different phosphorus reagents mentioned above, affording the required phosphates **3s**−**3u** in good yields. 2,3-Dimethylquinoxaline *N*-oxide was capable of reacting with diethyl *H*-phosphonate, affording **3v** in good yield (80%). Moreover, thiazole, benzothiazole, and differentially substituted benzothiazoles were all suitable for reacting with diethyl *H*-phosphonate, affording **6a**−**6e** in good

Scheme 3. Scope of the Phosphorylation of 2-Methylheteroaromatic *N*-Oxides[a,b]

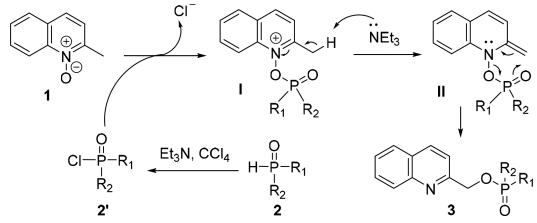


[a]Reaction conditions: **1** (0.5 mmol), **2** (5 equiv), Et_3N (4 equiv), CCl_4 (0.5 mL), THF (5.0 mL) for 5 h. [b]Isolated yields. * New compound.

yields. Among the 27 *N*-heteroarylmethyl phosphates synthesized, 24 are new compounds.

A mechanism based upon literature precedents is proposed as depicted in Scheme 4. According to the Atherton−Todd

Scheme 4. Proposed Mechanism



reaction,[11] dialkyl *H*-phosphonate **2** initially reacts with CCl_4 and Et_3N to form dialkylchlorophosphate **2′**. Following that, nucleophilic addition−elimination of 2-methyl quinolone *N*-oxide **1** to **2′** would give positively charged intermediate **I** together with a chloride anion. Et_3N removes the acidic hydrogen in **I**, giving neutral intermediate **II** which undergoes spontaneous [3,3]-rearrangement leading to the formation of dialkyl quinolin-2-ylmethyl phosphate **3**. The [3,3]-rearrangement is presumably driven by the fact that such a rearrangement can restore the energetically favorable aromatic framework of quinoline.

The mechanism was also investigated using the Gaussian 09 program. All the structures were optimized at the ωB97XD/6-311++(d, p) level in THF solvent using the integral equation formalism polarizable continuum model (IEF-PCM), then the corresponding frequency calculations at the same level were carried out for the Gibbs free energy correction, and more

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details can be found in the Supporting Information. As shown in Figure 1, the cation I^+ is deprotonated by Et_3N forming

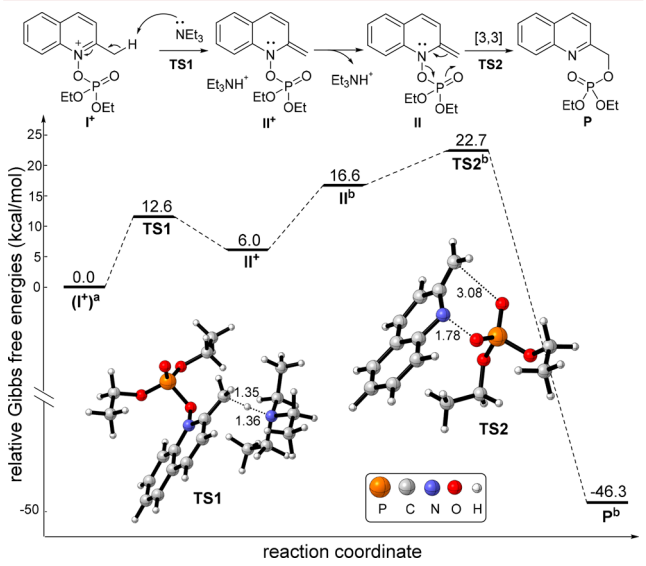
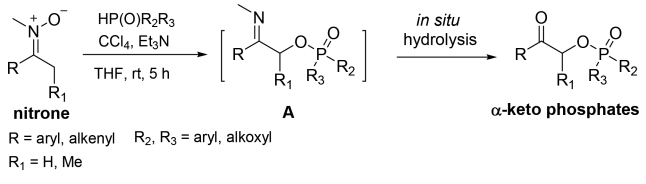


Figure 1. Energy profiles of the organic reaction (energy: kcal/mol, distance: Å); superscript "a" represents adding the energy of Et_3N, and superscript "b" represents adding the energy of Et_3NH^+.

intermediate **II** via transition state **TS1**, and then the intermediate **II** dissociates with Et_3NH^+ to generate intermediate **III**, which can be structurally transformed to product **P** via transition state **TS2**. The energy barrier of the whole process should be the energy difference between the reactants and transition state **TS2**, which is 22.7 kcal/mol, indicating the process can occur smoothly under the experimental conditions. Thus, far, efforts to locate the corresponding transition states when the Me group of **I** is changed to the Et group have been unsucessful. Attempts to experimentally observe the rearrangement with 2-ethylpyridine or quinoline systems have also been unsuccessful to this point.

We next set out to test the scope of this novel type of [3,3]-sigmatropic rearrangement. Scheme 5 shows that this method

Scheme 5. A New Synthesis toward α-Keto Phosphates

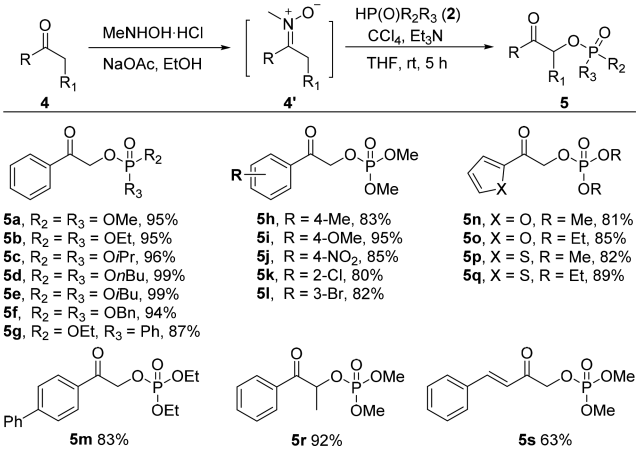


can be utilized to access biologically relevant α-keto phosphates, which serve as sugar analogs and important precursors for phospholipids and nucleotides.[12] Scheme 5 depicts our designed reaction, in which, in the presence of Et_3N and CCl_4, nitrone reacts with dialkyl *H*-phosphonates to give intermediate **A**, followed by *in situ* hydrolysis to yield the target product α-keto phosphates. Up to this point, only a limited number of synthetic methods toward α-keto phosphates have been reported.[13] In 1988, Koser et al. successfully developed a two-step synthetic method toward some α-keto phosphates.[13f] By comparison, the new method has some advantages, as it takes place under mild reaction conditions, with a simple operating procedure, uses readily available reactants, and gives a wide scope of products (for a detailed comparison of Koser's method with this method, see Supporting Information). Recently, Ahmed reported an approach toward α-keto phosphates, starting from dialkyl *H*-phosphonates addition into 1,2-dicarbonyl compounds, followed by C−P to O−P rearrangement promoted by a strong base.[13g] The method reported is milder and more practical and thus offers an elegant and practical alternative to the best available chemistry.

In 2000, Goldstein et al. developed a synthetic method for nitrone from ketone and MeNHOH.[14] Starting from this synthesis, we set up our model reaction to screen the optimal reaction conditions, in which acetophenone **4a** was first employed as the starting substrate to react MeNHOH to form nitrone **4a′**. After filtration and evaporation, the reaction residue was then treated with $(MeO)_2P(O)H$ **2b** and CCl_4 for 5 h to afford the α-keto phosphate **5a** (for details concerning optimization of reaction conditions, see Table S2). The optimal reaction conditions were finally established as follows: to be **4a** (0.5 mmol), **2b** (5 equiv), Et_3N (5 equiv), and CCl_4 (0.5 mL) were mixed in THF at 25 °C for 5 h (yield 95%).

With the optimal reaction conditions in hand, we next set out to examine substrate scope, as shown in Scheme 6. It can be

Scheme 6. Scope of the Phosphorylation of Nitrones[a,b]



[a]Reaction conditions: **4** (0.5 mmol), MeNHOH·HCl (1.5 equiv), NaOAc (3 equiv), EtOH (1 mL) at 25 °C for 3 days; filtration and solvent removal by vacuum evaporation; addition of **2** (5 equiv), Et_3N (5 equiv), CCl_4 (0.5 mL), and THF (5 mL) to the reaction residue, 25 °C, 5 h. [b]Isolated yield.

seen that various acetophenones, as well as all of the phosphorus reagents mentioned above (as shown in Scheme 3), were compatible with the newly developed synthesis, affording the corresponding α-keto phosphates in good to excellent yields (**5a**−**5m**). Indeed, 2-acetylfuran and 2-acetylthiophene, as well as propiophenone and 4-phenylbut-3-en-2-one, are suitable reactants, leading finally to the formation of the corresponding α-keto phosphates in good to excellent yields.

Following this, we performed two related scale-ups (gram level) as shown in Table S3 with the targeted reaction products (**3a** and **5a**) being obtained in good and excellent yields, respectively.

In conclusion, we report a novel multiheteroatom (N, O, and P) [3,3]-sigmatropic rearrangement, from which two strategies have been developed for synthesizing both 2-(*N*-heteroaryl) methyl phosphates and α-keto phosphates. A wide scope of *N*-

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heteroarylmethyl phosphates, including quinolin-2-ylmethyl phosphates, pyridin-2-ylmethyl phosphates, thiazol-2-ylmethyl phosphates, and benzothiazol-2-ylmethyl phosphates, was prepared by the one-pot reaction of 2-methylheteroaromatic *N*-oxides with dialkyl *H*-phosphonates in the presence of CCl_4 and Et_3N in THF for 5 h at 70 °C. The merits of the method include the use of readily available reactants, the considerable scope of substrates that are amenable to the chemistry, and the relatively mild conditions employed for the one-pot synthetic procedure. Using this approach, a large variety of biologically relevant α-keto phosphates were smoothly synthesized by reaction of nitrones with dialkyl *H*-phosphonates in the presence of CCl_4 and Et_3N in THF in one pot for 5 h at room temperature. Further studies on the applications of this strategy will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02852.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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