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Room Temperature DBN Initiated Phospha-Brook Rearrangement of α-Hydroxyphosphonates to Phosphates

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A series of substituted aryl phosphate esters have been synthesized from their α-hydroxyphosphonates substrates, using DBN (1,5 diazabicyclo(4.3.0)non-5-ene) at room temperature, via a phospha-Brook rearrangement. The aryl-substrate dependence of the rearrangement was explored, and excellent yields of the phosphate esters were achieved irrespective of whether the aryl moiety was activated or unactivated. A plausible mechanism for the rearrangement has been proposed. Based on the low temperature ^{31}P-NMR, the mechanism of the phospha-Brook rearrangement is proposed to take place via an oxaphosphirane intermediate.

Introduction

Organophosphorus compounds are prevalent in nature, and due to their distinct chemical properties, play an important role in many fields.[1] The synthesis of this class of compound has received much interest recently due to their antiviral, antibacterial, anticancer, pesticides and enzyme inhibitory activities.[2] Organophosphorus compounds also play an important role in organometallics, pharmaceutics, and photoelectric materials as a result of their high chelation affinity and easy manipulation to useful functionalities.[3]

Organophosphates are a class of compound that have been studied extensively as they play important roles in many physiological processes such as energy transfer and photosynthesis.[4] As a result, the synthesis of this class of compounds has recently been of significant interest. The traditional preparation of phosphates includes the phosphorylation of alcohols with phosphorus halides under basic conditions, however these halides are very hazardous and air sensitive.[5] The first rearrangement of an α-hydroxyphosphonate to a phosphate was investigated in the common insecticide trichlorfon.[6] Trichlorfon, a pro-drug, is transformed, via elimination of HCl, into 2,2-dichlorovinyl dimethyl phosphate an acetylcholinesterase inhibitor. Under basic conditions, the base mediated conversion of an α-hydroxyphosphonate to the corresponding phosphate is known as the phospha-Brook rearrangement. Strong bases such as NaOEt,[7] NaH,[8] and ^{t}BuOK[9] have been previously reported for the rearrangement reaction. Triethylamine catalyzed reactions only showed positive transformations in the presence of activated cyclic phosphonates due to ring strain.[9,10] More recently chiral homogeneous bases have resulted in promising yields for the phospha-Brook rearrangement.[11] Benzyl phosphates have also been synthesized in a one-pot tandem Pudovik reaction followed by the phospha-Brook rearrangement. This type of reaction was performed efficiently in the presence of BuLi, a strong base; the reaction is proposed to proceed via formation of an activated Li-diethyl phosphite followed by reaction with an aldehyde or ketone to form the corresponding carbanion intermediate.[12] Reactions were substrate dependent in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)[13] and the superbase DTD (diazatetracyclo[4.4.0.13,10.15,8]dodecane).[14] Electron withdrawing substituents on the aromatic ring have been reported to facilitate the phospha-Brook rearrangement, under milder reaction conditions, in comparison to electron-rich aryl substituents.[13,15,16]

The majority of the reactions reported to date have shortcomings as they require stoichiometric amounts of base, elevated temperatures, use of hazardous solvents and inconvenient handling procedures. Herein, we report the simple use of DBN (1,5-diazabicyclo(4.3.0)non-5-ene) activated phospha-Brook rearrangement of substituted α-hydroxyphosphonates to the corresponding benzyl phosphates under mild reaction conditions.

Results and Discussion

α-Hydroxyphosphonates were prepared using a modified version of the Pudovik reaction reported by Wadgaonkar.[17] Using a small excess of phosphite with 5 mol% of K_3PO_4 in dichloromethane, a range of α-hydroxyphosphonates were prepared in very good to excellent yields (Scheme 1).

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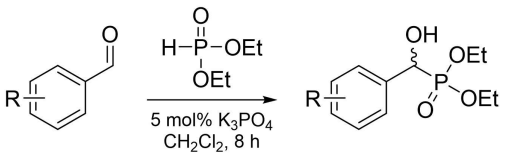


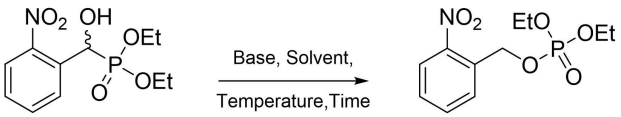
1a R= H	**2a** 94%
1b R= 4-Me	**2b** 94%
1c R= 2-NO_2	**2c** 93%
1d R= 3-NO_2	**2d** 90%
1e R= 4-NO_2	**2e** 85%
1f R= 2-CN	**2f** 62%
1g R= 3-CN	**2g** 91%
1h R= 4-CN	**2h** 80%
1i R= 2-OMe	**2i** 86%
1j R= 2-Cl	**2j** 91%
1k R= 3-Cl	**2k** 86%
1l R= 4-Cl	**2l** 85%
1m R= 4-F	**2m** 84%

Scheme 1. Synthesis of α-hydroxyphosphonates **2**.

The 2-nitro derivative **2c** was chosen as the model substrate to optimize conditions for the phospha-Brook rearrangement (Table 1).

Initially, the reaction was examined with different bases. Reaction of α-hydroxyphosphonate **2c** with sodium hydride in THF or acetonitrile at room temperature for 8 hours fortunately afforded the desired diethyl (hydroxy(2-nitrophenyl)methyl)phosphonate **3c** in 26% and 48% yield respectively (entries 1–2). The J_{POC} coupling constant observed for phosphate **3c** in the ^{13}C NMR was smaller (4.5 Hz) in comparison to the J_{PC} coupling constant in the starting α-hydroxyphosphonate **2c** (161.7 Hz) is ascribed to the benzylic carbon atom being further away from the phosphorus atom. Leaving the reaction for 16 hours improved the yield marginally to 58% (entry 3). The use of triethylamine unfortunately did not afford any of the desired product, whereas the use of inorganic bases such as potassium carbonate and potassium *t*-butoxide resulted in low yields (entries 4–6). Encouragingly employing non nucleophilic amidine bases DBU and DBN resulted in 82% and 85% of **3c** respectively at room temperature (entries 7–8). Quaternary ammonium salts have been previously used in the phospha-Brook rearrangement.[18] When 10% trioctylmethylammonium bromide was used in the presence of sodium hydroxide in a biphasic CH_2Cl_2 and water mixture a 75% yield of the desired product was isolated (entry 9). DBN was the best base and conditions were further optimized by changing solvent, concentration, time, temperature, equivalence and carrying the reaction out under atmospheric conditions (entries 10–19). Unfortunately, changing the solvent to THF resulted in a lower yield (62%) of **3c**. Altering the reaction concentration to 0.05 M or 0.2 M, with respect α-hydroxyphosphonate **2c**, resulted in slightly lower yields (82% and 83% respectively). Isolation of the desired product **3c** using DBN after 1 hour resulted in a detrimental yield (43%), whereas leaving the reaction for 16 hours improved the yield to 90%. Heating the reaction to 65 °C resulted in a lower yield (58%) however at 0 °C there was no significant change to the optimized conditions. Use of DBN as a catalytic base at room temperature only afforded the phosphate in 26% whereas two

Table 1. Optimization of the phospha-Brook rearrangement reaction conditions.



2c **3c**

Entry	Base [1 equiv.]	Solvent	Time [h]	Concentration [M]	Temperature [°C]	Yield [%]
1	NaH	THF	8	0.1	RT	26
2	NaH	MeCN	8	0.1	RT	48
3	NaH	MeCN	16	0.1	RT	58
4	NEt3	MeCN	8	0.1	RT	–
5	K2CO3	MeCN	8	0.1	RT	31
6	KtOBu	MeCN	8	0.1	RT	15
7	DBU	MeCN	8	0.1	RT	82
8	DBN	MeCN	8	0.1	RT	85
9	NaOH/Trioctylmethylammonium	CH2Cl2/H2O	8	0.1	RT	75
10	DBN	THF	8	0.1	RT	62
11	DBN	MeCN	8	0.05	RT	82
12	DBN	MeCN	8	0.2	RT	83
13	DBN	MeCN	1	0.1	RT	43
14	**DBN**	**MeCN**	**16**	**0.1**	**RT**	**90**
15	DBN	MeCN	8	0.1	0	89
16	DBN	MeCN	8	0.1	65	58
17[a]	DBN	MeCN	8	0.1	RT	26
18[b]	DBN	MeCN	8	0.1	RT	78
19[c]	DBN	MeCN	16	0.1	RT	83
20[d]	DBN	MeCN	8	0.1	RT	90

[a] Experiment was carried out using 0.5 eq. of DBN. [b] Experiment was carried out using 2 eq. of DBN. [c] Experiment was carried out under atmospheric conditions. [d] Experiment was carried out with an acid work up.

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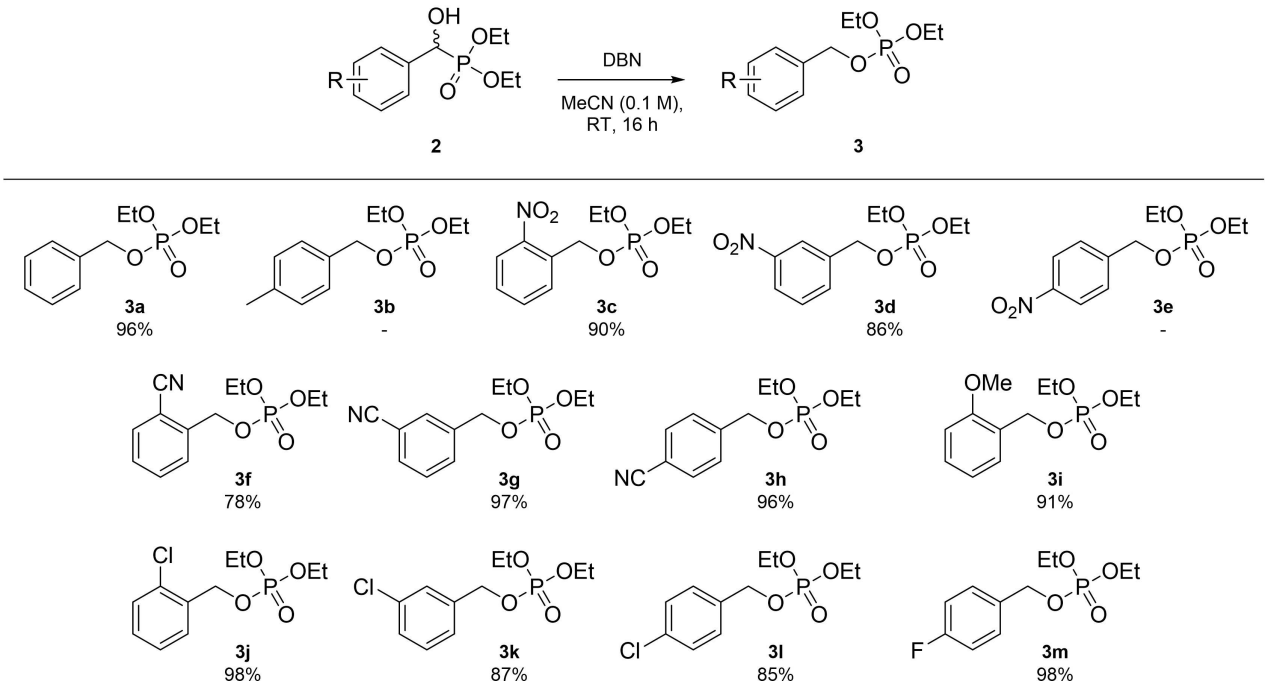


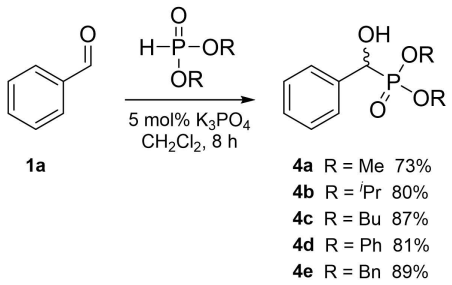
Scheme 2. Synthesis of diethyl (aryl) phosphates **3**.

equivalence of DBN resulted in a slightly lower yield of 78%. A slight decrease in the yield was observed when the reaction was undertaken using atmospheric conditions (entry 19). Acidic work up had no effect at the end of the reaction (entry 20). Optimal conditions for the phospha-Brook rearrangement were obtained under inert atmosphere, using 1 eq. of DBN at room temperature in 0.1 M acetonitrile for 16 hours (entry 14).

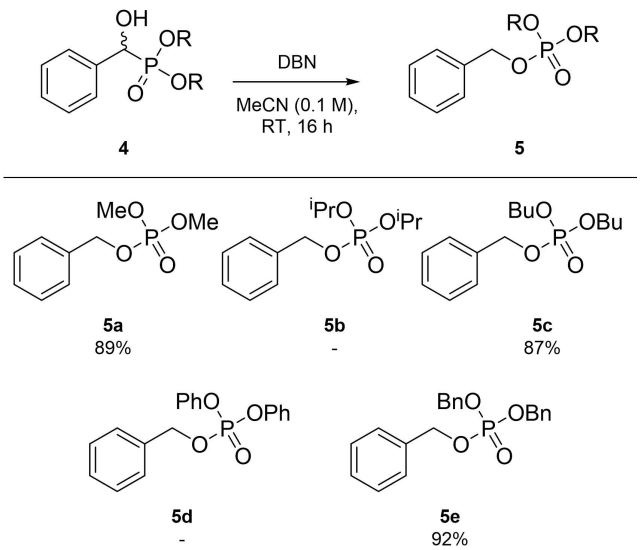
With the optimized conditions in hand, a range of organophosphates (**3a**–**3m**) were synthesized (Scheme 2). All the α-hydroxybenzyl-diethyl phosphonates **2** yielded the respective phosphates **3** in excellent yields with the exception of the 4-methyl and 4-nitro derivatives (**3b** and **3e**) which yielded recovered starting material, even when heated at higher temperatures. It is difficult to rationalize these exceptions,[2a,14] however in the case of the 4-methyl derivative **3b**, the α-hydroxybenzyl-dimethyl phosphonate derivative has only been reported to undergo the phospha-Brook rearrangement at elevated temperatures.[12a,19] The 4-nitro derivative **3e** has not been prepared using the phospha-Brook rearrangement and is typically synthesized via a chlorophosphate.[20] Results indicate that both electron rich and electron poor α-hydroxyphosphonates were well tolerated showing similar reactivity to produce the corresponding phosphates in very good yields unlike in previous studies.[13,15,16]

The substrate scope was further explored by preparation of a series of α-hydroxybenzyl phosphonate diester derivatives in excellent yields using the method reported previously using K_3PO_4 (Scheme 3).[17]

The obtained α-hydroxybenzyl phosphonate diesters were subjected to the optimal phospha-Brook rearrangement reaction conditions (Scheme 4). The dimethyl, **4a**, dibutyl, **4c**, and dibenzyl, **4e**, α-hydroxybenzyl phosphonates yielded the rear-



Scheme 3. Synthesis of benzyl dialkyl phosphonates **4**.



Scheme 4. Attempted synthesis of benzyl dialkyl phosphates **5**.

ranged phosphate products in excellent yields. Unfortunately, the diisopropyl, **4b**, and diphenyl, **4d**, derivatives did not yield any of the corresponding phosphates. This has been attributed to the steric clash between the larger DBN base and larger ester groups. This finding agrees with that reported by Ahmed *et al.* where no phosphate product was detected when α-hydroxybenzyl phosphonates were treated with potassium *t*-butoxide.[21]

The mechanism for the phospha-Brook rearrangement α-hydroxymethylphosphonates to phosphates has been recently studied by Keglevich using quantum chemical calculations.[18] Keglevich has proposed that initially a deprotonation of the α-hydroxyphosphonate takes place to form the anion **7**. The anion attacks the phosphorus atom affording the oxaphosphirane intermediate **8**, followed by P–C bond fission and rearrangement via the benzyl anion **9** (Scheme 5). These theoretical findings are in agreement with those reported by Zhang *et al.* who carried out mechanistic studies for the one-pot transformation of phosphoric esters from aldehydes and secondary phosphine oxides.[16]

In order to better understand the mechanism for this transformation, the phospha-Brook rearrangement of 2-nitro α-hydroxyphosphonate **2c** with DBN was investigated *in situ* using NMR; the ^{31}P-NMR signals of the reaction mixture were monitored at different time intervals at 0 °C (Figure 1). The peak at 21.4 ppm (peak A) is representative of the 2-nitro α-hydroxyphosphonate **2c** and the corresponding phosphate **3c** appears at −0.8 ppm (peak B). After 30 min a new peak appeared at 8.6 ppm (peak C) in the ^{31}P NMR. With the progress of the reaction this increases a small amount by 5 hours and receded by the end of the reaction (24 hours). This observation could perhaps demonstrate that peak C is an intermediate which is formed *in situ* during the reaction and gradually converted to the product (peak B). NMR spectra of oxaphosphiranes have only been reported as metal complexes and therefore direct comparisons cannot be made.[22] However, the four membered oxaphosphetane ring has been reported to appear at 6.4 ppm in the phosphorus NMR.[23] Due to the similarity of the strained P–O ring system, peak B has tentatively been assigned to the oxaphosphirane intermediate **8** proposed previously. Studies by Chatterjee tentatively assigned intermediates for the phospha-Brook rearrangement between diethyl phosphite and acetophenone as a result of stabilization through coordination of the Li^+ ion to either the oxygen atom of the P=O or OEt of the ester moiety.[12b] In our experiment, the intermediate signal differs from that previously reported because the reaction commenced from the α-hydroxyphosphonate **2c** and as a result of an organic base being used, no stabilization to a metal cation through the oxygen atoms is possible. A further cross-over experiment between hydroxyphosphonates **2c** and **4a** resulted in only in intramolecular phospha-Brook rearrangement products, **3c** and **5a**, reinforcing formation of intermediate **8** as peak C observed in the NMR study.

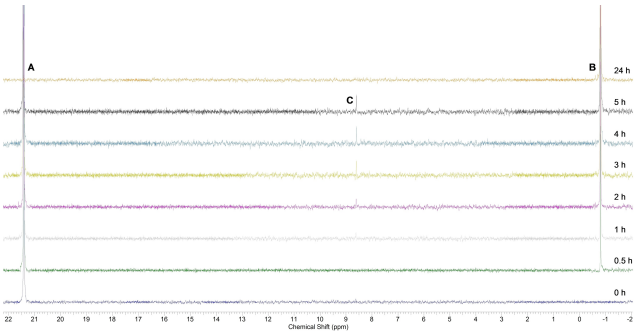
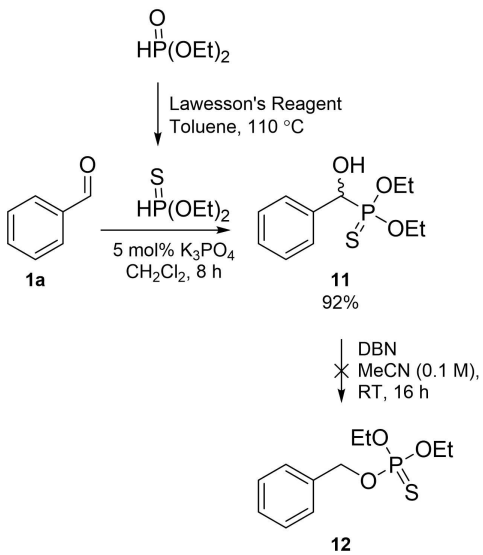
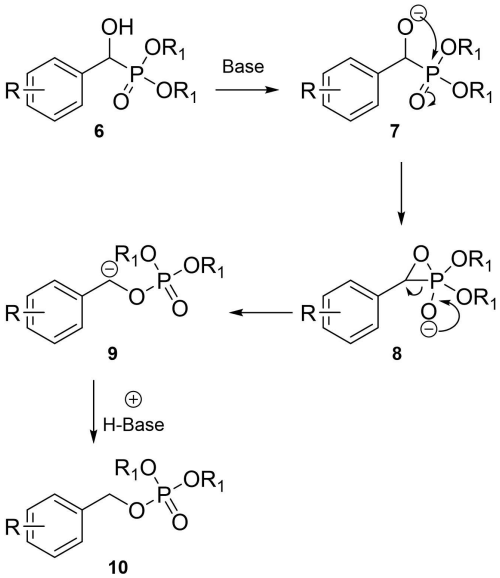


Figure 1. ^{31}P-NMR study of the phospha-Brook rearrangement.



Scheme 6. Synthesis of *O*, *O*-diethyl (hydroxy(phenyl)methyl)thiophosphonate **12**.



Scheme 5. Proposed mechanism for the phospha-Brook rearrangement.

The formation of the oxaphosphirane **8** was explored further by replacing the oxygen atom in the P=O bond of phosphonate by a sulfur atom (Scheme 6).[24,25] Thiophosphonates are reported to show less electrophilicity of phosphorus in comparison to the phosphonate,[26,27] implying formation of the oxaphosphirane would be slowed down or not occur. The α-hydroxythiophosphonate **11** was prepared using Lawesson's reagent.[24] When subjected to the rearrangement reaction with DBN, no reaction was observed and starting material was recovered suggesting oxaphosphirane formation was not occurring.

Conclusion

In summary, the phospha-Brook rearrangement of α-hydroxyphosphonates has been optimized using equimolar amounts of DBN in acetonitrile at room temperature for 16 hours. A range of phosphate diesters have been produced successfully in excellent yields using this method, with the exception of the 4-methyl, 4-nitro derivatives, which have been synthesized previously using elevated temperatures or starting from a chlorophosphate, and the benzyl-diisopropyl **5b** and benzyl-diphenyl **5d** phosphate derivatives possibly due to steric hindrance. A mechanistic NMR study has indicated the possible formation of an intermediate in the phospha-Brook rearrangement, which has been tentatively ascribed as the oxaphosphirane **8**, supporting previous quantum chemical calculations.[12b,18] Further investigation into the synthetic applications of these phosphates is currently in progress.

Experimental Section

General procedure for the synthesis of substituted diethyl (hydroxy(aryl)methyl)phosphonates (**2**): To a stirred mixture of an aromatic aldehyde (1 eq.) and diethyl phosphite (1.1 eq.) in dichloromethane (2 mL) was added potassium phosphate (0.05 eq.) and stirred for 8 h at room temperature. Dichloromethane (40 mL) was added. After stirring for five minutes, the catalyst was separated by centrifugation (10,000 rpm for 10 min) and organic extract was decanted into a round bottom flask and concentrated under reduced pressure. The solid was filtered and washed with a 9:1 mixture of hexane: diethyl ether (20 mL) to give the α-hydroxy diethyl phosphonates as the product.

General procedure for the synthesis of diethyl (aryl) phosphates (**3**): To α-hydroxy diethyl phosphonate (1 eq.) in acetonitrile (0.1 M) was added DBN (1 eq.) and stirred at room temperature for 16 h. The reaction was concentrated under reduced pressure and the crude residue was purified by column chromatography (2:8 hexane: diethyl ether) to give the phosphate as the product.

General procedure for the synthesis of dialkyl (hydroxy(phenyl)methyl)phosphonates (**4**): To a stirred mixture of a benzaldehyde (1 eq.) and dialkyl phosphite (1.1 eq.) in dichloromethane (2 mL) was added potassium phosphate (0.05 eq.) and stirred for 8 h at room temperature. Dichloromethane (40 mL) was added. After stirring for five minutes, the catalyst was separated by centrifugation (10,000 rpm for 10 min) and organic extract was decanted into a round bottom flask and concentrated under reduced pressure.

General procedure for the synthesis of substituted benzyl dialkyl phosphates (**5**): To α-hydroxyphosphonate (1 eq.) in acetonitrile (0.1 M) was added DBN (1 eq.) and stirred at room temperature for 16 h. The reaction was concentrated under reduced pressure and the crude residue was purified by column chromatography (2:8 hexane: diethyl ether) to give the phosphate as the product.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: α-Hydroxyphosphonate · Mechanistic studies · Phospha-Brook rearrangement · Phosphate ester · Pudovik reaction

[1] W. Ren, Q. Yang, S. Yang, *Pure Appl. Chem.* **2019**, *91*, 87–94.
[2] a) A. Szymańska, M. Szymczak, J. Boryski, J. Stawiński, A. Kraszewski, G. Collu, G. Sanna, G. Giliberti, R. Loddo, P. La Colla, *Bioorg. Med. Chem.* **2006**, *14*, 1924–1934; b) A. H. Kategaonkar, R. U. Pokalwar, S. S. Sonar, V. U. Gawali, B. B. Shingate, M. S. Shingare, *Eur. J. Med. Chem.* **2010**, *45*, 1128–1132; c) L. Wu, X. Yuan, G. Yang, C. Xu, Z. Pan, L. Shi, C. Wang, L. Fan, *J. Saudi Chem. Soc.* **2021**, *25*, 101273.
[3] Q. Chen, Y. Teng, F. Xu, *Org. Lett.* **2021**, *23*, 4785–4790.
[4] a) P. G. Loncke, P. J. Berti, *J. Am. Chem. Soc.* **2006**, *128*, 6132–6140; b) C. Meier, *Angew. Chem. Int. Ed.* **1993**, *32*, 1704–1706; *Angew. Chem.* **1993**, *105*, 1854–1856; c) F. H. Westheimer, S. Huang, F. Covitz, *J. Am. Chem. Soc.* **1988**, *110*, 181–185; d) F. H. Westheimer, *Science* **1987**, *235*, 1173–1178; e) N. H. Williams, P. Wyman, *Chem. Commun.* **2001**, 1268–1269; f) R. Wolfenden, C. Ridgway, G. Young, *J. Am. Chem. Soc.* **1998**, 833–834.
[5] S. Pisarek, H. Bednarski, D. Gryko, *Synlett* **2012**, 2667–2671.
[6] W. Lorenz, A. Henglein, G. Schrader, *J. Am. Chem. Soc.* **1955**, *77*, 2554–2556.
[7] N. Long, X. J. Cai, B. A. Song, S. Yang, Z. Chen, P. S. Bhadury, D. Y. Hu, L. H. Jin, W. Xue, *J. Agric. Food Chem.* **2008**, *56*, 5242–5246.
[8] X. C. Huang, M. Wang, Y. M. Pan, X. Y. Tian, H. S. Wang, Y. Zhang, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5283–5289.
[9] S. Kumaraswamy, R. S. Selvi, K. C. K. Swamy, *Synthesis* **1997**, 207–212.
[10] Z. Rádai, G. Keglevich, *Molecules* **2018**, *23*, 1493.
[11] M. Hayashi, S. Nakamura, *Angew. Chem. Int. Ed.* **2011**, *50*, 2249–2252; *Angew. Chem.* **2011**, *123*, 2297–2300.
[12] a) G. Pallikonda, R. Santosh, S. Ghosal, M. Chakravarty, *Tetrahedron Lett.* **2015**, *56*, 3796–3798; b) S. Ranga, M. Chakravarty, T. Chatterjee, S. Ghosal, *New J. Chem.* **2019**, *43*, 9886–9890.
[13] L. El Kaim, L. Gaultier, L. Grimaud, A. Dos Santos, *Synlett.* **2005**, 2335–2336.
[14] J. Galeta, M. Potáček, *J. Mol. Catal. Chem.* **2014**, *395*, 87–92.

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doi.org/10.1002/ejoc.202201101

[15] Z. Rádai, *Phosphorus Sulfur Silicon Relat. Elem.* **2019**, *194*, 425–437.
[16] Y. Qian, Q. Dai, Z. Li, Y. Liu, J. Zhang, *Org. Lett.* **2020**, *22*, 4742–4748.
[17] M. A. Kulkarni, U. P. Lad, U. V. Desai, S. D. Mitragotri, P. P. Wadgaonkar, *C. R. Chim.* **2013**, *16*, 148–152.
[18] Z. Rádai, R. Szabó, A. Szigetvári, N. Z. Kiss, Z. Mucsi, G. Keglevich, *Curr. Org. Chem.* **2020**, *24*, 465–471.
[19] N. Z. Kiss, Z. Rádai, R. Szabó, Y. Aichi, L. Laasri, S. Sebti, *Phosphorus Sulfur Silicon Relat. Elem.* **2019**, *194*, 370–371.
[20] M. McLaughlin, *Org. Lett.* **2005**, *7*, 4875–4878.
[21] S. Khan, S. Battula, Q. N. Ahmed, *Tetrahedron* **2016**, *72*, 4273–4279.
[22] N. Volk, P. Malik, A. G. Alcaraz, A. E. Ferao, R. Streubel, *Coord. Chem. Rev.* **2021**, *437*, 213818.
[23] S. Kojima, M. Sugino, S. Matsukawa, M. Nakamoto, K. Y. Akiba, *J. Am. Chem. Soc.* **2002**, *124*, 7674–7675.
[24] C. M. Jessop, A. F. Parsons, A. Routledge, D. J. Irvine, *Eur. J. Org. Chem.* **2006**, 1547–1554.
[25] S. Pignard, C. Lopin, G. Gouhier, S. R. Piettre, *J. Org. Chem.* **2006**, *71*, 31–37.
[26] J. A. A. Ketelaar, H. R. Gresmann, K. Koopmans, *Rec. Trav. Chim. Pays-Bas* **1952**, *71*, 1253–1258.
[27] I. H. Um, K. Akhtar, Y. H. Shin, J. Y. Han, *J. Org. Chem.* **2007**, *72*, 3823–3829.

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