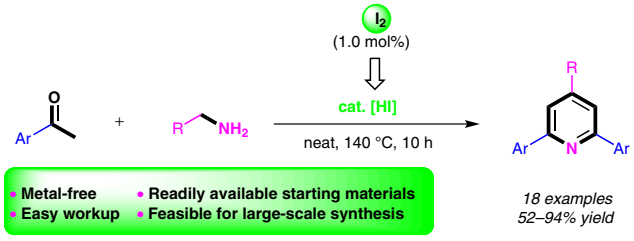
Synthesis H. Xu et al. Paper

Metal-Free Synthesis of 2,4,6-Trisubstituted Pyridines via Iodine-Initiated Reaction of Methyl Aryl Ketones with Amines under Neat Heating

Hui Xu
Ji-Chao Zeng
Fang-Jian Wang
Ze Zhang*

School of Biological and Chemical Engineering,
Anhui Polytechnic University, Wuhu 241000,
P. R. of China
zhangze@ustc.edu.cn



Received: 06.10.2016
Accepted after revision: 29.11.2016
Published online: 15.12.2016
DOI: 10.1055/s-0036-1588380; Art ID: ss-2016-h0701-op

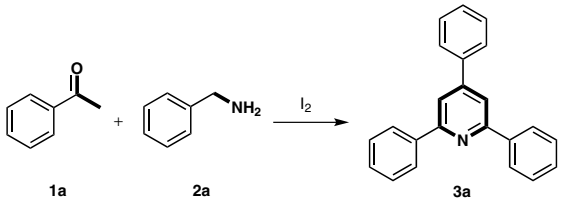
Abstract A neat heating protocol has been developed for metal-free synthesis of various 2,4,6-trisubstituted pyridines via iodine-initiated (in situ generated HI-catalyzed) condensation of methyl aryl ketones with amines and the following cyclization-aerobic oxidation. Large-scale synthesis and mechanistic investigation were also performed.

Key words 2,4,6-trisubstituted pyridine, molecular iodine, metal-free, neat heating, methyl aryl ketone

Multi-substituted pyridines, especially 2,4,6-trisubstituted pyridines (Kröhnke pyridines),[1] have been broadly applied for chemosensors,[2] asymmetric catalysis,[3] and as photosensitizers.[4] Such moieties are also very important building blocks in supramolecular chemistry due to their π-stacking ability along with directional H-bonding capacity.[5] In addition, the outstanding thermal stabilities of these pyridines have attracted growing interests for their use as monomeric building blocks in thin films and organometallic polymers.[6] Hence their synthesis has drawn a great deal of attention. Since Kröhnke's original report on the synthesis of 2,4,6-trisubstituted pyridines, there has been a plethora of research targeting their synthesis, and enormous number of preparative approaches have been developed, most of which are summarized by Katritzky.[7] In contrast, the most commonly used approaches to 2,4,6-trisubstituted pyridines involve cyclocondensation reaction of acetophenones and benzaldehydes with ammonium acetate; and various new catalysts or conditions have been reported.[8] Recently, some new methods were developed by employing other starting materials, including solvent-free heating of acetophenone oximes with aldehydes or acetophenones with benzyl halides,[9,10] I_2-mediated process based on catabolism and reconstruction behaviors of amino acids with ketones,[11] TfOH- or $Cu(OTf)_2$-catalyzed cyclization of amines with ketones,[12,13] and photoredox catalysis of aryl ketones with benzyl amines.[14]

During our investigation on iodine-mediated cascade condensation-cyclization of aryl methyl ketones with anilines for straightforward synthesis of 1,2,4-triarylpyrroles,[15]

Table 1 Optimization of the Reaction Conditions for the Synthesis of 2,4,6-Triphenylpyridine (**3a**)[a]



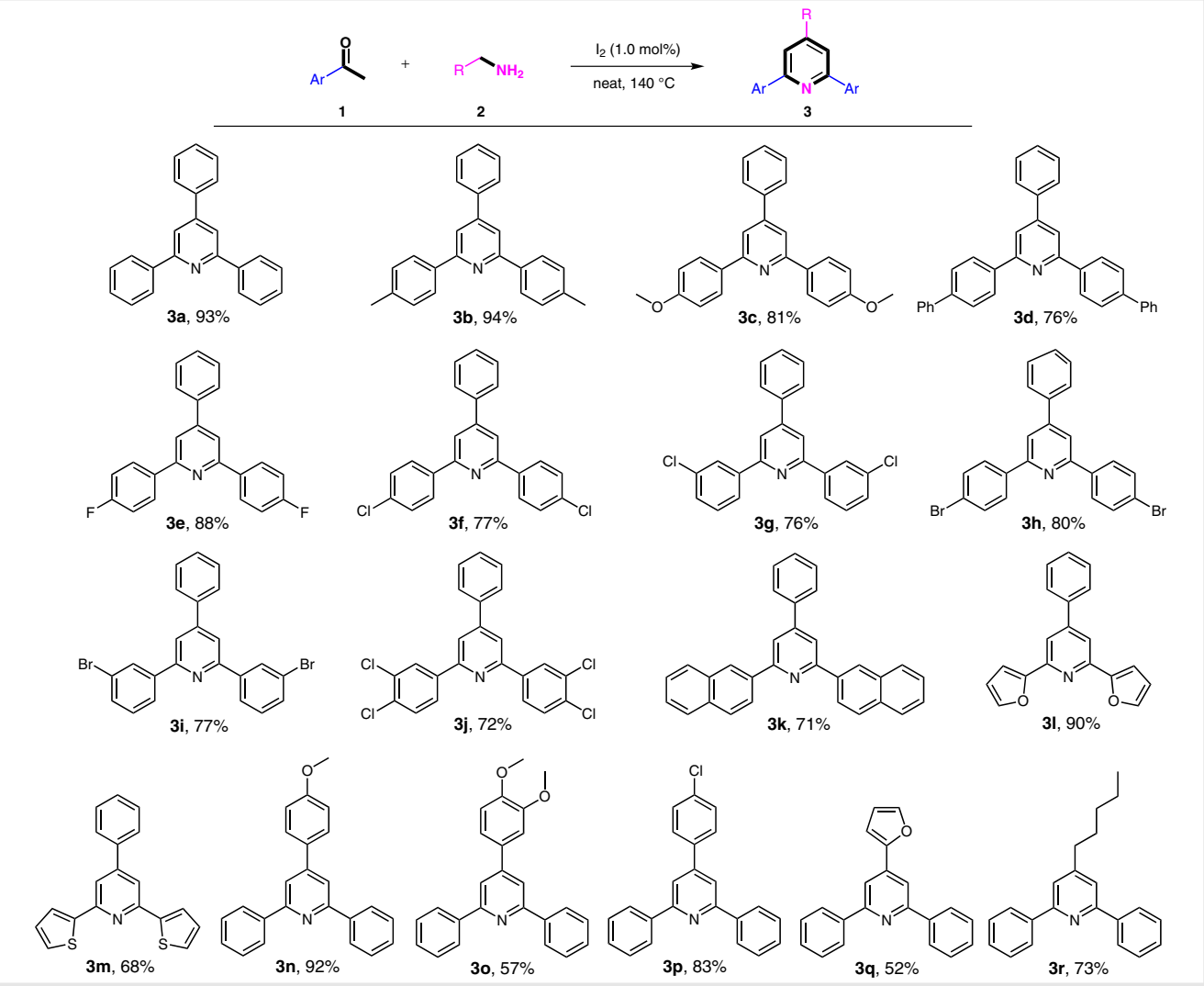
1a **2a** **3a**

Entry	Ratio (**1a**/**2a**/I_2)	Solvent	Temp (°C)	Yield (%)[b]
1	2:2:1	PhCl	140	89
2	2:2:0.2	PhCl	140	90
3	2:2:0.1	PhCl	140	90
4	2:2:0.01	PhCl	140	90
5	2:2:0	PhCl	140	10
6	2:2:0.01	neat	140	94
7	2:2:0.01	neat	120	63
8	2:2:0.01	neat	100	47
9	2:1.5:0.01	neat	140	93
10	2:1:0.01	neat	140	93
11[c]	2:1:0.01	neat	140	65

[a] A mixture of acetophenone (**1a**; 2 mmol), benzylamine (**2a**), I_2, and solvent (entries 1–5, 5 mL) was stirred for 10 h in a 25 mL sealed Schlenk tube full of air and opened to air for further 1 h stirring.
[b] Isolated yield based on **1a**.
[c] Reaction was carried out open to air.

it was unexpectedly found that 2,4,6-triphenylpyridine but not 1,2,4-triphenylpyrrole was obtained when benzylamine (**2a**) was employed instead of anilines to react with acetophenone (**1a**) in PhCl by heating at 140 °C for 10 hours in the presence of 50 mol% iodine (Table 1, entry 1). To the best of our knowledge, this iodine-promoted transformation is a new alternative for the construction of 2,4,6-trisubstitutted pyridine. In view of green synthesis, we wanted to optimize the reaction with more efficient and milder conditions to further increase the yield and simplify the workup (Table 1).

Since usage of excess of iodine often leads to tedious extraction and washing operation with aqueous sodium thiosulfate, we therefore attempted to reduce the amount of iodine (Table 1, entries 2–4). To our delight, decreasing the usage of iodine has no significant effect on the reaction efficiency, and even only 1.0 mol% iodine can still afford 90% yield. However, only minor amount of the product was generated in the absence of I_2 (entry 5). To avoid the use of high boiling PhCl as solvent, this reaction was performed directly under neat heating. Surprisingly and gratifyingly, this protocol exhibited obviously higher efficiency (entry 6), in which acetophenone (**1a**) was completely consumed. In contrast, there was more or less residual acetophenone (**1a**) left in all experiments with PhCl as solvent. When the reaction temperature was lowered with fixed molar ratio of acetophenone (**1a**), benzylamine (**2a**), and I_2 at 2:2:0.01 under neat heating for 10 hours, large amounts of starting materials remained, thus decreasing the yield significantly (entries 7, 8). Based on the fact that the stoichiometric ratio of acetophenone (**1a**) to benzylamine (**2a**) is 2:1, we further attempted to reduce the usage amount of benzylamine (**2a**)



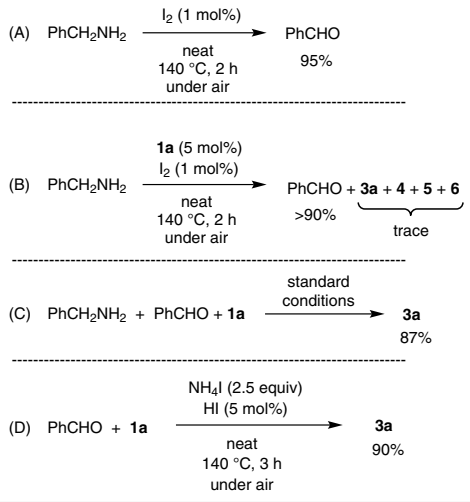
Scheme 1 I_2-initiated reaction of methyl aryl ketones **1** with amines **2** for the synthesis of 2,4,6-trisubstituted pyridines (**3**) under neat heating. *Reaction conditions*: a mixture containing **1** (2.0 mmol), **2** (1.0 mmol), and I_2 (0.01 mmol) was stirred in a 25 mL sealed Schlenk tube full of air under neat heating (140 °C) for 10 h. Isolated yields after short flash column chromatography are shown.

up to 0.5 equivalent. To our delight, the reaction still proceeded completely with no decrease in the yield (entries 9, 10). Therefore, the best reaction condition for this iodine-promoted transformation of acetophenone (**1a**) and benzylamine (**2a**) to 2,4,6-triphenylpyridine is neat heating at 140 °C with a 2:1:0.01 molar ratio of acetophenone (**1a**), benzylamine (**2a**), and I_2 (entry 10). It is worth mentioning that a reduced yield of 65% was achieved when the reaction was carried out opened to air (entry 11). This result may be ascribed to the possible sublimation of some iodine, and it can be further understood from the possible reaction mechanism in which some in situ generated ammonia may escape (see Scheme 3, vide infra). In sealed Schlenk tube, these problems were avoided, and the filled air accompanied with further stirring in open air ensured complete aromatization of the in situ generated 1,4-dihydropyridine into the final product.

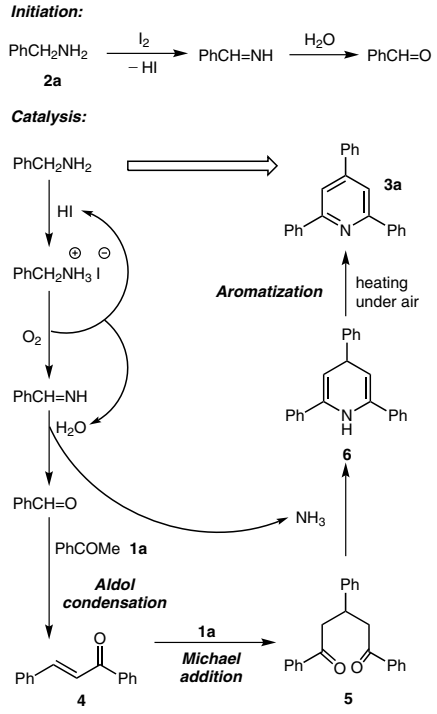
Then the optimized reaction condition was applied to various methyl aryl ketones and amines, and a series of 2,4,6-trisubstituted pyridines were obtained in moderate to good yields. The results are summarized as outlined in Scheme 1.

First, various methyl aryl ketones were employed to react with benzylamine, including substituted acetophenones **3a–k** and heterocyclic aryl ketones **3l**, **m**. Then some other substituted benzylamines **3n–p**, 2-furanmethylamine (**3q**), and long-chain aliphatic amine **3r** were chosen to react with acetophenone. In these cases, substrates bearing either electron-donating or electron-withdrawing group all can afford the corresponding products efficiently, showing no obvious difference from substituent effect. Thus, this protocol exhibited a broad scope of substrates and high substituent compatibility. The reaction was performed under neat heating and just a trace of iodine was involved, and the resulting reaction mixture was directly subjected to a very short column chromatography, accomplishing facile isolation of the desired products without extractive workup. Furthermore, a large scale synthesis of **3a** has also been attempted under the standard condition. A mixture of acetophenone (**1a**; 40 mmol), benzylamine (**2a**; 20 mmol), and iodine (0.2 mmol) was stirred for 24 hours in a 25 mL sealed Schlenk tube under constant bubbling of O_2. Then cold water containing EtOH (10 mL, v/v = 1:1) was added to the cooled reaction mixture under stirring, and the desired product **3a** was simply obtained just by filtration, washing, and desiccation (82% yield, >96% purity).

During the reaction, we found that the deep purple color of iodine disappeared rapidly, which implies that herein employed I_2 was consumed and acted as initiator but not as catalyst. On the other hand, controlled experiment showed that benzylamine (**2a**) was efficiently transferred into benzaldehyde and ammonia in the presence of a catalytic amount of iodine by neat heating under air (Scheme 2, A). Therefore, a plausible reaction mechanism is proposed as shown in Scheme 3. First, I_2-initiated oxidation of benzylamine provides the corresponding imine and afterward benzaldehyde via hydrolysis. The in situ generated HI further transforms benzylamine into its ammonium iodide, which is oxidized to imine via dehydration in the presence of oxygen. Benzaldehyde and NH_3 are formed through hydrolysis of the imine, and HI gets regenerated for next cycles. Then the reaction may undergo the following steps for the formation of the product, in which HI may still be involved in catalysis: aldol condensation of acetophenone (**1a**) with the in situ generated benzaldehyde from benzylamine (**2a**) to afford chalcone (**4**); afterward Michael addition to accomplish the 1,5-diketone **5**; further cyclization with in situ generated NH_3 to form the precursor 1,4-dihydropyridine **6**, and aromatization to the final product **3a**. This mechanism is somewhat similar to what have been reported,[8b,16] and is further confirmed by several other controlled experiments as shown in Scheme 2, B–D. A stirred mixture containing benzylamine (**2a**), acetophenone (**1a**; 5 mol%), and I_2 (1 mol%) was heated at 140 °C for 2 hours, affording majority of benzaldehyde (>90% yield), and a trace of product **3a**; intermediates **4–6** were also detected (Scheme 2, B). On the other hand, a three-component reaction of $PhCH_2NH_2$, PhCHO, and PhCOMe (1:1:2) under the standard condition afforded 2,4,6-triphenylpyridine in comparable yield (87%), but some PhCHO remained and minor side products were generated (Scheme 2, C). Furthermore, a comparative reaction of PhCHO (1.0 mmol), PhCOMe (2.0 mmol), NH_4I (2.5 mmol), and HI (5.0 mol%) was performed by neat heating at 140 °C for 3 hours (Scheme 2, D). As expected, the corresponding 2,4,6-triphenylpyridine was obtained in 90% yield, and the formation of the aldol/chalcone adduct and the Michael adduct 1,5-diketone was also detected during the reaction process.



Scheme 2 Controlled experiments



Scheme 3 Proposed reaction mechanism

In summary, a simple and efficient method has been successfully developed for the metal-free synthesis of various 2,4,6-trisubstituted pyridines starting from methyl aryl ketones and amines via cascade condensation-cyclization-aromatization process. The transformation was accomplished in moderate to excellent yield in the presence of catalytic (1.0 mol%) molecular iodine acting as an initiator to generate HI in situ as the actual catalyst, followed by aerobic oxidation under neat heating conditions. This expeditious protocol exhibits several advantages such as employment of readily accessible and easily handled starting materials, no use of any metal catalyst or additional oxidant, broad scope of substrates and high functional group compatibility, great potential for large scale synthesis, and no tedious extractive workup. These merits make the present method a concise and low-cost access to construct 2,4,6-trisubstituted pyridines.

NMR spectra were recorded on a Bruker AV400 or AV500 NMR instrument in $CDCl_3$. All melting points were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and are not corrected. High-resolution mass spectra (HRMS) were recorded on a Bruker MicroTOF-QII mass instrument (ESI). TLC was performed on precoated glass plates and visualized with UV light at 254 nm. Flash column chromatography was performed on silica gel with PE–EtOAc as the eluent.

2,4,6-Trisubstituted Pyridines; General Procedure

A mixture of methyl aryl ketone **1** (2.0 mmol), amine **2** (1.0 mmol), and molecular I_2 (2.5 mg, 0.01 mmol) was stirred at 140 °C for 10 h in a 25 mL sealed Schlenk tube, followed by further 1 h stirring in open air. After completion, the reaction mixture was directly subjected to a short silica gel column chromatography with PE–EtOAc as the eluent, affording the desired product **3** as a white solid.

Details of all the products are given in the Supporting Information; analytical and spectral data for some selected new compounds are given below.

2,6-Bis(3-chlorophenyl)-4-phenylpyridine (3g)

White solid; yield: 285.1 mg (76%); mp 151–153 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.15 (m, 2 H), 8.05 (dt, *J* = 6.9, 1.9 Hz, 2 H), 7.86 (s, 2 H), 7.74–7.70 (m, 2 H), 7.56–7.40 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.19 (2 C), 150.65, 141.10 (2 C), 138.50, 134.87 (2 C), 130.02 (2 C), 129.30, 129.24 (2 C), 129.20 (2 C), 127.26 (2 C), 127.19 (2 C), 125.23 (2 C), 117.68 (2 C).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{16}Cl_2N$ [M + H]$^+$: 376.0660; found: 376.0667.

2,6-Bis(3-bromophenyl)-4-phenylpyridine (3i)

White solid; yield: 356.4 mg (77%); mp 172–174 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (s, 2 H), 8.12 (d, *J* = 7.8 Hz, 2 H), 7.86 (s, 2 H), 7.76–7.72 (m, 2 H), 7.60 (d, *J* = 7.9 Hz, 2 H), 7.56 (t, *J* = 7.3 Hz, 2 H), 7.53–7.49 (m, 1 H), 7.40 (t, *J* = 7.9 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.09 (2 C), 150.63, 141.36 (2 C), 138.48, 132.10 (2 C), 130.27 (2 C), 130.16 (2 C), 129.28, 129.22 (2 C), 127.17 (2 C), 125.72 (2 C), 123.05 (2 C), 117.66 (2 C).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{16}Br_2N$ [M + H]$^+$: 463.9649; found: 463.9656.

2,6-Bis(3,4-dichlorophenyl)-4-phenylpyridine (3j)

White solid; yield: 319.0 mg (72%); mp 194–196 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 1.8 Hz, 2 H), 8.00 (dd, *J* = 8.3, 1.8 Hz, 2 H), 7.83 (s, 2 H), 7.72 (d, *J* = 7.1 Hz, 2 H), 7.60–7.50 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.23 (2 C), 150.94, 139.03 (2 C), 138.22, 133.50 (2 C), 133.12 (2 C), 130.73 (2 C), 129.46, 129.29 (2 C), 128.92 (2 C), 127.15 (2 C), 126.18 (2 C), 117.54 (2 C).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{14}Cl_4N$ [M + H]$^+$: 443.9880; found: 443.9892.

4-Pentyl-2,6-diphenylpyridine (3r)

Colorless oil; yield: 219.8 mg (73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.19–8.15 (m, 4 H), 7.54 (s, 2 H), 7.51 (t, *J* = 7.5 Hz, 4 H), 7.44 (t, *J* = 7.3 Hz, 2 H), 2.77–2.72 (m, 2 H), 1.79–1.72 (m, 2 H), 1.44–1.37 (m, 4 H), 0.94 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.91 (2 C), 153.17, 139.82 (2 C), 128.81 (2 C), 128.63 (4 C), 127.09 (4 C), 119.09 (2 C), 35.78, 31.50, 30.28, 22.53, 14.00.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{22}H_{24}N$ [M + H]$^+$: 302.1909; found: 302.1901.

Acknowledgment

We are grateful for the financial support from National Natural Science Foundation of China (21242013) and Key Projects for Outstanding Young Talents in Colleges and Universities of Anhui Province (No. gxyqZD2016121).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588380.

References

(1) Kröhnke, F. *Synthesis* **1976**, 1.
(2) Fang, A. G.; Mello, J. V.; Finney, N. S. *Tetrahedron* **2004**, *60*, 11075.
(3) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129.
(4) Islam, A.; Sugihara, H.; Arakawa, H. *J. Photochem. Photobiol., A* **2003**, *158*, 131.
(5) (a) Newkome, G. R.; Wang, P. C.; Moorefield, N.; Cho, T. J.; Mohapatra, P. P.; Li, S.; Hwang, S. H.; Lukoyanova, O.; Echegoyen, L.; Palagallo, J. A.; Iancu, V.; Hla, S. W. *Science* **2006**, *312*, 1782. (b) Constable, E. C.; Dunphy, E. L.; Housecroft, C. E.; Kylberg, W.; Neuberger, M.; Schaffner, S.; Schofield, E. R.; Smith, C. B. *Chem. Eur. J.* **2006**, *12*, 4600. (c) Wang, P.; Moorefield, C. N.; Newkome, G. R. *Angew. Chem. Int. Ed.* **2005**, *44*, 1679.
(6) Lohmeijer, B. G. G.; Schubert, U. S. *J. Polym. Sci., A: Polym. Chem.* **2003**, *41*, 1413.
(7) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Tymoshenko, D. O.; Essawy, S. A. *Synthesis* **1999**, 2114.
(8) For some selected examples in recent years, see: (a) Moosavi-Zare, A. R.; Zolfigol, M. A.; Rezanejad, Z. *Can. J. Chem.* **2016**, *94*, 626. (b) Tabrizian, E.; Amoozadeh, A.; Rahmani, S.; Imanifar, E.; Azhari, S.; Malmir, M. *Chin. Chem. Lett.* **2015**, *26*, 1278. (c) Zarnegar, Z.; Safari, J.; Borjian-borujeni, M. *Chem. Heterocycl. Compd.* **2015**, *50*, 1683. (d) Maleki, B. *Org. Prep. Proced. Int.* **2015**, *47*, 173. (e) Alinezhad, H.; Tajbakhsh, M.; Ghobadi, N. *Synth. Commun.* **2015**, *45*, 1964. (f) Moosavi-Zare, A. R.; Zolfigol, M. A.; Farahmand, S.; Zare, A.; Pourali, A. R. *Synlett* **2014**, *25*, 193.
(9) Mahernia, S.; Mahdavi, M.; Adib, M. *Synlett* **2014**, *25*, 1299.
(10) Adib, M.; Ayashi, N.; Mirzaei, P. *Synlett* **2016**, *27*, 417.
(11) Xiang, J.-C.; Wang, M.; Cheng, Y.; Wu, A.-X. *Org. Lett.* **2016**, *18*, 24.
(12) Zhang, X.; Wang, Z.-Q.; Xu, K.; Feng, Y.-Q.; Zhao, W.; Xu, X.-F.; Yan, Y.-L.; Yi, W. *Green Chem.* **2016**, *18*, 2313.
(13) Huang, H.-W.; Ji, X.-C.; Wu, W.-Q.; Huang, L.-B.; Jian, H.-F. *J. Org. Chem.* **2013**, *78*, 3774.
(14) Rohokale, R. S.; Koenig, B.; Dhavale, D. D. *J. Org. Chem.* **2016**, *81*, 7121.
(15) Xu, H.; Wang, F.-J.; Xin, M.; Zhang, Z. *Eur. J. Org. Chem.* **2016**, 925.
(16) Amoros-Marin, L.; Carlin, R. B. *J. Am. Chem. Soc.* **1959**, *81*, 733.