Organic LETTERS

Letter

pubs.acs.org/OrgLett

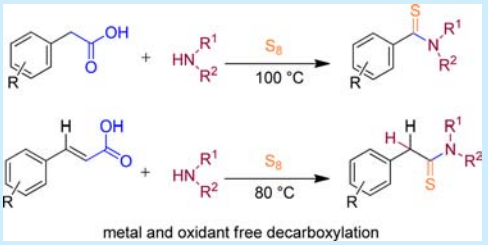
Decarboxylative Thioamidation of Arylacetic and Cinnamic Acids: A New Approach to Thioamides

Tirumaleswararao Guntreddi, Rajeshwer Vanjari, and Krishna Nand Singh*

Department of Chemistry (Centre of Advanced Study), Faculty of Science, Banaras Hindu University, Varanasi 221005, India

Supporting Information

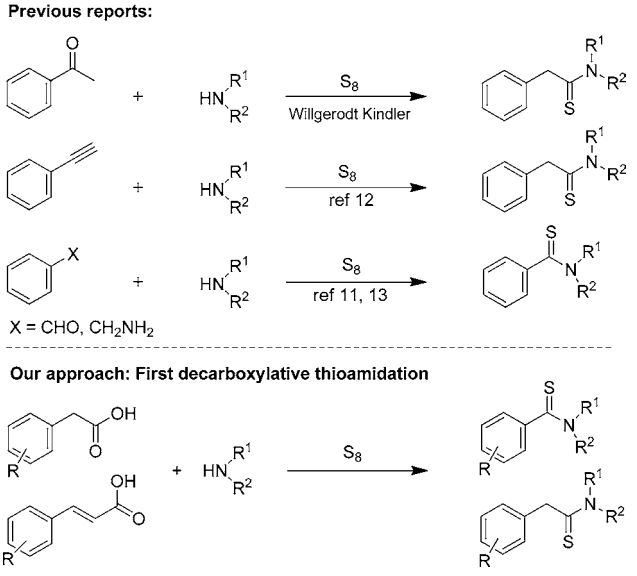
ABSTRACT: A new decarboxylative strategy has been developed for the synthesis of thioamides via a three-component reaction involving arylacetic or cinnamic acids, amines and elemental sulfur powder, without the need of a transition metal and an external oxidant.



Decarboxylative reactions have recently come out as a powerful advance to form carbon−carbon or carbon−heteroatom bonds in organic synthesis. The starting carboxylic acids are easily available at low cost in great structural diversity and are stable, nontoxic, and easy to store and handle.[1] However, most of the decarboxylative coupling reactions described so far necessitate transition-metal catalysts including palladium,[2] copper,[3,4] and other metals.[5] Therefore, the direct oxidative decarboxylation routes under metal-free conditions to form new C−C or C−heteroatom bonds is of overriding value and challenging.

Thioamides are vital structural motifs widely used as key intermediates[6] and versatile building blocks for the construction of biologically important sulfur-containing heterocycles.[7] The functionality is extremely crucial in the field of medical science and organic chemistry, and the advancement of creative strategies to achieve thioamides is a continuing synthetic venture owing to its huge synthetic utility.[8] Compared to the amide analogue, the synthetic methods for the formation of thioamides are somewhat limited. The most commonly used conventional methods are thionation[9] of amides and Willgerodt−Kindler[10] reaction involving aryl alkyl ketones, elemental sulfur, and amine. However, these methods have limited applications because of the harsh reaction conditions, long reaction time, and low yields. Recently, some three-component reactions have nicely exploited the use of benzylamine,[11] alkyne,[12] and aldehydes[13] in combination with elemental sulfur and amine for the synthesis of thioamides, albeit the use of benzylamine requires rather high temperature and prolonged reaction time. Therefore, the development of fresh strategies for the synthesis of thioamides employing new, readily available, inexpensive, and environmentally benign starting materials is highly desirable. In light of the above facts and as a part of our recent endeavors in C−H activation[14] and for development of other protocols,[15] we describe herein for the first time an efficient, one-pot, metal-free decarboxylation reaction for the synthesis of thioamides by the reaction of arylacetic acid or substituted cinnamic acid, amines, and elemental sulfur without the need of any transition metal and oxidant (Scheme 1).

Scheme 1. Thioamide Synthesis

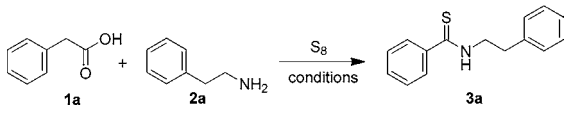


Our initial efforts were focused on the optimization of the reaction conditions employing phenylacetic acid, 2-phenethylamine, and elemental sulfur powder as model reactants by varying different parameters (Table 1). The product was finished in 90% yield in the absence of a catalyst and solvent at 100 °C in 10 h (entry 1). Increasing the reaction temperature to 110 °C did not enhance the yield of the product (entry 2), but decreasing the temperature to 80 °C decreased the yield

Received: April 2, 2014
Published: June 30, 2014

dx.doi.org/10.1021/ol501482g | Org. Lett. 2014, 16, 3624−3627

Table 1. Reaction Optimization[a]



entry	solvent (1 mL)	temp (°C)	yield[b] (%)
1		100	90
2		110	90
3		80	58
4	toluene	100	23
5	DMSO	100	83
6	chlorobenzene	100	35
7	DMF	100	86
8	pyridine	100	88
9	water	100	15
10	1,4-dioxane	100	19
11[c]		100	73
12[d]		100	89

[a]Conditions: phenylacetic acid (1 mmol), amine (2 mmol), sulfur (4 mmol, 128 mg) for 10 h. [b]Isolated yield. [c]Amine (1 mmol). [d]Under nitrogen atmosphere.

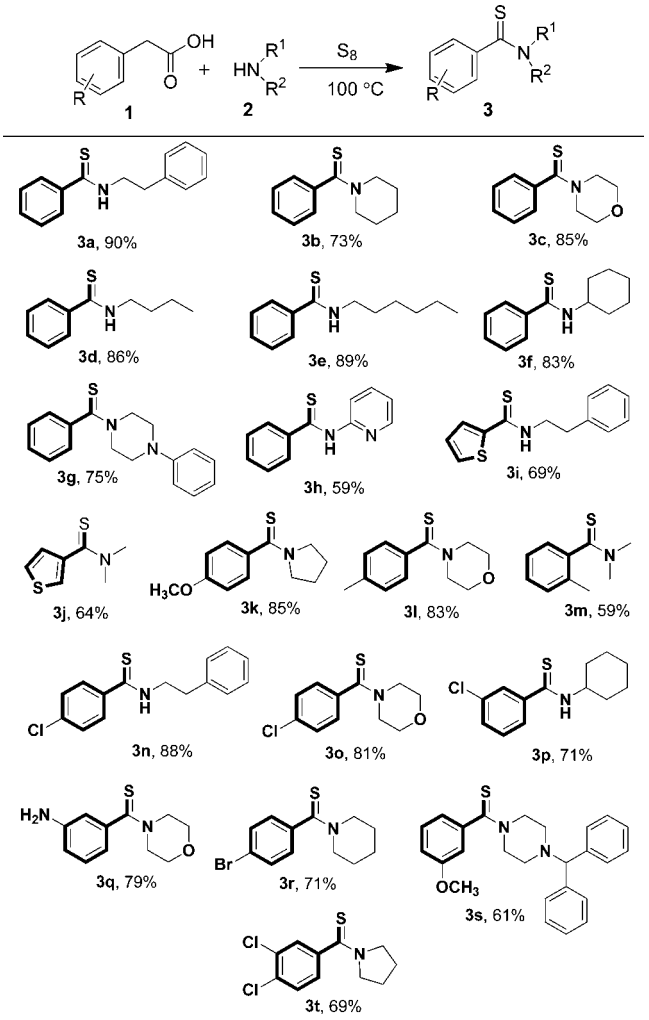
considerably (entry 3). In regard to the effect of different solvents (entries 4−10), the use of DMSO, DMF, and pyridine encouraged the reaction to a high extent (entries 5, 7, and 8), but toluene, chlorobenzene, water, and dioxane performed poorly (entries 4, 6, 9, and 10). However, none of them could match the yield obtained under solvent-free conditions. The best molar ratio of the reactants phenylacetic acid, amine, and elemental sulfur was found to be 1:2:4.

With the optimized conditions in hand, the scope and versatility of the decarboxylative thioamidation was then thoroughly examined, and the outcome is given in Scheme 2. A variety of aryl(hetaryl)acetic acids and amines were subjected to the reaction which effectively offered the desired products in high yields. Phenylacetic acids containing both the electron-rich and electron-deficient substituents on the aromatic ring could smoothly afford the thioamidated products. The location of the substituents on the aromatic rings was noticed to have some effect on the product yield; *ortho*-substitution provided inferior yield as compared to the *meta*- and *para*-substitution, which may be attributed to the steric effect. The nitro group was notably reduced to NH_2 group during the course of reaction, which remained intact in the reaction (**3q**). Heteroaromatic acids like 2- and 3-thiopheneacetic acid also underwent the transformation adequately to provide the corresponding thioamides **3i** and **3j**. 3-Methoxyphenylacetic acid was also made to react with 1-benzhydrylpiperazine to give the corresponding product **3s** in 61% yield. Functionalized amines like glycine and ethanolamine, however, could not undergo the desired conversion. Aromatic amines when tried under standard conditions were also unsuccessful, but the reaction using 2-aminopyridine could give the product **3h** in good yield.

As the aromatic amines did not work under the established conditions, it was imperative to explore some other suitable conditions to effect the reaction, and therefore, the use of a base like K_2CO_3 was realized to make the amine more nucleophilic for a model reaction involving phenylacetic acid, 4-methylaniline, and elemental sulfur.

As a result, the solvent-free conditions could not provide the desired product, but the use of DMF, DMSO, and pyridine gave rise to the product **5a** in 60, 75, and 66% yields,

Scheme 2. Reaction Scope Using Arylacetic Acids[a]



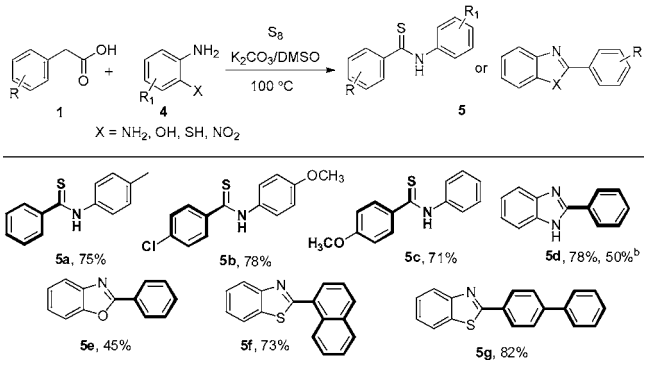
[a]Reaction conditions: arylacetic acid (1 mmol), amine (2 mmol), sulfur (4 mmol). Dimethylamine 40% aq solution (0.5 mL). Yields refer to isolated products.

respectively. Hence, the use of K_2CO_3/DMSO was adopted to bring about the reaction of different aromatic amines like aniline, 4-methoxyaniline, and 4-chloroaniline with some arylacetic acids to give the corresponding products **5a−c** in good yields (Scheme 3). It is interesting to note that the use of *ortho*-substituted anilines, viz. *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol, under the present conditions eventually led to cyclization to afford the substituted imidazole **5d**, oxazole **5e**, and thiazoles **5f** and **5g**, respectively. To our delight, *o*-nitroaniline also worked well to give the substituted imidazole **5d** under the present conditions.

Encouraged by the above findings, it was thought worthwhile to apply the optimized set of reaction conditions (100 °C, solvent-free) to cinnamic acids as well. Interestingly, the trial combination of cinnamic acid, 2-phenethylamine, and elemental sulfur, under the established conditions, gave rise to *N*-phenethyl-2-phenylethanethioamide in 87% isolated yield. In this case, a decrease in the reaction temperature to 80 °C distinctly provided similar yields, but further decrease in the temperature lowered the yield. Therefore, the same parameters with a lowered temperature (80 °C) were adopted to test the versatility and functional group tolerance of the reaction in

dx.doi.org/10.1021/ol501482g | *Org. Lett.* 2014, 16, 3624−3627

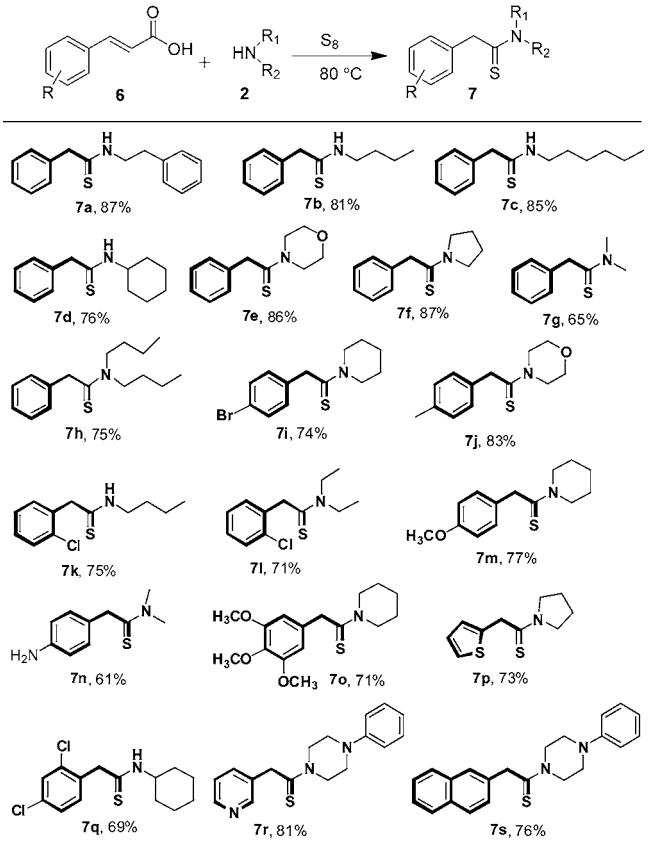
Scheme 3. Reaction Scope Using Aromatic Amines[a]



[a]Reaction conditions: phenylacetic acid (1.0 mmol), aromatic amine (1 mmol), sulfur (4 mmol), K_2CO_3 (2 mmol), DMSO (1 mL). [b]Using *o*-nitroaniline. Yields refer to isolated products.

subsequent studies. Different cinnamic acids having substituents such as *p*-Br, *p*-CH_3, *p*-NO_2, *p*-OCH_3, *o*-Cl, 3,4,5-trimethoxy, and 2,4-dichloro; bicyclic acid like 3-(naphthalen-2-yl)acrylic acid; and heterocyclic acids like 2-thiopheneacrylic acid and 3-(3-pyridyl)acrylic acid were reacted with numerous amines namely dimethylamine, piperidine, pyrrolidine, *n*-butylamine, *n*-hexylamine, cyclohexylamine, diethylamine, dibutylamine, 1-phenylpiperazine and morpholine to afford the corresponding 2-arylethanethioamidated products in practically high yields (Scheme 4). The nitro group was again

Scheme 4. Reaction Scope Using Cinnamic Acids[a]



[a]Reaction conditions: cinnamic acid (1 mmol), amine (2 mmol), sulfur (4 mmol). Yields refer to isolated products.

reduced to a NH_2 group during the course of reaction and remained intact under established conditions (**7n**). Aromatic amines such as aniline as well as functionalized amines such as glycine, however, failed to undergo the reaction even under K_2CO_3/DMSO combination.

The structures of two representative products **3c** and **7j**, one each from both the categories, have been conclusively proved by the single-crystal XRD (Figure 1).[16]

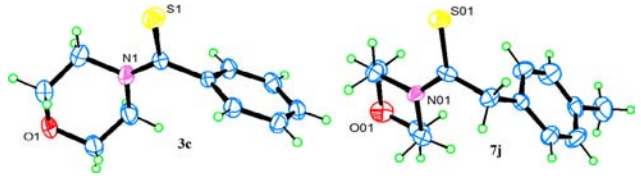


Figure 1. X-ray crystal structures of **3c** (**3ac** in CIF, Supporting Information) and **7j** (**4ca** in CIF, Supporting Information).

On the basis of the existing literature[12,17] and isolation of products, a plausible mechanism is briefly outlined in Figure 2 (cf. Supporting Information for details).

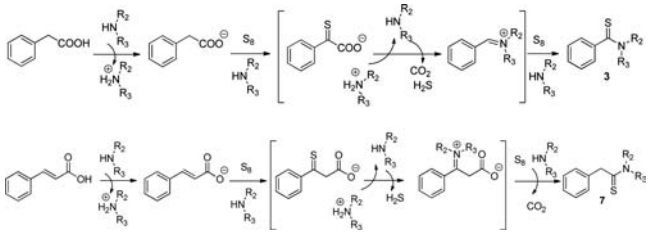


Figure 2. Proposed mechanism.

In conclusion, the present report describes a practical and easy approach to thioamides and benzazoles adopting a novel decarboxylative approach. The methodology employs a new class of readily available and inexpensive reactant, offers many advantages, and is free from the use of metals and external oxidants.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: knsingh@bhu.ac.in, knsinghbhu@yahoo.co.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are thankful to the Department of Science and Technology, Government of India, New Delhi, for providing financial assistance (Grant No. SR/S1/OC-78/2012). T.G. and R.V. are thankful to the CSIR for research fellowships.

■ REFERENCES

(1) For recent decarboxylation reviews, see: (a) Dzik, W. I.; Lange, P. P.; Goossen, L. J. *J. Chem. Sci.* **2012**, 3, 2671. (b) Shang, R.; Liu, L. *Sci.*

Chin. Chem. **2011**, *54*, 1670. (c) Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030.
(2) (a) Shang, R.; Yang, Z.-W.; Wang, Y.; Zhang, S.-L.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391. (b) Haley, C. K.; Gilmore, C. D.; Stoltz, B. M. *Tetrahedron* **2013**, *69*, 573. (c) Shang, R.; Huang, Z.; Xiao, X.; Lu, X.; Fu, Y.; Liu, L. *Adv. Synth. Catal.* **2012**, *354*, 2465. (d) Shang, R.; Ji, D.-S.; Chu, L.; Fu, Y.; Liu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4470. (e) Shang, R.; Huang, Z.; Chu, L.; Fu, Y.; Liu, L. *Org. Lett.* **2011**, *13*, 4240.
(3) (a) Zhao, D.; Gao, C.; Su, X.; He, Y.; You, J.; Xue, Y. *Chem. Commun.* **2010**, *46*, 9049. (b) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792. (c) Song, Q.; Feng, Q.; Zhou, M. *Org. Lett.* **2013**, *15*, 5990. (d) Feng, Q.; Song, Q. *Adv. Synth. Catal.* **2014**, *356*, 1697. (e) Song, Q.; Feng, Q.; Yang, K. *Org. Lett.* **2014**, *16*, 624.
(4) (a) Ranjit, S.; Duan, Z.; Zhang, P.; Liu, X. *Org. Lett.* **2010**, *12*, 4134. (b) Yang, H.; Sun, P.; Zhu, Y.; Yan, H.; Lu, L.; Qu, X.; Li, T.; Mao, J. *Chem. Commun.* **2012**, *48*, 7847. (c) Cui, Z.; Shang, X.; Shao, X. F.; Liu, Z. Q. *Chem. Sci.* **2012**, *3*, 2853. (d) He, Z.; Luo, T.; Hu, M.; Cao, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3944. (e) Li, Z.; Cui, Z.; Liu, Z. Q. *Org. Lett.* **2013**, *15*, 406.
(5) (a) Yang, H.; Sun, P.; Zhu, Y.; Lu, L.; Liu, D.; Rong, G.; Mao, J. *Green Chem.* **2013**, *15*, 976.
(6) (a) Suzuki, Y.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5026. (b) Iwata, M.; Yazaki, R.; Chen, I. H.; Sureshkumar, D.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5554. (c) Prokopcová, H.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 4440.
(7) For selected recent examples, see: (a) Lo, W. S.; Hu, W. P.; Lo, H. P.; Chen, C. T.; Kao, C. L.; Vandavasi, J. K.; Wang, J. J. *Org. Lett.* **2010**, *12*, 5570. (b) Iwata, M.; Yazaki, R.; Chen, I. H.; Sureshkumar, D.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5554. (c) Goossen, L. J.; Blanchot, M.; Salih, K. S.M.; Karch, R.; Rivas-Nass, A. *Org. Lett.* **2008**, *10*, 4497. (d) Chaudhari, P. S.; Pathare, S. P.; Akamanchi, K. G. *J. Org. Chem.* **2012**, *77*, 3716. (e) Wang, H.; Wang, L.; Shang, J.; Li, X.; Wang, H.; Gui, J.; Lei, A. W. *Chem. Commun.* **2012**, *48*, 76.
(8) (a) Ebert, S. P.; Wetzel, B.; Myette, R. L.; Conseil, G.; Cole, S. P. C.; Sawada, G. A.; Loo, T. W.; Bartlett, M. C.; Clarke, D. M.; Detty, M. R. *J. Med. Chem.* **2012**, *55*, 4683. (b) Angehrn, P.; Goetschi, E.; Gmuender, H.; Hebeisen, P.; Hennig, M.; Kuhn, B.; Luebbers, T.; Reindl, P.; Ricklin, F.; Schmitt-Hoffmann, A. *J. Med. Chem.* **2011**, *54*, 2207. (c) Mehanna, A. S.; Belani, J. D.; Kelley, C. J.; Pallansc, L. A. *J. Med. Chem.* **2007**, *3*, 513. (d) Yu, K. L.; Torri, A. F.; Luo, G.; Cianci, C.; Grant-Young, K.; Danetz, S.; Tiley, L.; Krystalb, M.; Meanwella, N. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3379. (e) Murai, T.; Moto, Y. *Chem. Lett.* **2012**, *41*, 2.
(9) (a) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061. (b) Brillon, D. *Sulfur Rep.* **1992**, *12*, 297. (c) Cho, D.; Ahn, J.; De Castro, K. A.; Ahn, H.; Rhee, H. *Tetrahedron* **2010**, *66*, 5583. (d) Shibahara, F.; Sugiura, R.; Murai, T. *Org. Lett.* **2009**, *11*, 3064. (e) Bergman, J.; Pettersson, B.; Hasimbegovic, V.; Svensson, P. H. *J. Org. Chem.* **2011**, *76*, 1546.
(10) (a) Willgerodt, C. *Ber. Dtsch. Chem. Ges* **1888**, *21*, 534. (b) Kindler, K. *Liebigs Ann. Chem.* **1923**, *431*, 187. (c) Wegler, R.; Kuhle, E.; Schafer, W. *Angew. Chem.* **1958**, *70*, 351.
(11) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 4274.
(12) Nguyen, T. B.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2014**, *16*, 310.
(13) (a) Zbruyev, O. I.; Stiasni, N.; Kappe, C. O. *J. Comb. Chem.* **2003**, *5*, 145. (b) Xu, H.; Deng, H.; Li, Z.; Xiang, H.; Zhou, X. *Eur. J. Org. Chem.* **2013**, *31*, 7054.
(14) (a) Vanjari, R.; Guntreddi, T.; Singh, K. N. *Org. Lett.* **2013**, *15*, 4908. (b) Guntreddi, T.; Vanjari, R.; Singh, K. N. *Tetrahedron* **2014**, *70*, 3887.
(15) (a) Singh, N.; Singh, R.; Raghuvanshi, D. S.; Singh, K. N. *Org. Lett.* **2013**, *15*, 5874. (b) Vanjari, R.; Guntreddi, T.; Singh, K. N. *Green Chem.* **2014**, *16*, 351. (c) Singh, R.; Raghuvanshi, D. S.; Singh, K. N. *Org. Lett.* **2013**, *15*, 4202. (d) Raghuvanshi, D. S.; Gupta, A. K.; Singh, K. N. *Org. Lett.* **2012**, *14*, 4326.
(16) Crystallographic data for compounds **3c** and **7j** (CCDC-994862-994863) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(17) (a) Priebbenow, L. D.; Bolm, C. *Chem. Soc. Rev.* **2013**, *42*, 7870. (b) Poupaert, J. H.; Duarte, S.; Colacino, E.; Depreux, P.; McCurdy, C. R.; Lambert, D. L. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 1959.