Phosphorylation of 2-Aryl Quinoxaline Derivatives via C-H/P-H Cross Coupling under Transition-Metal-Free Conditions

Rahman Karimi-Nami, Mehdi Adib, Forouzan Heydari, Saeideh Rajai-Daryasarei, and Idris Karakaya

ABSTRACT
In this study, we have developed an efficient protocol for synthesis of phosphorus-substituted heterocycles through reaction between 2-Aryl quinoxalines and dialkyl phosphites under transition-metal-free conditions. Here, K$_2$S$_2$O$_8$ has been used as the sole oxidant for the facile synthesis of phosphorus substituted derivatives. A variety of heteroaryl phosphonate derivatives have been synthesized under optimized conditions in good to excellent yields with this facile and environment friendly protocol.

ARTICLE HISTORY
Received 16 July 2021
Accepted 13 September 2021

KEYWORDS
Phosphorus-substituted heterocycles; 2-Aryl quinoxalines; dialkyl phosphites; C-H activation

Introduction
Organophosphorus based molecules are highly important in organic chemistry due to their wide spectrum biological properties and synthetic applications. These compounds have been used as bioactive molecules in medicinal chemistry, as privileged ligands for transition-metal catalysis and organocatalysts as building blocks in organic synthesis and also employed as additives or flame-retardants in polymer sciences. In light of their importance, development of efficient synthetic methods for construction of the carbon-phosphorus bond has been a recurring research focus since many years. The classical strategies for C—P bond construction commonly rely on the transition-metal catalyzed cross-coupling reaction and these reactions involve coupling between carbon nucleophiles such as organometallic reagents with an electrophilic P-reagent.

More recently, methods for the construction of C-P bonds through the addition of P-centered radicals to unsaturated systems leading to synthesis of organophosphorus compounds has grown in interest. Generally, P-centered radicals are obtained from radical initiators such as peroxides, azo compounds, manganese salts, R$_3$B/O$_2$, Ag/K$_2$S$_2$O$_8$, etc. Phosphorus-substituted heterocycles are class of compounds found in many biologically active molecules and advanced functional materials. Recently, Cui and coworkers reported an approach for the direct phosphorylation of quinoxalin-2(1H)-ones under the metal-free condition by using K$_2$S$_2$O$_8$ as an oxidant to generate a phosphorous-centered radical. As a continuation of our interest in reactions through such a radical pathway, herein, we have described the synthesis of 3-phosphonated quinoxalines with K$_2$S$_2$O$_8$ as an oxidant between various 2-aryl quinoxalines and dialkyl H-phosphonates in PhCl at 80 °C (Scheme 1).
Results and discussion

Initially the reaction of 2-phenylquinoxaline \(1a\) with dimethyl phosphite \(2a\) was carried out in the presence \(\text{K}_2\text{S}_2\text{O}_8\) as an oxidant in chlorobenzene under ambient atmosphere (Table 1). Dimethyl (3-phenylquinoxalin-2-yl)phosphonate \(3a\) was obtained in 14\% yield at room temperature for 3 h. Then we performed a series of screening reactions for increasing the yield of the desired product \(3a\) (entry 1). Therefore, The effect of different parameters such as oxidants, reaction solvents, and reaction temperature were investigated. The corresponding product was obtained in 63\% and 88\% yield at 50\°C and 80\°C respectively (entries 2 and 3). Elevation in temperature (100\°C and 120\°C) led to reduction in product yield. (entry 4 and 5). By increasing amount of \(\text{K}_2\text{S}_2\text{O}_8\) to 3 eq. or 4 eq., no improvement was observed and even a slight decrease in yield (84\% and 82\%) was observed (entry 6 and 7). Reaction was carried out in presence of different solvents like DCE, CH\(_3\)CN, Toluene, DMSO, and H\(_2\)O to improve the yield,. From the

![Scheme 1. Direct phosphonation of quinoxaline derivatives under transition-metal-free condition.](image)

| Entry | Oxidant (eq.) | Temp \(\text{o} \text{C}\) | Solvent | Yield (%)[b] |
|-------|---------------|-----------------|---------|--------------|
| 1     | \(\text{K}_2\text{S}_2\text{O}_8\) (2.0) | rt              | PhCl    | 14           |
| 2     | \(\text{K}_2\text{S}_2\text{O}_8\) (2.0) | 50              | PhCl    | 63           |
| 3     | \(\text{K}_2\text{S}_2\text{O}_8\) (2.0) | 80              | PhCl    | 88           |
| 4     | \(\text{K}_2\text{S}_2\text{O}_8\) (2.0) | 100             | PhCl    | 73           |
| 5     | \(\text{K}_2\text{S}_2\text{O}_8\) (2.0) | 120             | PhCl    | 70           |
| 6     | \(\text{K}_2\text{S}_2\text{O}_8\) (3.0) | 80              | PhCl    | 84           |
| 7     | \(\text{K}_2\text{S}_2\text{O}_8\) (4.0) | 80              | PhCl    | 82           |
| 8     | \(\text{K}_2\text{S}_2\text{O}_8\) (2.0) | 80              | DCE     | 55           |
| 9     | \(\text{K}_2\text{S}_2\text{O}_8\) (2.0) | 80              | CH\(_3\)CN | 63         |
| 10    | \(\text{K}_2\text{S}_2\text{O}_8\) (2.0) | 80              | Toluene | 78           |
| 11    | \(\text{K}_2\text{S}_2\text{O}_8\) (2.0) | 80              | DMSO    | N.R[c]       |
| 12    | \(\text{K}_2\text{S}_2\text{O}_8\) (2.0) | 80              | H\(_2\)O | N.R          |
| 13    | \((\text{NH}_4)\text{S}_2\text{O}_8\) (2.0) | 80              | PhCl    | 87           |
| 14    | TBHP[d] (2.0) | 80              | PhCl    | 20           |
| 15    | BPO[e] (2.0)  | 80              | PhCl    | 19           |
| 16    | H\(_2\)O\(_2\)[f] (2.0) | 80              | PhCl    | 21           |
| 17    | \(\text{K}_2\text{S}_2\text{O}_8\) (2.0) | 80              | PhCl    | 80           |
| 18    | \(\text{K}_2\text{S}_2\text{O}_8\) (2.0) | 80              | PhCl    | 79           |
| 19    | –              | 80              | PhCl    | N.R          |

[a] Reaction conditions: \(1a\) (0.2 mmol), \(2a\) (0.5 mmol), oxidant, solvent (1 mL) for 3 h. [b] Isolated yield. [c] No reaction. [d] 70 wt\% \(\text{tBuOOH}\) in H\(_2\)O. [e] Benzoylperoxide. [f] 30 wt\% H\(_2\)O\(_2\) in H\(_2\)O. [g] Ratio of \((1a:2a): 1:3. [h] Ratio of \((1a:2a): 1:4.}
solvents, DCE, CH$_3$CN and toluene afforded the target product $3a$ in 55-78% yields (entries 8–10). Reaction did not proceed in DMSO and H$_2$O (entries 11 and 12). Different oxidants such as (NH$_4$)$_2$S$_2$O$_8$, TBHP, BPO and H$_2$O$_2$, were used and (NH$_4$)$_2$S$_2$O$_8$ provided $3a$ in 87% yield (entry 13). While TBHP, BPO and H$_2$O$_2$ provided desired product in modest yields (19–22%) (entries 14–16). In addition, the effect of reagent stoichiometry was examined by varying the ratio of Quinoxaline 1a/dimethyl phosphite 2 from 1:3 to 1:4 (entries 17 and 18). These results indicated no effect of additional phosphite on reaction turnover. The original 2.5 equiv. dimethyl phosphite was found to be the best choice to give the desired product in 88% yield (entry 3). As expected, in the absence of K$_2$S$_2$O$_8$ (entry 19), formation of $3a$ was not detected and this indicated the importance of K$_2$S$_2$O$_8$ for this reaction.

With optimized reaction conditions in hand, the substrate scope of coupling of various 2-aryl quinoxalines with dialkyl H-phosphonates was then investigated. The results are summarized in Scheme 2. A variety of 2-aryl quinoxalines bearing electron-rich (H, Me and OMe) and electron-withdrawing (Cl) moieties at different position of the aryl ring were reacted with dimethyl phosphite and diethyl phosphite to afford the corresponding products $3a$–f and $3h$–l in good to
excellent yields. In addition, 1-naphthyl substituted quinoxaline was tolerated under the optimal conditions, which provided the product 3g in 75% yield.

According to the proposed mechanism, firstly heat catalyzes the homolytical cleavage of persulfate to form two highly oxidizing sulfate radicals 4. These can perform H-atom abstraction on the weak P-H bond 2 to form the phosphine centered radical 5. The phosphine centered radical can then add into a transiently protonated heterocycle to form a Minisci type intermediate 6. Then, a subsequent H-atom abstraction/deprotonation sequence can result in the desired phosphonated product 3a-l.

**Conclusions**

In summary, we have described the synthesis of 3-phosphonated quinoxalines by using 2-aryl quinoxaline derivatives and commercially available dialkyl phosphite as a P-radical precursor. Various 3-phosphonated quinoxalines were prepared with good to excellent yields. The K$_2$S$_2$O$_8$ was employed as the sole oxidant for the formation of C(sp$^2$)-P bonds under transition-metal-free conditions.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**Funding**

This research was supported by the Research Council of the University of Tehran.

**ORCID**

Idris Karakaya [http://orcid.org/0000-0002-3590-7206](http://orcid.org/0000-0002-3590-7206)
References

1. J. L. Montchamp, “Phosphinite Chemistry in the 21st Century: A Viable Alternative to the Use of Phosphorus Trichloride in Organophosphorus Synthesis,” *Accounts of Chemical Research* 47, no. 1 (2014): 77–87.

2. C. Queffelec, M. Petit, P. Janvier, D. A. Knight, and B. Bujoli, “Surface Modification Using Phosphonic Acids and Esters,” *Chemical Reviews* 112, no. 7 (2012): 3777–807.

3. H. Hussain, A. Al-Harrasi, A. Al-Rawahi, I. R. Green, and S. Gibbons, “Fruitful Decade for Antileishmanial Compounds from 2002 to Late 2011,” *Chemical Reviews* 114, no. 20 (2014): 10569–428.

4. F. R. Alexandre, A. Amador, S. Bot, C. Caillet, T. Convard, J. Jakubik, C. Musiu, B. Poddesu, L. Vargiu, M. Liuzzi, et al. “Synthesis and Biological Evaluation of Aryl-Phospho-Indole as Novel HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors,” *Journal of Medicinal Chemistry* 54, no. 1 (2011): 392–5.

5. X. Chen, D. J. Kopecky, J. Mihalic, S. Jeffries, X. Min, J. Heath, J. Deignan, S. Lai, Z. Fu, C. Guimaraes, et al. “Structure-Guided Design, Synthesis, and Evaluation of Guanine-Derived Inhibitors of the eIF4E mRNA-Cap Interaction,” *Journal of Medicinal Chemistry* 55, no. 8 (2012): 3837–51.

6. W. Tang, and X. Zhang, “New Chiral Phosphorus Ligands for Enantioselective Hydrogenation,” *Chemical Reviews* 103, no. 8 (2003): 3029–70.

7. Y. N. Ma, S. X. Li, and S. D. Yang, “New Approaches for Biaryl-Based Phosphine Ligand Synthesis via P=O Directed C-H Functionalizations,” *Accounts of Chemical Research* 50, no. 6 (2017): 1480–92.

8. H. Ni, W. Yao, A. Waheed, N. Ullah, and Y. Lu, “Enantioselective [4 + 2]-Annulation of Oxadienes and Allenones Catalyzed by an Amino Acid Derived Phosphate: Synthesis of Functionalized Dihydropyranas,” *Organic Letters* 18, no. 9 (2016): 2138–41.

9. Tsuneyuki Sato, Makoto Hasegawa, Makiko Seno, and Tomohiro Hirano, “Radical Polymerization Behavior of Dimethyl Vinylphosphonate: Homopolymerization and Copolymerization with Trimethoxyvinylsilane,” *Journal of Applied Polymer Science* 109, no. 6 (2008): 3746–52.

10. Dominik Lanzinger, Stephan Salzinger, Benedikt S. Soller, and Bernhard Rieger, *Poly(Vinylphosphonate)s as Macromolecular Flame Retardants for Poly carbonate,* *Industrial & Engineering Chemistry Research* 54, no. 6 (2015): 1703–12.

11. B. Yang, T. T. Yang, X. A. Li, J. J. Wang, and S. D. Yang, “A Mild, Selective copper-catalyzed oxidative phosphorylation of z-amino ketones ,” *Organic Letters* 15, no. 19 (2013): 5024–7.

12. C. G. Feng, M. Ye, K. J. Xiao, S. Li, and J. Q. Yu, “Pd(II)-Catalyzed Phosphorylation of Aryl C-H Bonds,” *Journal of the American Chemical Society* 135, no. 25 (2013): 9322–5.

13. L. Goudray, and J. L. Montchamp, “Recent Developments in the Addition of Phosphinylidene-Containing Compounds to Unactivated Unsaturated Hydrocarbons: Phosphorus-Carbon Bond-Formation via Hydrophosphinylation and Related Processes,” *European Journal of Organic Chemistry* 2008, no. 21 (2008): 3601–13.

14. Zhiyue Geng, Yudan Zhang, Lu Zheng, Jingya Li, Dapeng Zou, Yangjie Wu, and Yusheng Wu, “Pd-Catalyzed C-P Coupling of Heteroaryl Boronic Acid with H-Phosphonate Diester,” *Tetrahedron Letters* 57, no. 29 (2016): 3063–6.

15. D. Redmore, “Heterocyclic Systems Bearing Phosphorus Substituents. synthesis and Chemistry,” *Chemical Reviews* 71, no. 3 (1971): 314–7.

16. C. S. Demmer, N. Krogsgaard-Larsen, and L. Bunch, “Review on Modern Advances of Chemical Methods for the Introduction of a Phosphonic Acid Group,” *Chemical Reviews* 111, no. 12 (2011): 7981–8006.

17. H. Zhang, W. Li, and C. Zhu, “Copper-Catalyzed Cascade Phosphorylation Initiated Radical Cyclization: Access to 2-Phosphorylated Pyrrolo[1,2-a]Indole,” *The Journal of Organic Chemistry* 82, no. 4 (2017): 2199–204.

18. X. T. Zhu, Q. Zhao, F. Liu, A. F. Wang, P. J. Cai, W. J. Hao, S. J. Tu, and B. Jiang, “Silver-Mediated Radical 5-Exo-Dig Cyclization of 2-Alkynylbenzonitriles: Synthesis of Phosphinylated 1-Indenones,” *Chemical Communications (Cambridge, England)* 53, no. 51 (2017): 6828–31.

19. Y.-L. Zhu, D.-C. Wang, B. Jiang, W.-J. Hao, P. Wei, A.-F. Wang, J.-K. Qiu, and S.-J. Tu, “Metal-Free Oxidative Hydrophosphinylation of 1,7-Enynes,” *Organic Chemistry Frontiers* 3, no. 3 (2016): 385–93.

20. K. Luo, Y. Z. Chen, W. C. Yang, J. Zhu, and L. Wu, “Cross-Coupling Hydrogen Evolution by Visible Light Photocatalysis toward C(sp2)-P Formation: Metal-Free C-H Functionalization of Thiazole Derivatives with Diarylphosphine Oxides,” *Organic Letters* 18, no. 3 (2016): 452–5.

21. Christophe Lamarche, Florent Beaufils, Fabrice Dénès, Kurt Schenk, and Philippe Renaud, “Preparation of 5-Membered Rings via Radical Addition- Translocation-Cyclization (RATC) Processes Mediated by Diethyl Thiophosphites,” *Advanced Synthesis & Catalysis* 353, no. 8 (2011): 1353–8.

22. T. Wada, A. Kondoh, H. Yorimitsu, and K. Oshima, “Intermolecular Radical Addition of Alkylthio- and Arylthiodiphenylphosphines to Terminal Alkynes,” *Organic Letters* 10, no. 6 (2008): 1155–7.
23. S. Gouault-Bironneau, S. Deprele, A. Sutor, and J. L. Montchamp, “Radical Reaction of Sodium Hypophosphite with Terminal Alkynes: Synthesis of 1,1-bis-H-Phosphinates,” *Organic Letters* 7, no. 26 (2005): 5909–12.

24. P. Rey, J. Taillades, J. C. Rossi, and G. Gros, “Et3B-Induced Radical Addition of Diphenylphosphine Oxide to Unsaturated Compounds,” *Tetrahedron Letters* 44, no. 32 (2003): 6169–71.

25. C. B. Xiang, Y. J. Bian, X. R. Mao, and Z. Z. Huang, “Coupling Reactions of Heteroarenes with Phosphites under Silver Catalysis,” *The Journal of Organic Chemistry* 77, no. 17 (2012): 7706–10.

26. X. Mao, X. Ma, S. Zhang, H. Hu, C. Zhu, and Y. Cheng, “Silver-Catalyzed Highly Regioselective Phosphonation of Arenes Bearing Electron-Withdrawing Groups,” *European Journal of Organic Chemistry* 2013, no. 20 (2013): 4245–8.

27. P. Zhou, B. Hu, L. Li, K. Rao, J. Yang, and F. Yu, “Mn(OAc)3-Promoted Oxidative Csp3-P Bond Formation through Csp2-Csp2 and P-H Bond Cleavage: Access to β-Ketophosphonates,” *The Journal of Organic Chemistry* 82, no. 24 (2017): 13268–76.

28. X. Q. Pan, J. P. Zou, G. L. Zhang, and W. Zhang, “Manganese(III)-Mediated Direct Phosphonation of Arylalkenes and Arylalkynes,” *Chemical Communications (Cambridge, England)* 46, no. 10 (2010): 1721–3.

29. R. F. Roush, E. M. Nolan, F. Lohr, and C. T. Walsh, “Maturation of an Escherichia coli Ribosomal Peptide Antibiotic by ATP-Consuming N-P Bond Formation in Microcin C7,” *Journal of the American Chemical Society* 130, no. 11 (2008): 3603–9.

30. L. Zhou, H. W. Zhang, S. Tao, L. Bassit, T. Whitaker, T. R. McBrayer, M. Ehteshami, S. Amiralaei, U. Pradere, J. H. Cho, et al., “β-D-2′-C-Methyl-2,6-diaminopurine Ribonucleoside Phosphoramidates are Potent and Selective Inhibitors of Hepatitis C Virus (HCV) and Are Bioconverted Intracellularly to Bioactive 2,6-Diaminopurine and Guanosine 5′-Triphosphate Forms,” *Journal of Medicinal Chemistry* 58, no. 8 (2015): 3445–58.

31. S. O. Jeon, and J. Y. Lee, “Comparison of Symmetric and Asymmetric Bipolar Type High Triplet Energy Host Materials for Deep Blue Phosphorescent Organic Light-Emitting Diodes,” *Journal of Materials Chemistry* 22, no. 15 (2012): 7239.

32. H. Onouchi, T. Miyagawa, A. Furuko, K. Maeda, and E. Yashima, “Enantioselective Esterification of Prochiral Phosphonate Pendants of a Polyphenylacetylene Assisted by Macromolecular Helicity: Storage of a Dynamic Macromolecular Helicity Memory,” *Journal of the American Chemical Society* 127, no. 9 (2005): 2960–5.

33. M. Gao, Y. Li, L. Xie, R. Chauvin, and X. Cui, “Direct Phosphonation of Quinoxalin-2(1H)-Ones under Transition-Metal-Free Conditions,” *Chemical Communications (Cambridge, England)* 52, no. 13 (2016): 2846–9.

34. M. Adib, R. Pashazadeh, S. Rajai-Daryasarei, R. Kabiri, and S. Gohari, “Transition-Metal-Free Acylation of Quinolines and Isoquinolines with Arylmethanols via Oxidative Cross-Dehydrogenative Coupling Reactions,” *Synlett* 27, no. 15 (2016): 2241–5.

35. M. Adib, S. Rajai-Daryasarei, R. Pashazadeh, M. Tajik, and P. Mirzaei, “Regioselective Transition Metal-Free Acylation of Coumarins via Cross-Dehydrogenative Coupling Reaction of Coumarins and Aldehydes,” *Tetrahedron Letters* 57, no. 33 (2016): 3701–5.

36. M. Adib, R. Pashazadeh, S. Rajai-Daryasarei, R. Kabiri, and M. Jahani, “Transition Metal-Free Cross-Dehydrogenative Coupling Acylation of Coumarins by the K2S2O8/Aliquat 336 Catalytic System: A Versatile Strategy towards 4-Aroylcoumarin Derivatives,” *RSC Advances* 6, no. 112 (2016): 110656–60.