Organic LETTERS

Letter

pubs.acs.org/OrgLett

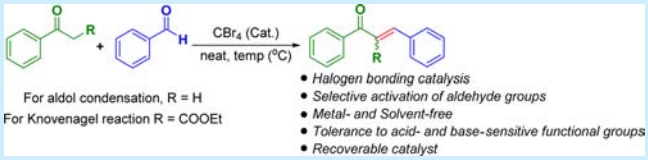
CBr_4 as a Halogen Bond Donor Catalyst for the Selective Activation of Benzaldehydes to Synthesize α,β-Unsaturated Ketones

Imran Kazi, Somraj Guha, and Govindasamy Sekar*

Department of Chemistry, Indian Institute of Technology Madras, Chennai, 600036, India

Supporting Information

ABSTRACT: CBr_4 has been employed as a halogen bond donor catalyst for the selective activation of aldehyde, to achieve an efficient solvent- and metal-free C=C bond forming reaction in the presence of strong acid sensitive groups such as methoxy, cyanide, ester, and ketal for the synthesis of α,β-unsaturated ketones. This unique capability of CBr_4 to act as a halogen bond donor has been explored and established using UV−vis as well as IR spectroscopy. Moreover, this unprecedented methodology enables the synthesis of the pharmaceutically important molecule licochalcone A.



A nonbonding interaction can be defined as a weak electromagnetic interaction between two molecules which does not involve the sharing of electrons.[1a] Studies on these weak interactions, which play crucial roles in biological processes,[1b] have so far been limited in the field of supramolecular chemistry spanning the areas of molecular self-assembly, host−guest chemistry, molecular recognition, etc.[1c] With only a few reports on hydrogen bond donor and halogen bond donor catalysts, these interactions still remain largely unexplored in the field of catalysis.[2] These catalysts offer mild but selective activation of a particular functional group as a consequence of its weak interaction with the substrates.

It is a well-known fact that Lewis bases form adducts with compounds having electrophilic halogens.[3] The investigation of such noncovalent interactions, which have recently been named as halogen bonding, and their subsequent application in the field of chemistry have come to the forefront in the past decade.[4] Just as thiourea derivatives take part in the activation of electrophilic substances such as carbonyls via hydrogen bonding, halogen bond donor catalysts, a new member in the field of organocatalysis, may take part in carbonyl activation as well.[5] In fact, halogen bonds are stronger than hydrogen bonds with high directionality.[6]

These halogen bond donor catalysts can be used as an alternative for strong and harsh Lewis acid catalysts.[7] Jungbauer et al. reported the activation of carbonyl groups with halogen bonding catalysis in Diels−Alder type reactions. They used a dicationic imidazolium-based catalyst as an alternative to the traditionally used strong Lewis acid catalysts.[8] However, use of a commercially available halogen-based reagent as a halogen bond donor catalyst in the field of organic synthesis is still unknown.[7b]

Recently, CBr_4 has drawn the attention of chemists as a metal-free organocatalyst.[9a] A stoichiometric amount of CBr_4 has been used for the formation of C−S[9b] and S−S[9c] bonds. A catalytic amount of CBr_4 has been used in the cross-dehydrogenative coupling of isocromans with aromatic ketone[9e] and the synthesis of α-amino phosphonate via a three-component reaction.[9d]

We envisioned that CBr_4, having vacant d and f orbitals in its bromine atoms, can be used as an easily available halogen bond donor catalyst to accomplish the synthesis of α,β-unsaturated ketones via selective activation of benzaldehyde in the presence of acid- and base-sensitive groups such as esters, cyanides, ketals, etc. (Figure 1).

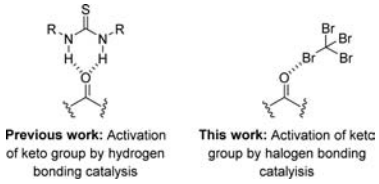


Figure 1. Activation of carbonyl group by nonbonding interaction.

α,β-Unsaturated ketones are important molecules in the field of synthetic chemistry.[10] They have antimalarial, antileishmanial, anticancer, anti-inflammatory, antimitotic, antitubercular, and cardiovascular activity[11] and are hence considered medicinally important. The classic ways of preparing chalcones include the Claisen−Schimdt reaction in the presence of a quantitative amount of strong bases or a catalytic amount of strong acids.[12,13] However, most of the reported reagents including the metal salts are hazardous, require harsh reaction conditions, have less tolerance to sensitive functional groups, and cannot be recovered.[14]

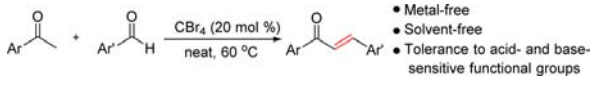
In addition, as organic solvents are known to have many adverse effects on the environment, more focus and attention are being given to solvent-free reactions. As part of our ongoing research endeavors toward developing metal-free organic reactions,[15] herein, for the first time we report the efficiency

Received: February 3, 2017
Published: February 17, 2017

DOI: 10.1021/acs.orglett.7b00348
Org. Lett. 2017, 19, 1244−1247

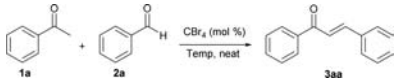
of CBr_4 as a halogen bond donor, a recoverable catalyst for the synthesis of chalcones from ketones and aldehydes under solvent-free conditions (Scheme 1).

Scheme 1. Metal- and Solvent-Free Synthesis of Chalcones Using CBr_4 as Catalyst



Initially, 1 equiv of acetophenone **1a** and 1.5 equiv of benzaldehyde **2a** in the presence of 20 mol % of CBr_4 as a catalyst under neat reaction conditions yielded 84% of the chalcone **3aa** at 60 °C in 24 h (Table 1, entry 1). Use of 1.0 equiv of **2a** reduced the yield of the product **3aa** to 71% (entry 2). Finally, it was inferred that 1.2 equiv of **2a** was sufficient for this reaction (entry 3).

Table 1. Optimization of CBr_4 Catalyzed Chalcone Synthesis[a]



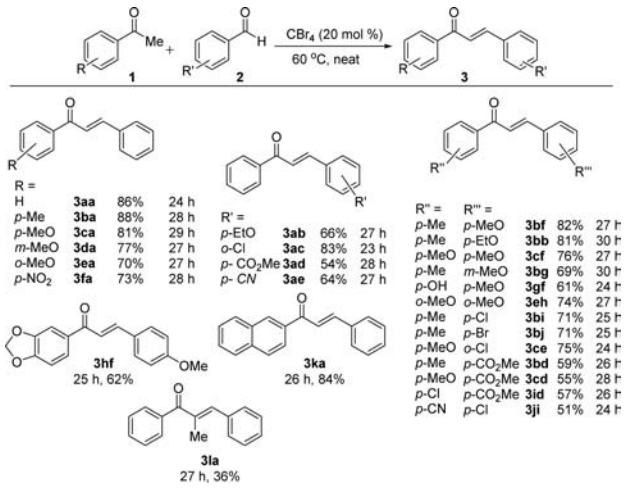
entry	2a (equiv)	catalyst (mol %)	solvent (mL)	temp (°C)	time (h)	yield (%)[b]
1	1.5	CBr_4 (20)	neat	60	24	84
2	1.0	CBr_4 (20)	neat	60	24	71
3	1.2	CBr_4 (20)	neat	60	24	86[c]
4	1.2	CBr_4 (20)	neat	80	36	84
5	1.2	CBr_4 (20)	neat	rt	36	trace
6	1.2	CBr_4(10)	neat	60	36	78
7	1.2	CBr_4 (5)	neat	60	36	72
8	1.2	CCl_4 (20)	neat	60	22	53
9	1.2	NIS (20)	neat	60	24	63
10	1.2	NBS (20)	neat	60	24	56
11	1.2	$CHCl_3$ (20)	neat	60	24	0[d]
12	1.2	DCE (20)	neat	60	24	0[d]
13	1.2	CBr_4 (20)	EtOH	60	24	77[e]
14	1.2	CBr_4 (20)	CH_3CN	60	24	53[e]
15	1.2	CBr_4 (20)	toluene	60	24	48[e]
16	1.2	HBr(10)	neat	60	24	57
17	1.2	HBr(20)	neat	60	24	60

[a]All the eactions are conducted in 1 mmol scale. [b]Isolated yield. [c]90% CBr_4 was isolated after completion of the reaction. [d]Reaction conducted in pressure tube. [e]2 mL of solvent were used.

We observed that there was negligible change in the yield of the desired product **3aa** when the temperature was increased (entry 4), whereas a decrease in the temperature and catalyst loading lowered the yield substantially (entries 5−7). To increase the efficiency of this synthetic transformation, a range of catalysts were further screened (entries 8−12). When CCl_4 was used, the yield of **3aa** reduced to 53% (entry 8). NIS and NBS also provided less product (entries 9 and 10). The reaction failed when $CHCl_3$ and DCE were used as catalysts (entries 11 and 12). Different solvents were screened in a bid to improve the yield of **3aa** (entries 13−15). It was observed that the methodology works best in neat conditions, and polar protic solvents such as ethanol provided better yields of **3aa** as compared to other aprotic solvents.

To investigate the scope of the CBr_4-catalyzed reaction, a library of acetophenones and benzaldehydes were examined under the optimized conditions (Table 1, entry 4), and the results are summarized in Scheme 2. A slight increase in the

Scheme 2. Scope of CBr_4 Catalyzed Chalcone Synthesis[a]



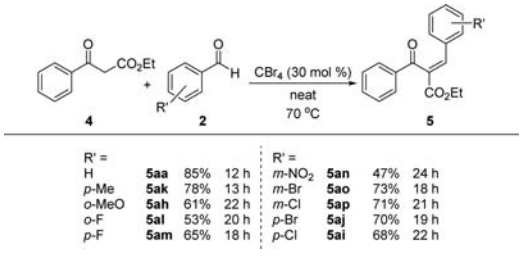
[a]Isolated yield.

yield was observed in the presence of electron-donating groups (Scheme 2, **3ba**−**3ea**) while a significant decrease in yield was observed when electron-withdrawing groups were present *para* to the keto group of the acetophenone moiety (**3fa**). The decrease in yield in the case of *ortho*-substituted moieties can be attributed to steric crowding (**3ea**) while the decrease in the case of **3ab** with an electron-donating group can be explained due to the reduced electrophilicity of the carbonyl group.

In contrast, good to excellent yields were obtained with benzaldehydes having electron-withdrawing groups (entries **3ac**−**3ae**). Moderate to good yields were obtained when electron-rich acetophenone was reacted with electron-deficient or -rich benzaldehydes (**3bf**−**3cd**). The yield was less when both the acetophenones and benzaldehydes are electron-deficient (**3id**−**3ji**). It is worth mentioning that substrates with sensitive functional groups such as ester (**3ad** and **3bd**−**3id**), cyano (**3ji** and **3ae**), and ketal (**3hf**) produced various chalcone derivatives in good yield while keeping the functional groups intact.[16] Ketones, having bulky aromatic rings such as naphthalene, gave good yields of product (**3ka**), while the yield drastically decreased in the case of propiophenone (**3la**). In all the cases, only the *E*-isomers formed which was confirmed by the ^1H NMR spectroscopy.[17]

β-Keto esters with the acid labile ester functionality located *α* to the ketones were examined to determine the feasibility of the reaction (Scheme 3). The ester group remained unaffected, and

Scheme 3. Scope of of the Methodology for *β*-Keto Esters[a]



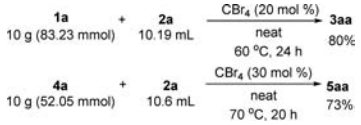
[a]Isolated yield.

DOI: 10.1021/acs.orglett.7b00348
Org. Lett. 2017, 19, 1244−1247

a moderate to good yield was obtained (Scheme 3). Electron-rich benzaldehydes gave good yields (**5ak**) except for the *ortho*-substituted one (**5ah**). The presence of strong electron-withdrawing substituents such as fluoro and nitro in benzaldehyde decreases the yield of the product (**5al**−**5an**). Good yields were obtained when weaker electron-withdrawing groups such as bromo and chloro were present (**5ao**−**5ai**). In all the cases reported thus far, a highly selective (>95%) *E*-product was obtained which was proven by X-ray crystallography of **5aa**.[18]

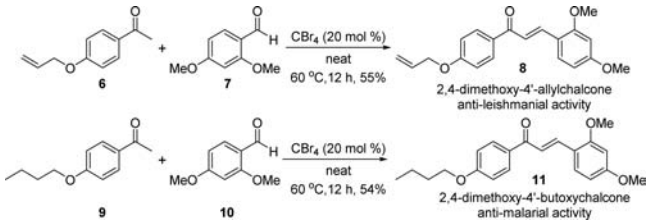
The scalability of the reaction was also examined, and for a 10 g scale reaction (Scheme 4), the optimized reaction

Scheme 4. Gram Scale Reaction



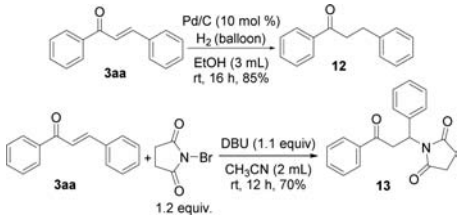
conditions gave an 80% yield of **3aa** and a 73% yield of **5aa.** Medicinally important compounds licochalcone A or oxygenated chalcones **8** and **11**, having antileishmanial and antimalarial activity, were prepared using this methodology resulting in a moderate yield in the presence of acid-sensitive groups such as methoxy and ether (Scheme 5).[11]

Scheme 5. One-Step Synthesis of Medicinally Important Licochalcones A



The synthetic application of chalcones has been demonstrated by its selective reduction to saturated benzylic ketones **12** which act as important precursors for different organic reactions. Treatment of chalcone with DBU and NBS resulted in affording *β*-amino ketone **13**, a Mannich base having anticancer, antifilarial, antibacterial, and antifungal activities (Scheme 6).[19]

Scheme 6. Synthetic Transformation of Chalcone 3aa



The mechanism of the reaction was interpreted noting the halogen bond donor property of CBr_4. An array of experiments were performed to rule out the possibility of the decomposition of CBr_4 to HBr, which may take part in catalyzing a background reaction during the course of the reaction.[20] Further, the coordination of CBr_4 with the aldehyde group was established with the help of IR spectroscopic experiments which showed the emergence of a new carbonyl band at lower frequency (1603.52 cm^{-1}). This may be attributed to the halogen bonding interaction of the aldehyde group with the bromine atom of CBr_4.[20] Subsequently, to establish this hypothesis, a UV−vis experiment[21] was carried out with a 1:1 mixture of CBr_4 and 3-nitrobenzaldehyde[22] after stirring it at 60 °C for 2 h. A broad band around 450 to 520 nm (Figure 2, spectrum R) clearly showed the pronounced halogen bonding interaction between CBr_4 and aldehyde group at 60 °C.[20]

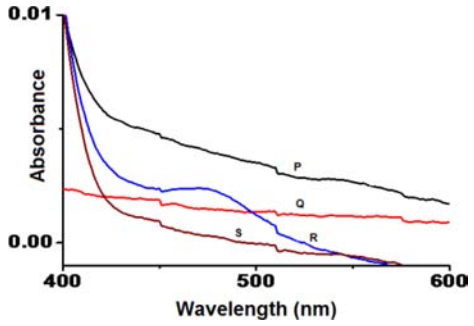
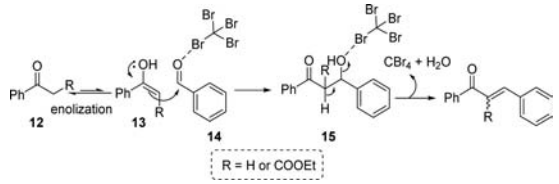


Figure 2. UV−vis experiment to support the halogen bonding interaction between CBr_4 and 3-nitrobenzaldehyde. P and Q are the spectra for 3-nitrobenzaldehyde and CBr_4. R and S are the spectra for their 1:1 mixture at 60 °C and rt.

On the basis of literature reports and our experimental evidence, it has been postulated that ketone **12** undergoes enolization to generate the enol **13** which further reacts with the activated aldehyde **14** to form the aldol **15**. Further, the interaction of CBr_4 with the hydroxyl group of aldol **15** helps in elimination of water to yield the final chalcone and the CBr_4 is regenerated in the reaction mixture (Scheme 7).

Scheme 7. Plausible Reaction Mechanism for the *α,β*-Unsaturated Ketones Synthesis



In conclusion, a recoverable CBr_4-catalyzed metal- and solvent-free methodology has been developed to synthesize chalcones. The methodology allows us to avoid the use of stoichiometric amounts of bases and strong acids which may lead to the hydrolysis of acid- and base-sensitive groups or may lead to a competitive Cannizaro reaction. Application of this methodology to synthesize the medicinally important molecule licochalcone A has been successfully demonstrated. Further studies to gain major insight into the role of CBr_4 as a halogen bond donor catalyst and the mechanism of interaction are presently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00348.

DOI: 10.1021/acs.orglett.7b00348
Org. Lett. 2017, 19, 1244−1247

Experimental methods; ^{1}H and ^{13}C NMR spectra of all compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: gsekar@iitm.ac.in.

ORCID

Govindasamy Sekar: 0000-0003-2294-0485

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank DST, New Delhi (SB/S1/OC-72/2013) for financial support. I.K. thanks IIT Madras for a fellowship. S.G. thanks CSIR, New Delhi for the SRF. We thank Ayan Bhattacharya and Dr. E. Prasad from IIT Madras for the UV−vis experiment.

REFERENCES

(1) (a) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2004; p 162. (b) Lodish, H.; Berk, A.; Zipursky, S. L.; Matsudaira, P.; Baltimore, D.; James, D. *Molecular Cell Biology*; Freeman & Co: New York, 2000. (c) Steed, W. J.; Atwood, J. L. *Supramolecular chemistry*; Wiley: United Kingdom, 2000; p 19.

(2) (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

(3) (a) Hassel, O.; Rømming, C. Q. *Q. Rev., Chem. Soc.* **1962**, *16*, 1. (b) Bent, H. A. *Chem. Rev.* **1968**, *68*, 587. (c) Weiss, R.; Miess, G. E.; Haller, A.; Reinhardt, W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 103. (d) Legon, A. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2686.

(4) (a) Kilah, N. L.; Wise, M. D.; Serpell, C. J.; Thompson, A. L.; White, N. G.; Christensen, K. E.; Beer, P. D. *J. Am. Chem. Soc.* **2010**, *132*, 11893. (b) Jentzsch, A. V.; Emery, D.; Mareda, J.; Metrangolo, P.; Resnati, G.; Matile, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11675. (c) Carlsson, A. -C. C.; Graefenstein, J.; Budnjo, A.; Laurila, J. L.; Bergquist, J.; Karim, A.; Kleinmaier, R.; Brath, U.; Erdelyi, M. *J. Am. Chem. Soc.* **2012**, *134*, 5706. (d) Raatikainen, K.; Rissanen, K. *Chem. Sci.* **2012**, *3*, 1235. (e) Cavallo, G.; Metrangolo, P.; Milani, R.; Pilati, T.; Priimagi, A.; Resnati, G.; Terraneo, G. *Chem. Rev.* **2016**, *116*, 2478.

(5) (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (b) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.

(6) (a) Metrangolo, P.; Meyer, F.; Pilati, T.; Resnati, G.; Terraneo, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6114. (b) Fourmigue, M. *Curr. Opin. Solid State Mater. Sci.* **2009**, *13*, 36. (c) Legon, A. C. *Phys. Chem. Chem. Phys.* **2010**, *12*, 7736. (d) Lu, Y.; Wang, Y.; Zhu, W. *Phys. Chem. Chem. Phys.* **2010**, *12*, 4543.

(7) (a) Walter, S. M.; Kniep, F.; Herdtweck, E.; Huber, S. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7187. (b) Bulfield, D.; Huber, S. M. *Chem. - Eur. J.* **2016**, *22*, 14434.

(8) Jungbauer, S. H.; Walter, S. M.; Schindler, S.; Rout, L.; Kniep, F.; Huber, S. M. *Chem. Commun.* **2014**, *50*, 6281.

(9) (a) Zhang, L.; Luo, Y.; Fan, R.; Wu, J. *Green Chem.* **2007**, *9*, 1022. (b) Tan, J.; Liang, F.; Wang, Y.; Cheng, X.; Liu, Q.; Yuan, H. *Org. Lett.* **2008**, *10*, 2485. (c) Abele, E.; Abele, R.; Lukevics, E. *J. Chem. Res., Synop.* **1999**, 624. (d) Wu, J.; Sun, W.; Sun, X.; Xia, H.-G. *Green Chem.* **2006**, *8*, 365. (e) Huo, C.; Wu, M.; Chen, F.; Jia, X.; Yuan, Y.; Xie, H. *Chem. Commun.* **2015**, *51*, 4708.

(10) (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (b) Milone, C.; Ingoglia, R.; Schipilliti, L.; Crisafulli, C.; Neri, G.; Galvagno, S. *J. Catal.* **2005**, *236*, 80.

(11) (a) Narender, T.; Reddy, K. P. *Tetrahedron Lett.* **2007**, *48*, 3177. (b) Zhai, L.; Chen, M.; Blom, J.; Theander, T. G.; Christensen, S. B.; Kharazmi, A. *J. Antimicrob. Chemother.* **1999**, *43*, 793.

(12) (a) Micheli, F.; Degiorgis, F.; Feriani, A.; Paio, A.; Pozzan, A.; Zarantonello, P.; Seneci, P. *J. Comb. Chem.* **2001**, *3*, 224. (b) Sinisterra, J. V.; Garcia-Raso, A.; Cabello, J. A.; Marinas, J. M. *Synthesis* **1984**, *1984*, 502. (c) Varma, S. K.; Kabalka, G. K.; Evans, L. T.; Pagni, P. M. *Synth. Commun.* **1985**, *15*, 279.

(13) (a) Szell, T.; Sohar, I. *Can. J. Chem.* **1969**, *47*, 1254. (b) Irie, K.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1366. (c) Mazza, L.; Guarna, A. *Synthesis* **1980**, *1980*, 41. (d) Ogiwara, Y.; Takahashi, K.; Kitazawa, F.; Sakai, N. *J. Org. Chem.* **2015**, *80*, 3101.

(14) Only a few catalysts are reported as recoverable for chalcone synthesis, and most of them are difficult to prepare. (a) Zhang, L.; Wang, A.; Wang, W.; Huang, Y.; Liu, X.; Miao, S.; Liu, J.; Zhang, T. *ACS Catal.* **2015**, *5*, 6563. (b) Yi, W.-B.; Cai, C. *J. Fluorine Chem.* **2008**, *129*, 524.

(15) Guha, S.; Rajeshkumar, V.; Kotha, S. S.; Sekar, G. *Org. Lett.* **2015**, *17*, 406.

(16) This reaction offers tolerance to the carbomethoxy group (COOMe) containing benzaldehydes which is only reported with basic alumina by Pagni et al. (see ref 12c). Methoxy, cyano, and nitro groups can deactivate the Lewis acid by coordinating with it, and hence those groups containing benzaldehydes are unsuitable as substrates in Lewis acid catalyzed reactions [see ref 13d].

(17) All the *E*- products were confirmed using the coupling constant *J* value of the olefinic protons. For details, see the Supporting Information.

(18) Hema, R.; Parthasarathi, V.; Ravikumar, K.; Sridhar, B.; Pandiarajan, K. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2006**, *62*, 708.

(19) (a) Kalluraya, B.; Chimbalkar, R. M.; Hegde, J. C. *Indian J. Heterocycl. Chem.* **2005**, *15*, 15. (b) Ivanova, Y.; Momekov, G.; Petrov, O.; Karaivanova, M.; Kalcheva, V. *Eur. J. Med. Chem.* **2007**, *42*, 1382.

(20) For details see Supporting Information

(21) Zou, W. S.; Han, J.; Jin, W. J. *J. Phys. Chem. A* **2009**, *113*, 10125.

(22) 3-Nitrobenzaldehyde has less tendency to be oxidized with respect to simple benzaldehyde.

DOI: 10.1021/acs.orglett.7b00348
Org. Lett. 2017, 19, 1244−1247