

Cite this: *Org. Chem. Res.* 2023, Vol. 9, 1-5.
DOI: 10.22036/org.chem.2024.443923.1325

Advanced Methods for the Synthesis of Nitro Compounds

Hassan Sepehrmansourie^a, Mahmoud Zarei^b

^aDepartment of Organic Chemistry, Faculty of Chemistry and Petroleum Sciences, Bu-Ali Sina University, Hamedan, Iran. Email: sepehr9129@yahoo.com

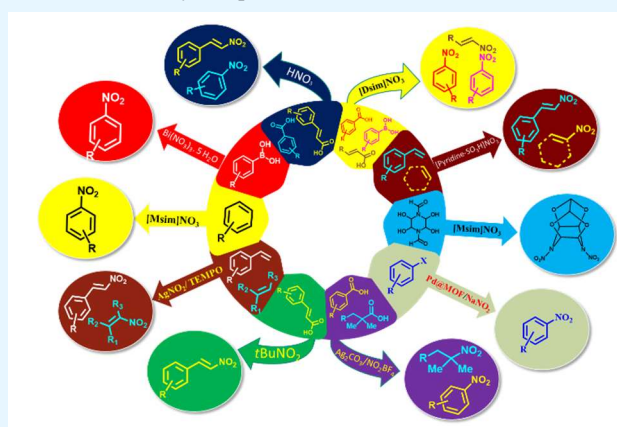
^bDepartment of Chemistry, Faculty of Science, University of Qom, Qom, 3716146611, Iran. Email: mahmoud8103@yahoo.com

Received: February 12, 2024; Accepted: March 30, 2024

Minireviews-Spotlight: Herein, the synthesis of various nitro compounds has been studied by the ipso-nitration reaction and other methods.

Abstract: The chemistry of nitration reactions is a powerful tool for the synthesis of pharmaceutical molecules and biological compounds. Carbon-nitrogen (C-N) bond formation is one of the most important reactions in organic synthesis, which plays a key role in the synthesis of biologically active and targeted molecules. Nitro compounds are very useful and have shown their importance in various medical, environmental and military fields for the synthesis of energetic and explosive compounds. Nitration reactions are conducted through various methods and employing diverse reagents, illustrating the multiplicity of their synthesis pathways. Diversifying the chemistry of nitro compounds offers a promising avenue for generating novel targeted molecules, showcasing the potential of these substances and the method itself. The objective herein is to highlight a selection of reagents and pathways for synthesizing nitro compounds that have garnered significant interest from research groups in recent years.

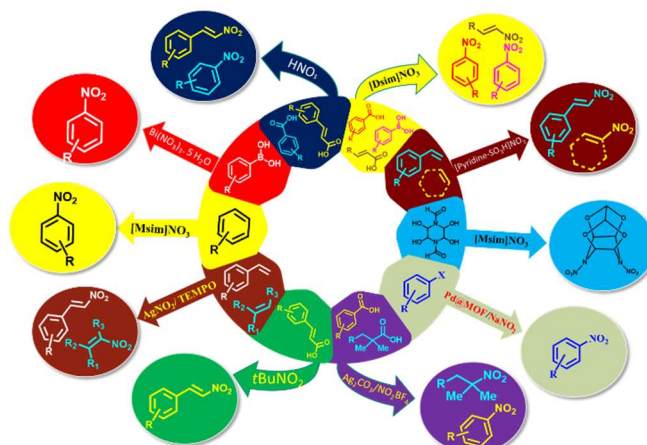
Keywords: Catalysis, Ipso nitration, Nitration, Nitro compounds, Selective nitration.



1. Introduction

Nitro compounds are playing important roles in organic chemistry because of their applications in the preparation of chemical intermediates for the synthesis of dyes, plastics, perfumes, energetic materials, and pharmaceuticals [1]. The electrophilic nitration of organic materials is one of the most extensively studied organic reactions, which involves the use of $\text{HNO}_3/\text{H}_2\text{SO}_4$ as a nitrating mixture under harsh reaction conditions. This method is challenged by issues of regioselectivity, resulting in the production of isomeric mixtures and oxidation byproducts. Thus, the advancement of a green chemistry approach and a straightforward procedure for regioselective nitration holds substantial value in the realm of nitro organic compounds. Nevertheless, many existing techniques face several limitations, such as low yields, extended reaction durations, excessive nitration, the necessity for substantial catalyst quantities, diminished regioselectivity, reagent oxidation, and safety concerns. Therefore, designing an efficient nitration protocol is still of practical importance. Research efforts toward regioselective nitration led to the discovery of ipso and Hunsdiecker reaction as a promising approach [2]. Olah and co-workers reported the first to ipso-nitration from aryl boronic acids, using Crivello's reagent (ammonium nitrate/trifluoro acetic anhydride) for this conversion [3]. The ipso-nitration reaction, employed for the

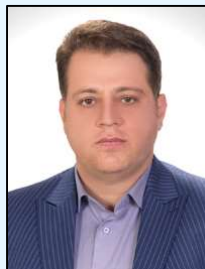
synthesis of a wide variety of nitro compounds, is a practical alternative to the classical electrophilic nitration reaction. Many groups such as alkyls, acyls, boric acids, esters, halogens, sulfonic acids and carboxylic acids can be replaced by a nitro group [4]. Herein, the synthesis of various nitro compounds has been studied by the ipso-nitration reaction and other methods (Scheme 1).



Scheme 1. Some reagents used in the synthesis of nitro compounds

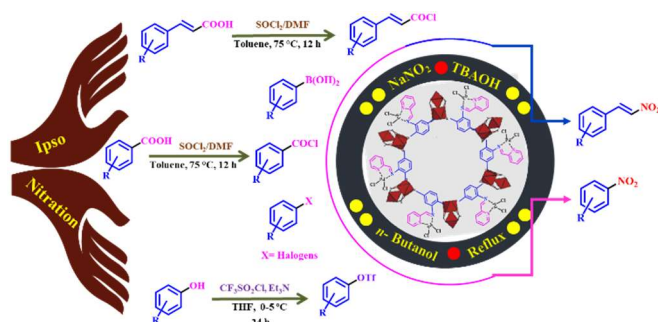


Hassan Sepehrmansourie was born in Hamedan, Iran in 1994. He received his B.Sc. in Applied Chemistry (2017) from Bu-Ali Sina University, Iran. He received his M.Sc. in Organic Chemistry (2019) under the supervision of Prof. Mohammad Ali Zolfigol. Also, He was accepted for a Ph.D. in organic chemistry at the Bu-Ali Sina University in the same year. He is a graduate of the PhD course in organic chemistry from Bu-Ali Sina University, Iran (2023). His research interest is the synthesis, characterization and applications of homogeneous and heterogeneous reagents and catalysts in organic synthesis. He has published more than 30 scientific articles in international journals.



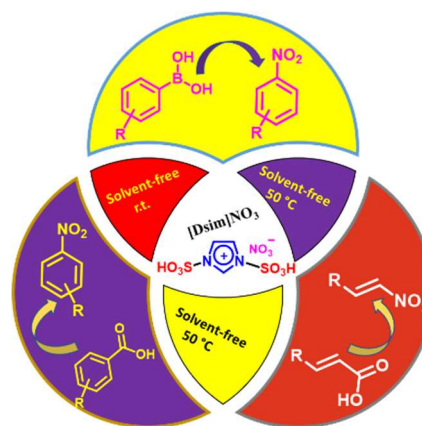
Mahmoud Zarei was born in Hamedan, Iran in 1986. He received his B.Sc. in Pure Chemistry (2010) and M.Sc. in Organic Chemistry (2013). Also, he received his Ph.D. in Organic Chemistry (2017) under the supervision of Prof. Mohammad Ali Zolfigol. His research interest is the synthesis, characterization and applications of homogeneous and heterogeneous reagent and catalyst in organic synthesis. He has been studying nanotechnology and nanoscience in chemistry. His current interests include metal nanoparticles, metal-organic framework (MOF) and organic synthesis. He is presently an assistant professor of organic chemistry at University of Qom, Iran.

Zolfigol *et al.* have reported selective nitration using MOFs/sodium nitrite catalytic system. In this report, a wide range of compounds such as boronic acids, aryl halides, aryl trifluoromethanesulfonate and aroyl chlorides in the presence of a catalytic amount of palladium (Pd) placed on MIL-101(Cr)-NH₂ as a nitrating system have been nitrated. The described method provides a useful and convenient strategy for the ipso-nitration reaction (Scheme 2) [5].



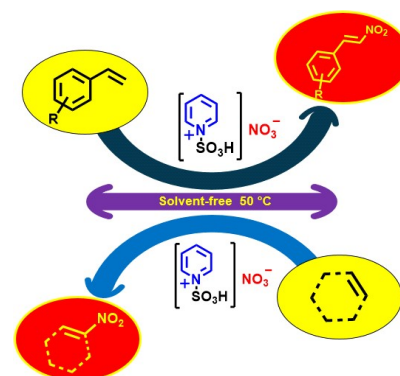
Scheme 2. Carrying out the nitration reaction using the Pd@MOF/NaNO₂ system

In 2018, Zolfigol *et al.* introduced novel Brønsted acidic ionic liquid and nitrating agent 1,3-disulfonic acid imidazolium nitrate [Dsim]NO₃ by reaction of imidazole, ClSO₃H and nitric acid. This reagent was tested for the synthesis of nitroolefins and nitroarenes. The promising features of the mentioned agent are the benign nature of the protocols, the ease of reaction procedures, the strong catalytic activity and the time-saving with excellent yields of the target molecules (Scheme 3) [6].



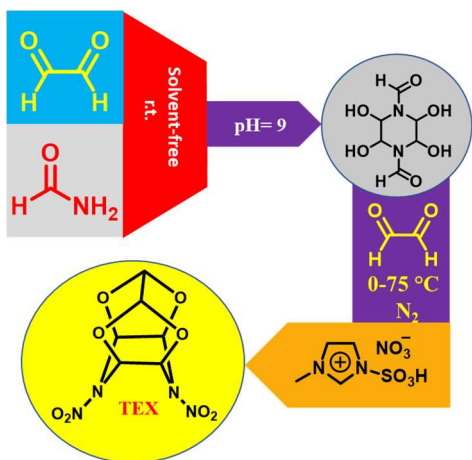
Scheme 3. Carrying out the nitration reaction using the [Dsim]NO₃ reagent

In another exploration, novel ionic liquid of 1-sulfonypyridinium nitrate, ([Pyridine-SO₃H]NO₃), has been used as a reusable reagent for the nitration of arenes. [Pyridine-SO₃H]NO₃ has been introduced as a nitrating agent for the nitration of arenes a highly efficient and organic reagent without the need of a co-catalyst and solvent for the nitration of various aromatic compounds at room temperature. Mechanistically, *in situ* generated nitrogen dioxide as a radical from the reagent is proposed for the presented nitration protocol (Scheme 4) [7].



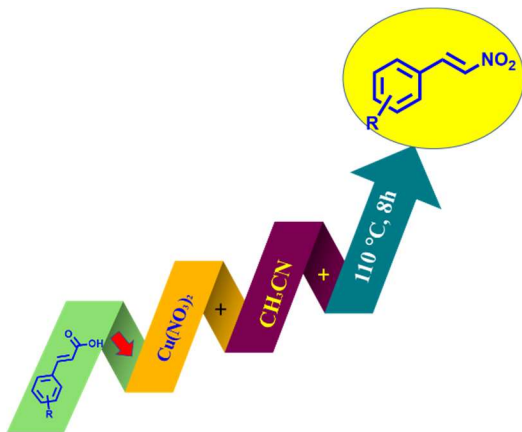
Scheme 4. Carrying out the nitration reaction using the [Pyridine-SO₃H]NO₃ reagent

In 2015, 3-methyl-1-sulfonic acid imidazolium nitrate ([Msim] NO_3) was synthesized and studied for the synthesis of 4,10 dinitro-2,6,8,12-tetraoxa-4,10 diazatetracyclo[5.5.0.0 $_{05}$.903,11]dodecane (TEX) via nitration of 1,4-diformyl-2,3,5,6-tetrahydropiperazine (DFTHP). The proposed method for the synthesis of TEX under solvent-free conditions. Synthesis reagent in this work, good performance, high purity and short reaction time are prepared by a simple training method (Scheme 5) [8].



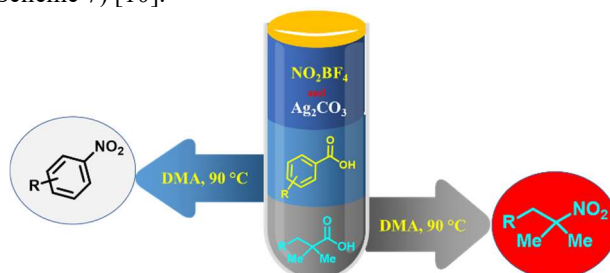
Scheme 5. Synthesis of high-energy substance TEX using [Msim] NO_3 reagent

The agent activity of the $\text{Cu}(\text{NO}_3)_2$, highly efficient, mild and green agent has been studied in the nitrodecarboxylation of α,β -unsaturated acids. Experimental experiments have shown that this reaction is likely to proceed through a radical pathway. The proposed protocol is a pleasant, simple, efficient, green method for the synthesis of (E)-nitroolefins with good prospects for industrialization. $\text{Cu}(\text{NO}_3)_2$ has been used as both a nitrating agent and a catalyst. In addition, the proposed method offers several advantages such as readily available and stable substrates, low-cost catalysts, high to excellent performance, short reaction times, and simple post-treatment methods (Scheme 6) [9].



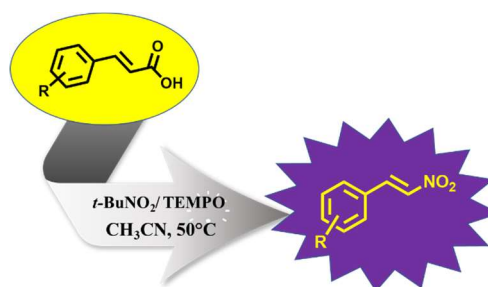
Scheme 6. Carrying out the nitration reaction using the $\text{Cu}(\text{NO}_3)_2$ reagent

Palani *et al.* have described a novel and efficient method for the nitration of series aliphatic and aromatic carboxylic acids to their respective nitro compounds using nitronium tetrafluoroborate and silver carbonate in dimethyl acetamide. This transformation is believed to proceed via the alkyl-silver or aryl-silver intermediate, which subsequently reacts with the nitronium ion to form nitro substances. Mild reaction conditions, tolerant of a broad range of functional groups, and formation of only the ipso-nitrated products are the key features of this methodology when compared to known methods for syntheses of nitro alkyls and nitroarenes (Scheme 7) [10].



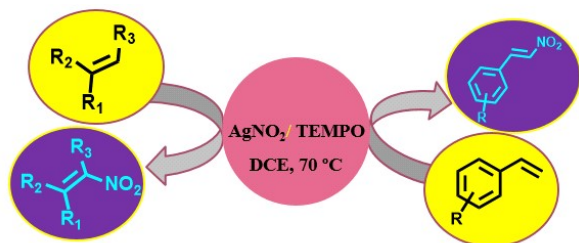
Scheme 7. Carrying out the nitration reaction using the nitronium tetrafluoroborate and silver carbonate reagent

In 2015 Srimanta reported an alternative metal-free decarboxylative nitration protocol for the preparation of the nitroolefins from unsaturated carboxylic acids using *t*-butyl nitrite (*t*-BuONO) and TEMPO. Unsaturated carboxylic acids bearing aromatic and heteroaromatic substituents gave (E)-nitroolefins exclusively under mild conditions. A radical based pathway has been proposed for this decarboxylative nitration reaction (Scheme 8) [11].



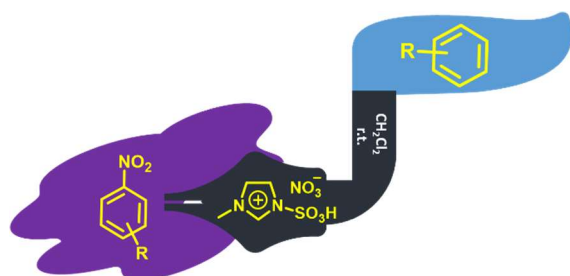
Scheme 8. Carrying out the nitration reaction using *t*-BuONO and TEMPO reagent

Nitroolefin is a common and versatile reagent, synthesis of which from olefin is generally limited by the formation of mixture of *cis*- and *trans*- compounds. In 2013, it was reported that silver nitrite (AgNO_2) along with TEMPO can promote regio- and stereoselective nitrate from a wide range of olefins. This work reveals a novel and efficient approach. This process is practical and a wide array of substrates including aromatic, aliphatic and heteroaromatic olefins can be nitrated in regio- and stereoselective manner. The strategy developed here can allow olefin nitration as a method for rationalizing complex molecule synthesis (Scheme 9) [12].



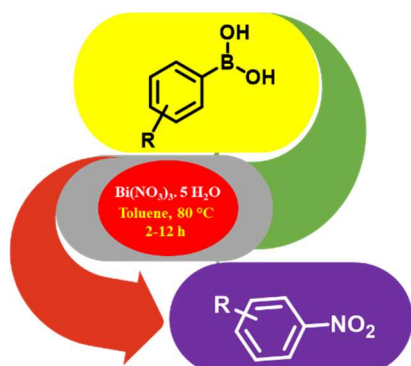
Scheme 9. Carrying out the nitration reaction using AgNO_2 and TEMPO reagent

In 2012, Zolfigol *et al.* introduced 3-methyl-1 sulfonic acid imidazolium nitrate ($[\text{Msim}]\text{NO}_3$) as a new Brønsted acidic ionic liquid and nitrating agent. $[\text{Msim}]\text{NO}_3$ was used as a reagent for nitrating aromatic compounds. The dramatic effect of this reagent on in-situ nitrogen dioxide production as an essential ingredient in aromatic compounds for nitrogen delivery has been investigated. The major advantages of the described are agent green synthesis, short reaction times and excellent yields of products (Scheme 10) [13].



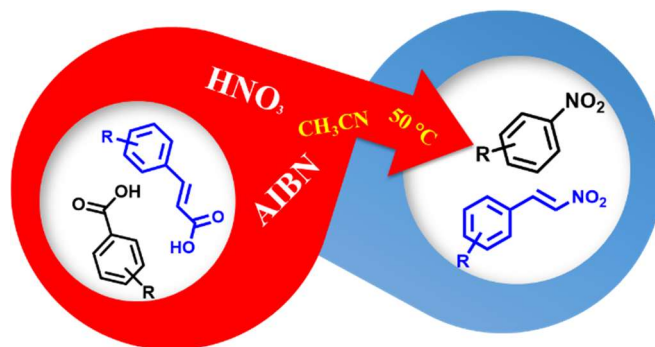
Scheme 10. Carrying out the nitration reaction using $[\text{Msim}]\text{NO}_3$ reagent

In another exploration, ipso-nitration of aryl boronic acids using bismuth (III) nitrate as nitrating agent, has been introduced. The features of this work include shorter reaction times with medium to excellent yields. This method is operationally simple, and robust to selection with excellent functional compatibility for nitrogen synthesis. Most importantly, the present protocol is catalyst-free, making it more ecofriendly, economical, and feasible for large scale synthesis of nitroarenes (Scheme 11) [14].



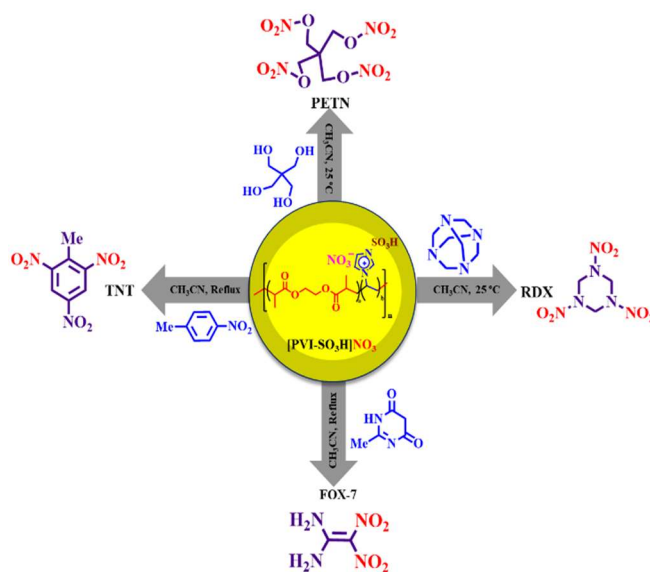
Scheme 11. Carrying out the nitration reaction using the bismuth(III)nitrate reagent

Nitrostyrenes are versatile building blocks in organic synthesis. In 2002, Jaya *et al.* introduced the nitro decarboxylation of aromatic unsaturated carboxylic acids and ring-activated benzoic acids by using nitric acid and catalytic AIBN in CH_3CN . A radical based pathway has been proposed for this decarboxylative nitration reaction (Scheme 12) [15].



Scheme 12. Some reagents used in the synthesis of nitro compounds

Zolfigol and coworkers have designed and synthesized poly(vinylimidazole) sulfonic acid nitrate reagent $[\text{PVI-SO}_3\text{H}]\text{NO}_3$ as a new polymeric nitrating agent for the preparation of four high-energy and explosive materials. The reagent created with the radical mechanism of explosive materials such as FOX-7, PETN, RDX and TNT has been created. The reported method stands out for its significant advantages, including the high yield of products without the need for any auxiliary catalysts, operation at low temperatures, reduced reaction times, and its broad applicability in the synthesis of energetic materials. (Scheme 13) [16].



Scheme 13. Synthesis of high-energy of explosive materials such as FOX-7, PETN, RDX and TNT using $[\text{PVI-SO}_3\text{H}]\text{NO}_3$ reagent

2. Conclusion

In summary, considering the importance of nitro compounds, the present review examines some types of methods and reagents used in the synthesis of nitro compounds. The electrophilic nitration of organic materials is one of the most extensively studied organic reactions, which involves the use of $\text{HNO}_3/\text{H}_2\text{SO}_4$ as a nitrating mixture under harsh reaction conditions. This method is plagued by issues of regioselectivity, leading to the production of a mix of isomers and oxidation by-products. Hence, developing a method for regioselective nitration that adheres to the principles of green chemistry and is operationally straightforward holds considerable importance for the field of nitro organic compounds. The pursuit of expanding these compounds through mild and environmentally friendly approaches ranks high among scientific priorities. Adhering to green chemistry principles and environmental objectives should be at the forefront, with the ensuing review serving as a comprehensive overview of various reports and advancements in methods for synthesizing nitro compounds. The critical role of nitro compounds in the production of dyes, plastics, perfumes, energetic materials, and pharmaceuticals has been clearly established.

Declaration of Interests

The authors declare that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author(s) ID

Hassan Sepehrmansourie : <https://orcid.org/0000-0002-9064-9078>

Mahmoud Zarei : <https://orcid.org/0000-0002-3701-9755>

References

1. a) M. A. Reddy, N. Jain, D. Yada, C. Kishore, V. J. Reddy, P. S. Reddy, A. Addlagatta, S. V. Kalivendi, B. Sreedhar, *J. Med. Chem.*, **2011**, *54*, 6751-6760. b) Y. E. Qian, L. Zheng, H. Y. Xiang, H. Yang, *Org. Biomol. Chem.*, **2021**, *19*, 4835-4851.
2. (a) B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.*, **2009**, *131*, 12898-12899. (b) G. K. S. Prakash, T. Mathew, *Angew. Chem., Int. Ed.*, **2010**, *49*, 1726-1728.
3. S. Salzbrunn, J. Simon, G. K. S. Prakash, N. A. Petasis, G. A. Olah, *Synlett*, **2000**, *10*, 1485-1487.
4. (a) I. Mosiagin, A. J. Fernandes, A. Budinská, L. Hayriyan, K. E. Ylijoki, D. Katayev, *Angew. Chem.*, **2023**, *135*, e202310851. (b) A. Dahiya, A. G. Gevondian, A. Selmani, F. Schoenebeck, *Org. Lett.*, **2023**, *25*, 7209-7213.
5. H. Sepehrmansourie, M. Zarei, M. A. Zolfigol, S. Kalhor, H. Shi, *Mol. Catal.*, **2022**, *531*, 112634.
6. M. Zarei, E. Noroozizadeh, A. R. Moosavi-Zare, M. A. Zolfigol, *J. Org. Chem.*, **2018**, *83*, 3645-3650.
7. A. R. Moosavi-Zare, M. A. Zolfigol, M. Zarei, E. Noroozizadeh, M. H. Beyzavi, *RSC Adv.*, **2016**, *6*, 89572-89577.
8. H. Ghaderi, M. A. Zolfigol, Y. Bayat, M. Zarei, E. Noroozizadeh, *Synlett*, **2016**, *27*, 2246-2250.
9. Z. G. Luo, F. Xu, Y. Y. Fang, P. Liu, X. M. Xu, C. T. Feng, J. He, *Res. Chem. Intermediat.*, **2016**, *42*, 6079-6087.
10. P. Natarajan, R. Chaudhary, P. Venugopalan, *J. Org. Chem.*, **2015**, *80*, 10498-10504.
11. S. Manna, S. Jana, T. Saboo, A. Maji, D. Maiti, *Chem. Comm.*, **2013**, *49*, 5286-5288.
12. S. Maity, S. Manna, S. Rana, T. Naveen, A. Mallick, D. Maiti, *J. Am. Chem. Soc.*, **2013**, *135*, 3355-3358.
13. M. A. Zolfigol, A. Khazaei, A. R. Moosavi-Zare, A. Zare, H. G. Kruger, Z. Asgari, M. Kazem-Rostami, *J. Org. Chem.*, **2012**, *77*, 3640-3645.
14. R. R. Yadav, R. A. Vishwakarma, S. B. Bharate, *Tetrahedron Lett.*, **2012**, *53*, 5958-5960.
15. J. P. Das, P. Sinha, S. Roy, *Org. Lett.* **2002**, *4*, 3055-3058.
16. H. Sepehrmansourie, M. Zarei, M. A. Zolfigol, A. Mehrzad, H. R. Hafizi-Atabak, *RSC Adv.*, **2021**, *11*, 8367-8374.