Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX-XXX

pubs.acs.org/OrgLett

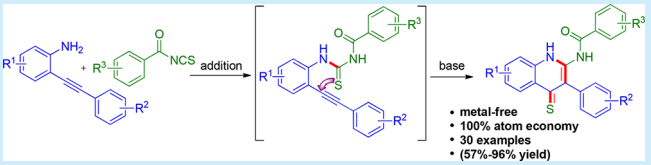
Base-Promoted Synthesis of Quinoline-4(1*H*)-thiones from *o*-Alkynylanilines and Aroyl Isothiocyanates

Anju Modi, Prasenjit Sau, and Bhisma K. Patel*

Department of Chemistry, Indian Institute of Technology Guwahati, North Guwahati 781039, India

Supporting Information

ABSTRACT: A base-promoted synthesis of quinoline-4(1*H*)-thiones has been accomplished from the in situ generated *o*-alkynylthiourea, obtained by reacting *o*-alkynylanilines with aroyl/acyl isothiocyanates. A 6-*exo*-*dig* *S*-cyclization of the in situ generated thiourea is followed by a rearrangement to give quinoline-4(1*H*)-thiones.

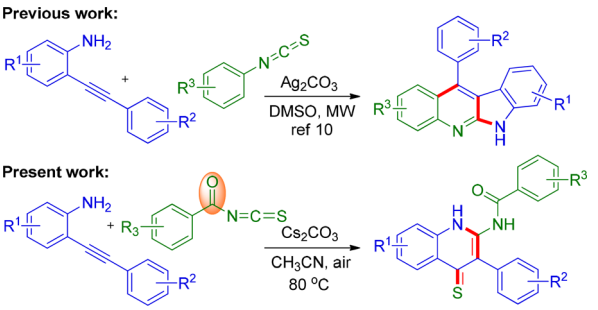


Construction of heterocycles with privileged scaffolds, which exhibit various biological activities, is in great demand in the field of chemical genetics.[1] Among numerous efforts devoted toward the development of these compounds, cascade reactions have emerged as a powerful synthetic tool in modern synthetic organic chemistry.[2] Compared to the traditional stepwise synthesis, cascade reactions have the advantage of sequential incorporation of multiple C−C and C−heteroatom bonds in one pot, thereby increasing the overall synthetic efficiency. Taking advantage of this strategy, several alkyne-based substrates, possessing internal nucleophiles at appropriate positions, are often utilized for the construction of interesting heterocycles.[3] Among various alkynes, *o*-alkynylanilines have been extensively employed for the construction of molecular frameworks such as indole,[4] quinoline,[5] quinazolinone,[6] benzoxazine,[7] and 4*H*-benzo[*d*][1,3]thiazine[8] using various metal salts such as palladium, copper, and silver.

Aroyl isothiocyanates, apart from being used as acylating[9a] and thiocyanating agents,[9a,b] have also been utilized for the synthesis of many biologically important heterocycles.[9c] Recently, we reported the synthesis of indolo[2,3-*b*]quinolines from *o*-alkynylanilines and aryl isothiocyantes in the presence of Ag_2CO_3 under microwave heating.[10] Interestingly, replacement of aryl isothiocyanate with an aroyl isothiocyanate completely changed the course of reaction and the product outcome, giving a quinoline-4(1*H*)-thione (Scheme 1).

Encouraged by this interesting result, we further investigated the reaction by reacting 2-(phenylethynyl)aniline (**1**) (1 equiv) and benzoyl isothiocyanate (**a**) (1 equiv) in the presence of CuI (10 mol %) and K_2CO_3 (4 equiv) in 1,4-dioxane at 110 °C (Table 1, entry 1). Spectroscopic analysis (IR, ^{1}HNMR, ^{13}CNMR, and HRMS) of the isolated product indicated its structure to be *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (**1a**). However, the exact structure of the product was fully ascertained by single-crystal X-ray diffraction of one of its derivative (**3a**) (Figure S1, see the Supporting Information), thereby confirming its structure to be *N*-(3-phenyl-4-thioxo-1,4-dihydroquinolin-2-yl)benzamide (**1a**). Interestingly, the benzoyl thiourea generated in situ underwent a 6-*exo*-*dig* *S*-attack onto the internal alkyne followed by rearrangement to give the quinoline-4(1*H*)-thione moiety in 100% atom economy. On the basis of recent studies, quinoline-4(1*H*)-thione derivatives are found to be inhibitors of virulence factor elastase of the human pathogen *Pseudomonas aeruginosa* (Figure S2, **I**).[11a,b] Some of the quinoline-4(1*H*)-thione derivatives (Figure S2, **II**) are reported to form oxovanadium complexes with $VO(acac)_2$, exhibiting cytotoxic activity and apoptosis in human malignant cell lines.[11c] Despite the importance of the quinoline-4(1*H*)-thione framework, there are only a few reports of their synthesis which mainly involve thioketolization of the preformed quinolin-4(1*H*)-ones with phosphorus pentasulfide (P_4S_{10}) or with Lawesson's reagent.[11,12] To the best of our knowledge, there is no report at this date for the synthesis of quinoline-4(1*H*)-thiones from *o*-alkynylanilines and aroyl isothiocyanate in the presence of base.

Scheme 1. Differential Reactivity of *o*-Alkynylanilines with Aryl and Aroyl Isothiocyanates

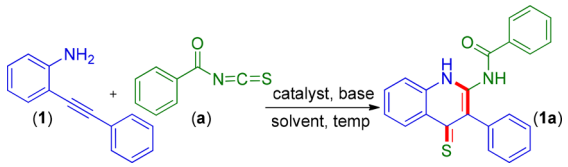


Encouraged by the synthesis of quinoline-4(1*H*)-thiones, further optimization of the reaction parameters were tuned to enhance the productivity of the reaction. Initially, a range of other copper salts such as CuBr (52%), $Cu(OAc)_2$ (41%), and $Cu(OTf)_2$ (37%) were examined, among which CuBr gave better yield (52%) compared to CuI (47%) (Table 1, entries

Received: September 24, 2017

DOI: 10.1021/acs.orglett.7b02993
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Screening of the Reaction Conditions[a]



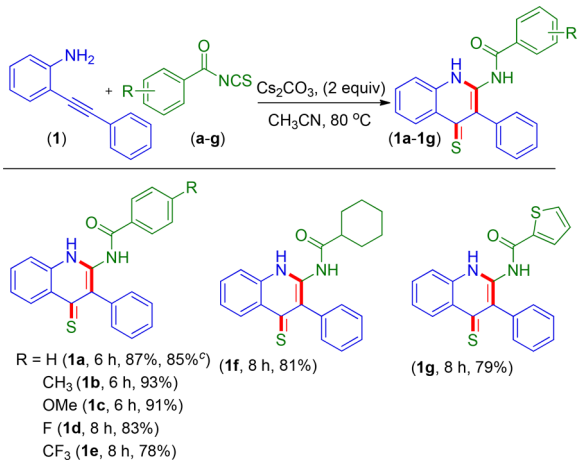
entry	catalyst (mol %)	base (equiv)	solvent	yield[d] (%)
1	CuI (10)	K_2CO_3 (4)	dioxane	47
2	CuBr (10)	K_2CO_3 (4)	dioxane	52
3	$Cu(OAc)_2$ (10)	K_2CO_3 (4)	dioxane	41
4	$Cu(OTf)_2$ (10)	K_2CO_3 (4)	dioxane	37
5	Ag_2CO_3 (10)	K_2CO_3 (4)	dioxane	18
6	CuBr (10)	Na_2CO_3 (4)	dioxane	9
7	CuBr (10)	Cs_2CO_3 (4)	dioxane	68
8	CuBr (10)	DBU (4)	dioxane	29
9	CuBr (10)	DABCO (4)	dioxane	11
10	CuBr (20)	Cs_2CO_3 (4)	dioxane	64
11	CuBr (5)	Cs_2CO_3 (4)	dioxane	69
12	CuBr (5)	Cs_2CO_3 (2)	dioxane	66
13		Cs_2CO_3 (2)	dioxane	77
14	CuBr (5)		dioxane	13
15		Cs_2CO_3 (2)	CH_3CN	83
16		Cs_2CO_3 (2)	DMSO	48
17		Cs_2CO_3 (2)	DMF	53
18		Cs_2CO_3 (2)	DCE	0
19[b]		Cs_2CO_3 (2)	CH_3CN	71
20[c]		Cs_2CO_3 (2)	CH_3CN	87

[a]Reaction conditions: **1** (0.25 mmol), **a** (0.25 mmol), catalysts (mol %), base (equiv), solvent (2 mL) under air at 110 °C for 6 h. [b]Reaction at 130 °C. [c]Reaction at 80 °C. [d]Yield of the isolated product.

1−4). The use alkyne activating silver salt viz. Ag_2CO_3 (18%), in lieu of copper salt, was not so effective (Table 1, entry 5). Other inorganic bases such as Na_2CO_3 and Cs_2CO_3 (Table 1, entries 6 and 7) and organic bases such as DBU and DABCO (Table 1, entries 8 and 9) were tested. Except Cs_2CO_3 (68%, Table 1, entry 7), none of the bases tested gave satisfactory results. Increasing the catalyst loading to 20 mol % was not beneficial (Table 1, entry 10), while decreasing the catalyst loading to 5 mol % (Table 1, entry 11) was equally effective to that of higher catalyst loading (10 mol %). A comparable yield of 66% was obtained when the amount of base used was reduced to 2 equiv (Table 1, entry 12). Surprisingly, when the reaction was carried out in absence of the catalyst under otherwise identical condition, the product yield improved considerably (77%), while in the absence of base only a trace (13%) of the product was observed (Table 1, entries 13 and 14). This result suggests the noninvolvement of catalyst and the essential requirement of base for this cascade reaction. Different solvents such as CH_3CN, DMSO, DMF, and DCE were screened, and solvent CH_3CN gave an improved yield of 83%, whereas DMSO and DMF provided reduced yields of 48% and 53%, respectively (Table 1, entries 15−17). No product formation was observed in DCE (Table 1, entry 18). To check the effect of temperature, reactions were performed at an elevated temperature (130 °C) and at lower temperature (80 °C). Unexpectedly, the increase in the reaction temperature was detrimental to the product formation, giving only 71% yield, whereas lowering the temperature provided an improved yield of 87% (Table 1, entries 19 and 20). Lower yield at higher temperature may be due to the decomposition or dimerization of the product. It may be noted that on prolonged reaction time (12 h) the obtained product oxidized, giving a dimeric (S−S bond) product (Scheme S1, SI).

The scope and generality of the base-promoted reaction was extended to a variety of *o*-alkynylanilines and aroyl isothiocyanates under the optimized reaction conditions (Table 1, entry 20). At first, the effect of different aroyl/acyl isothiocyanates (**a**−**g**) on 2-(phenylethynyl)aniline (**1**) was examined, and the results are summarized in Scheme 2. The

Scheme 2. Substrate Scope of 2-(Phenylethynyl)aniline with Aroyl Isothiocyanates[a−c]



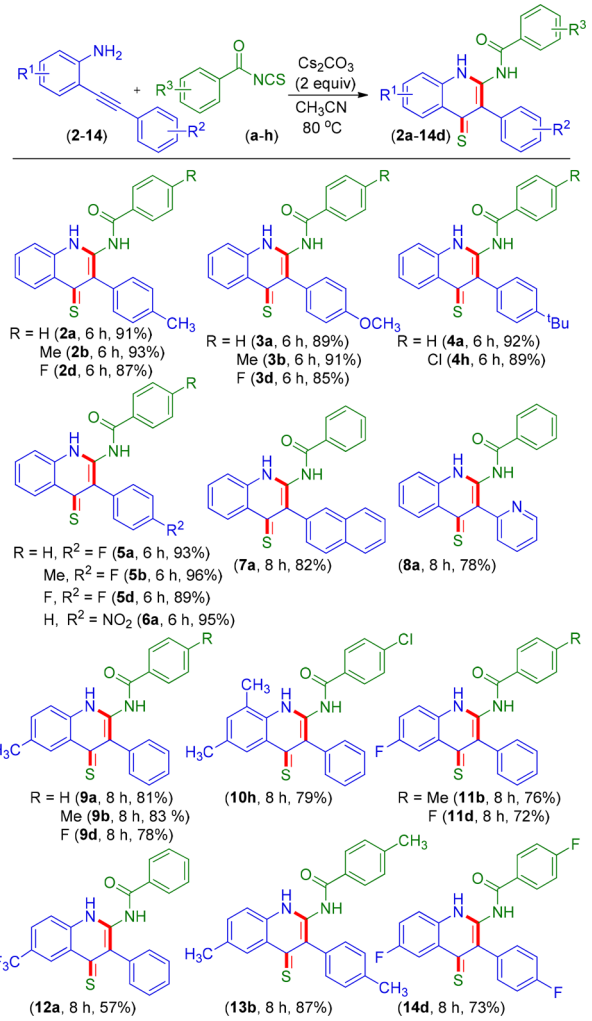
[a]Reaction conditions: 2-(phenylethynyl)aniline (**1**) (0.25 mmol), aroyl isothiocyanates (**a**−**g**) (0.25 mmol), Cs_2CO_3 (0.5 mmol) in CH_3CN (2 mL) under air at 80 °C for 6−8 h. [b]Isolated yield. [c]1 mmol scale.

phenyl ring of benzoyl isothiocyanates bearing electron-donating groups such as *p*-CH_3 (**b**) and *p*-OCH_3 (**c**) provided excellent yields of **1b** (93%) and **1c** (91%) compared to the unsubstituted analogue **1a** (87%). However, lower yields of products **1d** (83%) and **1e** (78%) (Scheme 2) were obtained when moderately electron-withdrawing *p*-F (**d**) and strongly electron-withdrawing *p*-CF_3 (**e**) groups were present on the phenyl ring of benzoyl isothiocyanates. Acyclic as well as heterocyclic carbonyl isothiocyantes such as cyclohexanecarbonyl isothiocyanate (**f**) and thiophene-2-carbonyl isothiocyanate (**g**) reacted competently with **1** to give good yields of the product **1f** (81%) and **1g** (79%), respectively. These results suggest that, irrespective of the substituents present on the aroyl isothiocyanates, all reacted well with **1** to give the corresponding products.

Next, the effect of the substituents R^2 present on the alkyne side of the phenyl ring in 2-(phenylethynyl)anilines (**2**−**14**) was tested by reacting them with various benzoyl isothiocyantes (**a**−**h**) (Scheme 3). 2-(Phenylethynyl)aniline derivatives, bearing either electron-donating (*p*-CH_3 (**2**), *p*-OCH_3 (**3**), and *p*-^{t}Bu (**4**)) or electron-withdrawing (*p*-F (**5**), *p*-NO_2 (**6**)) groups on the alkyne side of the phenyl ring reacted efficiently with benzoyl isothiocyanate (**a**) to give good yields of their products (**2a**−**6a**) in the range of 89−95% yield. When both the substituents R^2 in alkynylaniline and R^3 in aroyl isothiocyanate were electron-donating, such as *p*-CH_3 (**2**)/*p*-CH_3 (**b**) and *p*-OCH_3 (**3**)/*p*-CH_3 (**b**), excellent yields of their product (**2b**, 93%) and (**3b**, 91%) were obtained. On the other

DOI: 10.1021/acs.orglett.7b02993
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Substrate Scope for Substituted 2-(Phenylethynyl)aniline and Benzoyl Isothiocyanates[a,b]



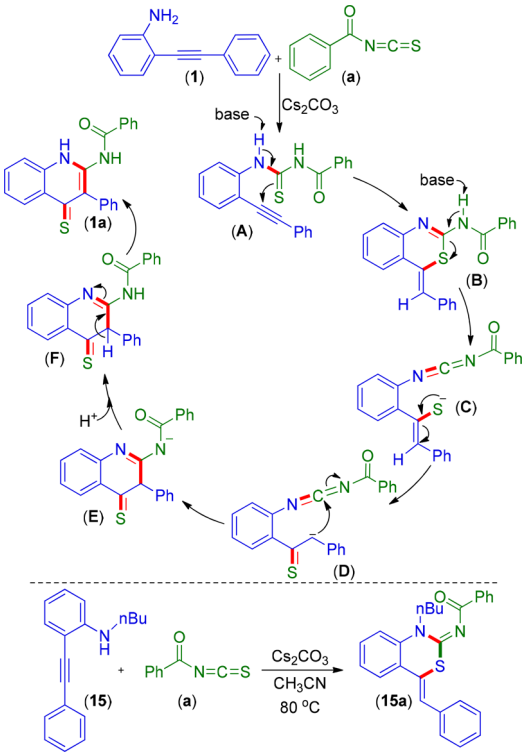
[a]Reaction conditions: 2-(phenylethynyl)aniline (**2**–**13**) (0.25 mmol), benzoyl isothiocyanates (**a**–**h**) (0.25 mmol), Cs_2CO_3 (0.5 mmol) in CH_3CN (2 mL) under air at 80 °C for 6–8 h. [b]Isolated yields.

hand, when substituent R^2 was electron-donating and R^3 was electron-withdrawing, combinations such as *p*-CH_3 (**2**)/*p*-F (**d**), *p*-OCH_3 (**3**)/*p*-F (**d**), and *p*-^{t}Bu (**4**)/*p*-Cl (**h**), the yields of their products were slightly lower (**2d**, 87%; **3d**, 85%; and **4h**, 89%). However, when R^2 was electron-withdrawing, i.e., *p*-F (**5**), it gave comparatively higher yields of their products (**5b**, 96%) and (**5d**, 89%), irrespective of the nature of substituents R^3 (either electron-donating, *p*-CH_3 (**b**) or electron-withdrawing *p*-F (**d**)). 2-(Naphthalen-2-ylethynyl)aniline (**7**) and 2-(pyridin-2-ylethynyl)aniline (**8**) also reacted efficiently with benzoyl isothiocyanate (**a**) to give their respective products **7a** and **8a** in 82 and 78% yields.

Further, the effect of substituents R^1 present on the amine-bearing ring of 2-(phenylethynyl)anilines (**9**–**12**) was investigated. When the substituent R^1 was electron-donating, such as *p*-CH_3 (**9**) and 2,4-di-CH_3 (**10**), good yields of the products **9a** (81%), **9b** (83%), **9d** (78%), and **10h** (79%) were obtained on reaction with benzoyl isothiocyantes (**a**, **b**, **d**, and **h**). On the other hand, when R^1 was moderately electron-withdrawing such as *p*-F (**11**), the products **11b** and **11d** were obtained in 76% and 72% yields, respectively. With a strong electron-withdrawing group such as *p*-CF_3 (**12**), the yield dropped further to 57% (Scheme 3). Moreover, when all substituents R^1, R^2, and R^3 were either *p*-CH_3 (**13**) or *p*-F (**14**), their products **13b** and **13d** were furnished in 87% and 73% yields, respectively. When aliphatic groups like cyclopropyl and butyl were present instead of phenyl rings on the alkyne side of 2-(phenylethynyl)aniline, the intermediate thiourea generated did not undergo any further reaction. To demonstrate the potential application of the present method, a gram-scale reaction was carried out with 2-(phenylethynyl)aniline (**1**) (6.2 mmol, 1.19 g) and benzoyl isothiocyanate (**a**) (6.2 mmol, 1.01 g) under the standard reaction conditions. The reaction proceeded smoothly to afford 77% isolated yield of (**1a**).

On the basis of the literature reports, a plausible pathway has been proposed for the base-promoted cascade reaction (Scheme 4). Reaction of 2-(phenylethynyl)aniline (**1**) and

Scheme 4. Plausible Reaction Mechanism



benzoyl isothiocyanate (**a**) generates an intermediate thiourea **A**.[13a,b] A 6-*exo*-*dig* *S*-attack onto the internal alkyne is facilitated via the abstraction of a thioamidic nitrogen proton attached to the phenyl ring to give intermediate **B**.[13a−c] Abstraction of a second proton from the intermediate **B** generates a carbodiimide intermediate **C**. The thiolate **C** so generated undergoes thioketolization, giving a diphenylethane thione nucleophilic moiety **D**.[13d] Intramolecular nucleophilic attack of the heterocumulene generates a cyclic anionic intermediate **E**, which upon protonation gave **F**. Finally, a proton migration produces the desired quinoline-4(1*H*)-thiones product (**1a**). The reaction of aroyl isothiocyanate (**a**) with secondary amine based *o*-alkynylanilines (**15**) gave product **15a** in 92% yield (Scheme 4). The inability of the product **15a** to undergo further ring opening cyclization is due to the absence second NH proton, there by supporting our proposed mechanism.

DOI: 10.1021/acs.orglett.7b02993
Org. Lett. XXXX, XXX, XXX−XXX

In conclusion, we have demonstrated a metal-free approach for the synthesis of quinoline-4(1*H*)-thione derivatives. This is the first example of a base-promoted synthesis of quinoline-4(1*H*)-thiones from *o*-alkynylanilines and aroyl isothiocyanate. Through the cascade process, simultaneous formation of three C−C, C−N, and C−S bonds has been accomplished. This protocol shows wide functional group tolerance with good to excellent yields of the product in 100% atom economy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02993.

X-ray data for **3a** (CIF)

Experimental procedures, spectral and analytical data of all products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: patel@iitg.ernet.in.

ORCID

Bhisma K. Patel: 0000-0002-4170-8166

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

B.K.P. acknowledges the support of this research by the Department of Science and Technology (DST/SERB) (EMR/2016/007042), DST-FIST, and MHRD: 5-5/2014-TS-VII.CIF, IIT Guwahati for instrumental facilitities. A.M. thanks the CSIR for a fellowship.

■ REFERENCES

(1) (a) Arya, P.; Chou, D. T. H.; Baek, M.-G. *Angew. Chem., Int. Ed.* **2001**, *40*, 339. (b) Schreiber, S. L. *Science* **2000**, *287*, 1964. (c) Walsh, D. P.; Chang, Y.-T. *Chem. Rev.* **2006**, *106*, 2476.

(2) (a) Zeng, X. *Chem. Rev.* **2013**, *113*, 6864. (b) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (c) Wang, Y.; Lu, H.; Xu, P.-F. *Acc. Chem. Res.* **2015**, *48*, 1832. (d) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 400. (e) Liu, J.; Ng, T.; Rui, Z.; Ad, O.; Zhang, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 136 and references cited therein.. (f) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

(3) (a) Cai, Z.-J.; Li, F.-H.; Wang, S.-Y.; Ji, S.-J. *Org. Lett.* **2016**, *18*, 4810. (b) Yu, J.; Zhang-Negrerie, D.; Du, Y. *Org. Lett.* **2016**, *18*, 3322. (c) Senadi, G. C.; Gore, B. S.; Hu, W.-P.; Wang, J.-J. *Org. Lett.* **2016**, *18*, 2890. (d) Jash, M.; Das, B.; Chowdhury, C. *J. Org. Chem.* **2016**, *81*, 10987.

(4) (a) Gogoi, A.; Guin, S.; Rout, S. K.; Patel, B. K. *Org. Lett.* **2013**, *15*, 1802. (b) Gogoi, A.; Modi, A.; Guin, S.; Rout, S. K.; Das, D.; Patel, B. K. *Chem. Commun.* **2014**, *50*, 10445. (c) Nair, R. N.; Lee, P. J.; Grotjahn, D. B.; Rheingold, A. L. *Chem. - Eur. J.* **2010**, *16*, 7992. (d) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 4160.

(5) (a) Zhao, J.; Peng, C.; Liu, L.; Wang, Y.; Zhu, Q. *J. Org. Chem.* **2010**, *75*, 7502. (b) Peng, C.; Wang, Y.; Liu, L.; Wang, H.; Zhao, J.; Zhu, Q. *Eur. J. Org. Chem.* **2010**, *2010*, 818. (c) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 4160. (d) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765.

(6) (a) Gimeno, A.; Medio-Simón, M.; Ramirez de Arellano, C.; Asensio, G.; Cuenca, A. B. *Org. Lett.* **2010**, *12*, 1900. (b) Wang, H.; Liu, L.; Wang, Y.; Zhang, J.; Zhu, Q. *Tetrahedron Lett.* **2009**, *50*, 6841.

(7) Saito, T.; Ogawa, S.; Takei, N.; Kutsumura, N.; Otani, T. *Org. Lett.* **2011**, *13*, 1098.

(8) Tang, R.-Y.; Luo, P.-S.; Zhang, X.-G.; Li, J.-H.; Zhong, P. *Synlett* **2010**, *2010*, 1345.

(9) (a) Modi, A.; Ali, W.; Patel, B. K. *Org. Lett.* **2017**, *19*, 432. (b) Palsuledesai, C. C.; Murru, S.; Sahoo, S. K.; Patel, B. K. *Org. Lett.* **2009**, *11*, 3382. (c) Bedane, K. G.; Singh, G. S. *ARKIVOC* **2015**, No. v, 206.

(10) Ali, W.; Dahiya, A.; Pandey, R.; Alam, T.; Patel, B. K. *J. Org. Chem.* **2017**, *82*, 2089.

(11) (a) Szamosvári, D.; Reichle, V. F.; Jureschi, M.; Böttcher, T. *Chem. Commun.* **2016**, *52*, 13440. (b) Prothiwa, M.; Szamosvári, D.; Glasmacher, S.; Böttcher, T. *Beilstein J. Org. Chem.* **2016**, *12*, 2784. (c) Yamaguchi, T.; Watanabe, S.; Matsumura, Y.; Tokuoka, Y.; Yokoyama, A. *Chem. Pharm. Bull.* **2012**, *60*, 508.

(12) (a) Bergman, J.; Pettersson, B.; Hasimbegovic, V.; Svensson, P. H. *J. Org. Chem.* **2011**, *76*, 1546. (b) Escribano, J.; Rivero-Hernández, C.; Rivera, H.; Barros, D.; Castro-Pichel, J.; Pérez-Herrán, E.; Mendoza-Losana, A.; Angulo-Barture n, I.; Ferrer-Bazaga, S.; Jiménez-Navarro, E.; Ballell, L. *ChemMedChem* **2011**, *6*, 2252.

(13) (a) Ding, Q.; Wu, J. *J. Comb. Chem.* **2008**, *10*, 541. (b) Ding, Q.; Cao, B.; Zong, Z.; Peng, Y. *J. Comb. Chem.* **2010**, *12*, 370. (c) Zhao, P.; Liao, Q.; Gao, H.; Xi, C. *Tetrahedron Lett.* **2013**, *54*, 2357. (d) Wang, B.; Sun, S.; Yu, J.-T.; Jiang, Y.; Cheng, J. *Org. Lett.* **2017**, *19*, 4319.

DOI: 10.1021/acs.orglett.7b02993
Org. Lett. XXXX, XXX, XXX−XXX