Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Generation of 4-iodoisocoumarins through a TBAI-mediated oxidative cyclization of 2-alkynoates

Jin Luo, M. He, P. Chen & J. Li

To cite this article: Jin Luo, M. He, P. Chen & J. Li (2018): Generation of 4-iodoisocoumarins through a TBAI-mediated oxidative cyclization of 2-alkynoates, Synthetic Communications, DOI: 10.1080/00397911.2018.1465094

To link to this article: https://doi.org/10.1080/00397911.2018.1465094

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2018.1465094

Taylor & Francis
Taylor & Francis Group

Generation of 4-iodoisocoumarins through a TBAI-mediated oxidative cyclization of 2-alkynoates

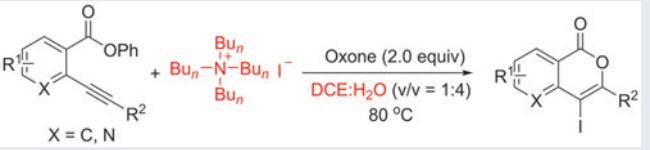
Jin Luo[a], M. He[b], P. Chen[a] and J. Li[a]

[a]Analytical and Testing Center, Jiangxi Normal University, Nanchang, Jiangxi, China; [b]College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, Jiangxi, China

ABSTRACT

A tetra-butylammonium iodide (TBAI)-mediated oxidative iodocyclization of 2-alkynoates for the synthesis of various 4-iodoisocoumarin is described herein, and the reaction is highly efficient and shows broad functional group tolerance. This newly developed reaction uses a mixture of water and DCE as co-solvent, and avoids the use of iodine as iodine source for the electrophilic halocyclization.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 16 November 2017

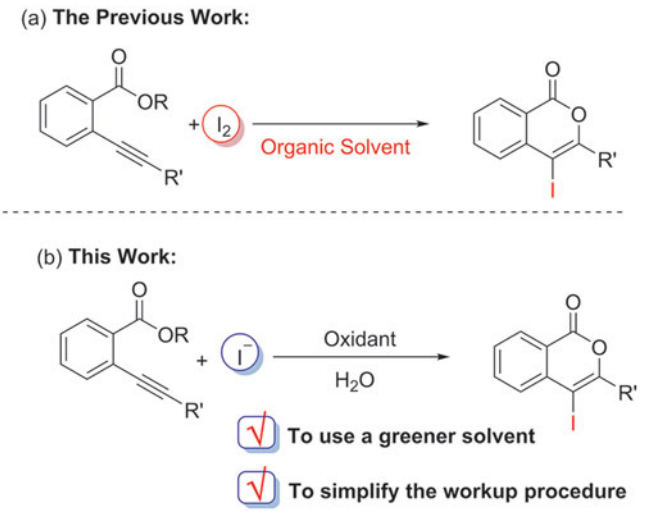
KEYWORDS
2-Alkynoate; 4-iodoisocoumarin; electrophilic iodocyclization; Oxone

Introduction

Isocoumarin is one of the most important privileged structural cores due to its ubiquity in natural products.[1] Many synthetic compounds with the isocoumarin skeleton exhibited important biological activities.[2] Accordingly, tremendous efforts have been directed toward its direct preparation to ultimately construct a library of structurally complex and functionally diverse compounds for bioactivity assays by high-throughput screening. To the best of our knowledge, 2-alkynoates are a versatile synthon for preparing the isocoumarin core.[3] Various transition metals and Lewis acids have been used to promote the 6-*endo* cyclization of 2-alkynoates for the synthesis of isocoumarin derivatives.[4] Subsequently, the halo substituent (such as bromo or iodo) was installed at the C4-position of the isocoumarin core by an electrophilic 6-*endo* cyclization. It was important that this reactive substituent was introduced since the halo group can be converted into other building blocks through classical coupling reaction combined and other transformations.

An initial precedent involving the electrophilic cyclization of 2-alkynoates was reported by Oliver and Grandour.[5] According to their findings, bromine could trigger the

CONTACT Jin Luo jinluo@jxnu.edu.cn Analytical and Testing Center, Jiangxi Normal University, Nanchang, Jiangxi, China.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data for this article can be accessed on the publisher's website.



Scheme 1. Proposed route for the synthesis of 4-iodoisocoumarin via iodide-mediated cyclization of 2-alkynoates.

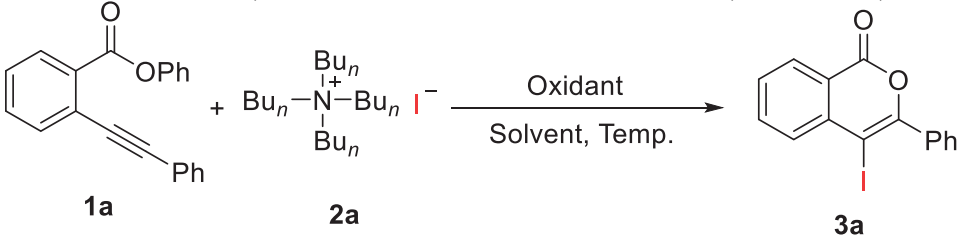
electrophilic cyclization of 2-alkynoate to generate 4-bromoisocoumarins. However, the versatility of this method and the generality of this electrophilic bromocyclization were poor. Larock et al.[6] as well as other research groups were inspired by the reaction efficiency of electrophilic halocyclization of 2-alkynoates. To date, various electrophiles including Br_2, I_2, NIS and ICl, etc. have been developed. As presented in Scheme 1a, the I_2-mediated cyclization proceeded smoothly, and the corresponding 4-iodoisocoumarins were generated in good yields. Generally, the I_2-promoted electrophilic iodocyclization of 2-alkynoate required the use of an organic solvent. Moreover, after completion of the reaction, $Na_2S_2O_3$ was needed to remove the excess I_2, which makes the workup procedure relatively inconvenient. Inspired by the precedent mentioned above, we were inspired to explore a simple alternative for the synthesis of 4-iodoisocoumarin. The protocol developed herein employed a solvent and iodine source that are more eco-friendly. In addition, the reactions delivered the final products with a simple workup procedure. Thus, we have developed an iodide-mediated oxidative cyclization of 2-alkynoates for the synthesis of 4-iodoisocoumarin derivatives.

Results and discussion

As illustrated in Scheme 1b, an iodide salt was oxidized *in situ* to the corresponding hypervalent iodine by an inorganic salt,[7] which could go on to promote the electrophilic iodocyclization. Notably, the iodide-mediated oxidative cyclization avoids the use of elemental iodine. In addition, thanks to its high solubility in water, iodide and the oxidant inorganic salt can be directly by extraction, which simplifies the workup procedure. Encouraged by the above results, we started to explore this proposed transformations.

Initially, the reaction of 2-alkynoate **1a** was selected as a model reaction. Considering that an ammonium salt could improve the solubility of **1a** in water, tetra-butylammonium iodide (TBAI) was employed as the iodine source. The factors influencing the reaction

Table 1. Initial studies for the synthesis of 4-iodoisocoumarin via iodide salt-mediated cyclization of 2-alkynoate **1a**[a].



Entry	Oxidant	Solvent	Temp. (°C)	Yield (%)[b]
1	/	H_2O	80	N.R.
2	$Cu(OAc)_2$	H_2O	80	12
3[c]	CAN	H_2O	80	35
4	Oxone	H_2O	80	67
5	$K_2S_2O_8$	H_2O	80	63
6	Oxone	H_2O	100	65
7	Oxone	H_2O	60	59
8	Oxone	H_2O:DCE (v/v, 1:1)	80	79
9	Oxone	H_2O:THF (v/v, 1:1)	80	66
10	Oxone	H_2O:DCE (v/v, 2:1)	80	83
11	**Oxone**	**H_2O:DCE (v/v, 4:1)**	**80**	**88**
12	Oxone	H_2O:DCE (v/v, 10:1)	80	83

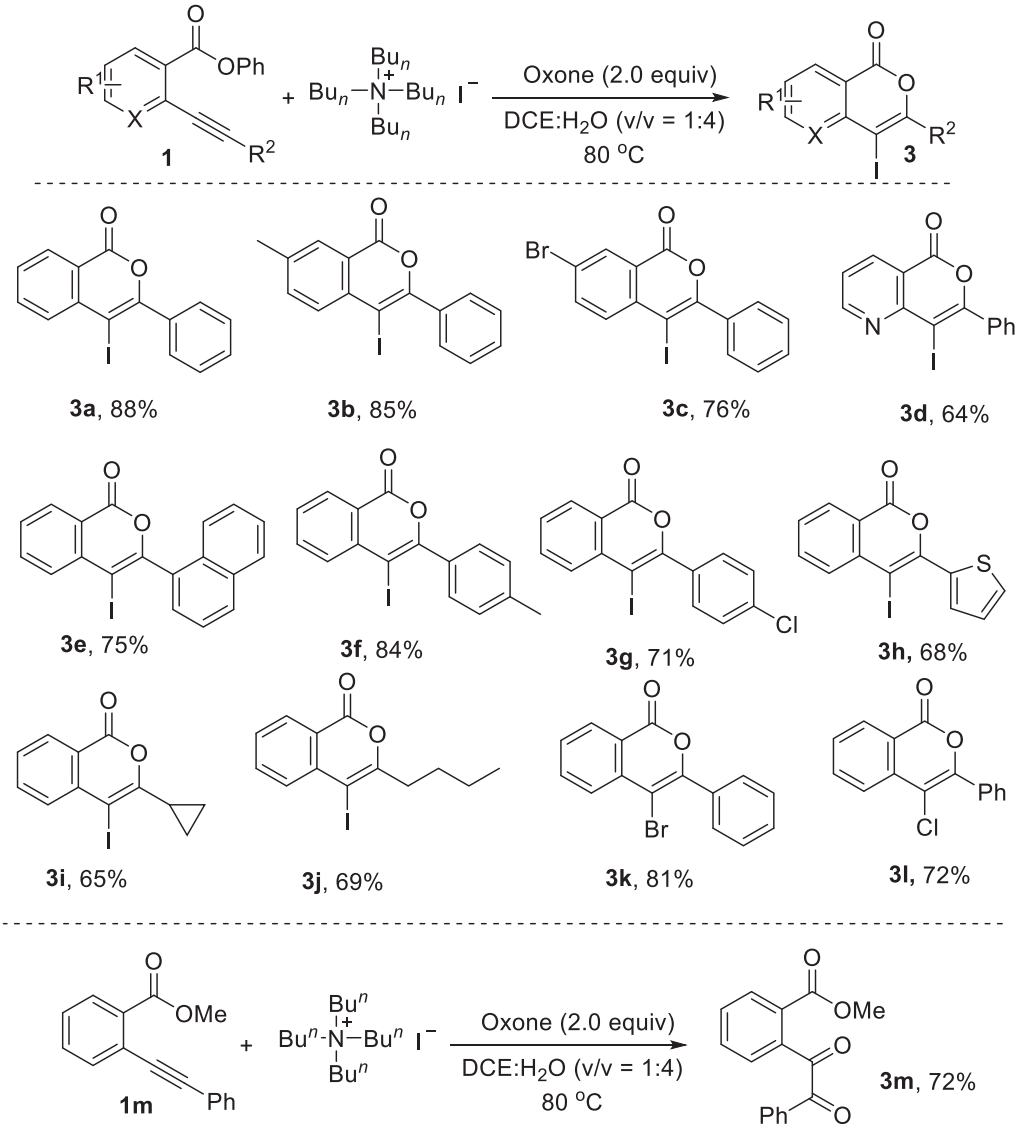
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), oxidant (2.0 equiv), 8 h.
[b]Isolated yield based on 2-alkynoate **1a**.
[c]CAN = $Ce(NH_4)_2(NO_3)_6$; THF = tetrahydrofuran; DCE = 1,2-dichloroethane; N.R. = no reaction.

outcome, including the oxidant, solvent and temperature, were evaluated. The results from the oxidant screening suggested that an oxidant was required and Oxone (the triple salt: $KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) was the best choice as it provided 4-iodoisocoumarin in 67% yield (entries 1–5, Table 1). Other inorganic salt oxidants such as $Cu(OAc)_2$, CAN and $K_2S_2O_8$ gave inferior results. Interestingly, the combination of an ammonium halide salt with an oxidant has been employed in halohydrations of alkynes, dihalohydrations of alkynes and diketonizations of alkynes. These findings indicated that water was pivotal for the reaction and likely influenced the reaction pathway.[8]

The reaction temperature was screened as well. The results showed that increasing the reaction temperature to 100 °C impacted the reaction only slightly, and a similar yield of the final product was observed (entry 6, Table 1). Decreasing the temperature negatively impacted the reaction outcome (entry 7, Table 1). In the above experiments, we found that the starting material (2-alkynoate **1a)** was not completely consumed likely due to the poor solubility of **1a** in water. Consequently, we turned our attention to the use of an organic solvent as a co-solvent with water. To our delight, the use of a co-solvent (H_2O:DCE, v/v = 1:1) greatly improved the reaction efficiency, leading to the formation of 4-iodoisocoumarin **3a** in 79% isolated yield (entry 8, Table 1). Encouraged by this result, other co-solvents and various ratios of water and DCE were examined accordingly. Fortunately, the use of a mixture of co-solvent H_2O:DCE (v/v = 4:1) was the best choice, producing the final molecule 4-iodoisocoumarin **3a** in 88% yield (entry 11, Table 1). The improvement of the reaction efficiency was attributed to the improved solubility of **1a** in the solvent system. Decreasing the percentage of DCE in the solvent system did not offer a better yield (entry 12, Table 1).

With the optimal reaction conditions in hand, we then examined the substrate scope of this transformation. The results are illustrated in Table 2. A series of 4-iodoisocoumarin

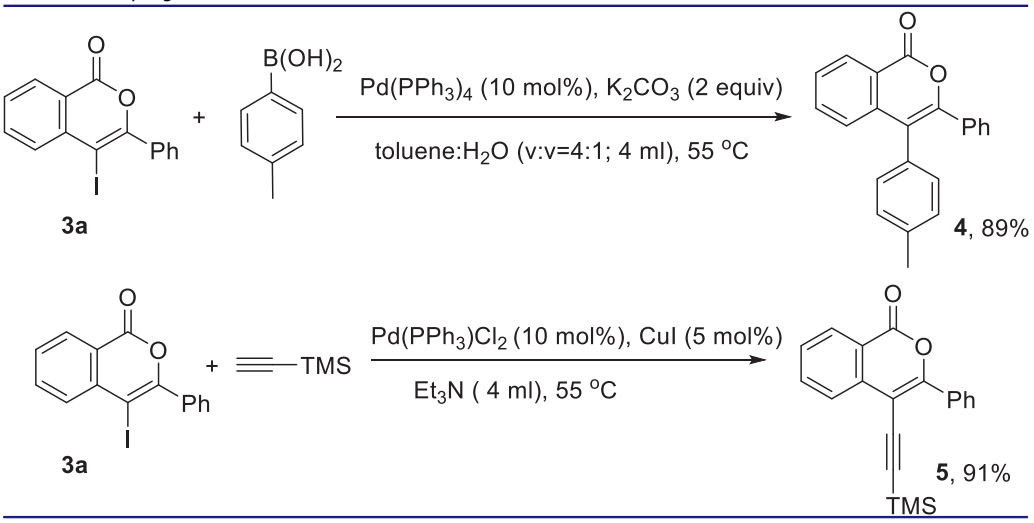
Table 2. The synthesis of 4-iodoisocoumarin via TBAI-mediated cyclization of 2-alkynoates **1**[a].



[a]Isolated yield based on 2-alkynoates **1**.

derivatives **3** were constructed as expected. For example, the substrates with methyl and bromo substituents were compatible with the reaction conditions, producing the corresponding 4-iodoisocoumarin derivatives **3b** in 85% yield and **3c** in 76% yield, respectively. The pyridine-substituted alkynoate was also tolerated, and the corresponding product **3d** was obtained in 64% yield. In addition, the variation of substituent at the R^2 position was also explored. The reactions of diverse aryl-, 1-naphthyl-, and alkyl-substituted alkynoates proceeded smoothly and afforded corresponding 4-iodoisocoumarins **3e–3j** in 65–84% yields. For instance, the substrates with 1-naphthyl moieties at the R^2-position was well-tolerated, generating corresponding product **3e** in 75% yield. Meanwhile, the reaction of the 2-thiothenyl-substituted substrate gave 4-iodo-3-(2-thiothenyl) isocoumarin **3h** in 68%

Table 3. Coupling reactions of 4-iodoisocoumarins[a].



[a]Isolated yield based on isocoumarin **3a.**

yield. From the screening results of various substrates with aryl substituents at R^2, it seemed that electron-rich aryl substituents was favorable for the reaction. The reaction of the substrate with a 4-methylaryl substituent at R^2 produced 4-iodoisocoumarin **3f** in 84% yield, while the reaction of the substrate with a 4-chloroaryl substituent at R^2 provided corresponding 4-iodoisocoumarin **3g** in just 71% yield. The substrates with the substituent cyclopropyl or *n*-butyl substituents at R^2 were compatible with the reaction conditions, and corresponding 4-iodoisocoumarin derivatives **3i** and **3j** were generated in good yields. Additionally, tetra-butylammonium bromide (TBAB) and tetra-butylammonium chloride (TBAC) were good halo sources, providing 4-bromoisocoumarin **3k** in 81% yield and 4-chloroisocoumrain **3l** in 72% yield, respectively, under the standard conditions, respectively. To our surprise, the reaction of methyl 2-alkynoate **1m** under the standard conditions did not gave rise to the corresponding isocoumarin derivative. A distinctive compound benzil-*o*-carboxylate **3m** was observed in 72% yield. This unexpected product inspired us to delve deeper into the relevant literature. To our delight, Qiu et al.[8] observed the similar results, which they attributed to a change in the reaction pathway due to the use of water as a co-solvent.

Finally, derivatization of 4-iodoisocoumarin was explored in this study. The results are shown in Table 3. Delightfully, both the Suzuki coupling and Sonogashira coupling reactions of 4-iodoisocoumarin **3a** provided the corresponding products **4** and **5** in good yields.

Conclusions

In conclusion, we have developed an alternative route for the generation of 4-iodoisocoumarins from 2-alkynaotes. The reaction proceeded smoothly in the presence of TBAI and Oxone, and an array of 4-iodoisocoumarins were generated with high reaction efficiency and excellent functional group tolerance. The reaction developed herein used a co-solvent system of water and DCE, and avoided the use of elemental iodine as iodine source for the electrophilic halocyclization.

Experimental

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60 Å pore size, 32–63 μm, standard grade). Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C. Commercial reagents and solvents were used as received. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 spectrometer with $CDCl_3$ as the solvent at 400 (^1H) and 101 MHz (^{13}C). LC-MS spectra were acquired on a 1100LC/MSD Trap spectrometer. Elementary analyses were conducted on a Vario EL III elemental analysis instrument. The supplemental materials contains sample 1H and 13C NMR for products 3–5, together with full characterization data.

General procedure

2-Alkynoate **1**, TBAI (1.5 equiv), and Oxone (2.0 equiv) were added to a test tube, and the co-solvent system DCE:H_2O (3 mL, v/v = 1:4) was then added. The mixture was stirred at 80 °C. After completion of the reaction, the mixture was cooled to room temperature, and ethyl acetate (3.5 mL) was added. Extraction, drying of the organic layer, concentration and flash column chromatography provided the desired 4-iodoisocoumarin **3**.

Funding

We thank the Natural Science Foundation of Jiangxi Province in China [No. 20161BAB213072] and the Scientific Research Fund of Jiangxi Provincial Education Department in China [No. GJJ150326] for their financial support.

References

[1] (a) Larsen, T. O.; Breinholt, J. *J. Nat. Prod.* **1999**, *67*, 858. (b) Dumontet, V.; Hung, N. V.; Adeline, M.-T.; Riche, C.; Chiaroni, A.; Sevenet, T.; Gueritte, F. *J. Nat. Prod.* **2004**, *67*, 858.

[2] (a) Hagen, S. E.; Vara Prasad, J. V. N.; Boyer, F. E.; Domagala, J. M.; Ellsworth, E. L.; Gajda, C.; Hamilton, H. W.; Markoski, L. J.; Steinbaugh, B. A.; Tait, B. D.; Lunney, E. A.; Tummino, P. J.; Ferguson, D.; Hupe, D.; Nouhan, C.; Gracheck, S. J.; Saunders, J. M.; VanderRoest, S. *J. Med. Chem.* **1997**, *40*, 3707. (b) Judge, T. M.; Phillips, G.; Morris, J. K.; Lovasz, K. D.; Romines, K. R.; Luke, G. P.; Tulinsky, J.; Tustin, J. M.; Chrusciel, R. A.; Dolak, L. A.; Mizsak, S. A.; Watt, W.; Morris, J.; Vander Velde, S. L.; Strohbach, J. W.; Gammill, R. B. *J. Am. Chem. Soc.* **1997**, *119*, 3627. (c) Deck, L. M.; Baca, M. L.; Salas, S. L.; Hunsaker, L. A.; Vander Jagt, D. L. *J. Med. Chem.* **1999**, *42*, 4250.

[3] (a) Hellal, M.; Bourguignon, J. J.; Bihel, F. J. J. *Tetrahedron Lett.* **2008**, *49*, 62. (b) Jacubert, M.; Provot, O.; Peyrat, J.-F.; Hamze, A.; Brion, J. D.; Alami, M. *Tetrahedron.* **2010**, *66*, 3775. (c) Jacubert, M.; Hamze, A.; Provot, O.; Peyrat, J. F.; Brion, J. D.; Alami, M. *Tetrahedron Lett.* **2009**, *50*, 3588. (d) Le Bras, G.; Hamze, A.; Messaoudi, S.; Provot, O.;

LeCalvez, P. B.; Brion, J. D.; Alami, M. *Synthesis*. **2008**, 10, 1607. (e) Li, Z.; Hong, J.; Weng, L.; Zhou, X. *Tetrahedron*. **2012**, *68*, 1552. (f) Wikims, L. C.; Guenther, B. A. R.; Walther, M.; Lawson, J. R.; Wirth, T.; Melen, R. L. *Angew. Chem. Int. Ed*. **2016**, *55*, 11292. (g) Li, Y.; Li, G.; Ding, Q. *Eur. J. Org. Chem*. **2014**, *23*, 5017. (h) Yuan, S. T.; Wang, Y. H.; Liu, J. B.; Qiu, G. Y. S. *Adv. Synth. Catal*. **2017**, *359*, **1981**; (i) Huang, B.; Ma, L. L.; Qiu, G. Y. S. *Tetrahedron Lett*. **2017**, *58*, 2140.

[4] (a) Liang, Y.; Xie, Y. X.; Li, J.-H. *Synthesis*. **2007**, *3*, 400. (b) Jithunsa, M.; Ueda, M.; Miyata, O. *Org. Lett*. **2011**, *13*, 518. (b) Sugioka, T.; Yoneda, E.; Onitsuka, K.; Zhang, S.-W.; Takahashi, S. *Tetrahedron Lett*. **1997**, *38*, 4989. (c) Wang, H.; Han, X.; Lu, X. *Tetrahedron*. **2013**, *69*, 8626. (d) Zhang, P.; Chen, D.; Song, G.; He, K.; Li, X. *J. Org. Chem*. **2012**, *77*, 1579. (e) Zhang, J.; Han, X.; Lu, X. *J. Org. Chem*. **2016**, *81*, 3423. (f) Chang, W. R.; Lo, Y. H.; Lee, C. Y.; Wu, M. J. *Adv. Synth. Catal*. **2008**, *350*, 1248. (g) Faizi, D. J.; Issaian, A.; Davis, A. J.; Blum, S. A. *J. Am. Chem. Soc*. **2016**, *138*, 2126. (h) Speranca, A.; Godoi, B.; Pinton, S.; Back, D.; Menezes, P.; Zeni, G. *J. Org. Chem*. **2011**, *76*, 6789. (i) Nagarajan, A.; Balasubramanian, T. R. *Indian J. Chem., Section B: Org. Chem. Including Med. Chem*. **1987**, *26B*, 917. (j) Komeyama, K.; Takahashi, K.; Takaki, K. *Org. Lett*. **2008**, *10*, 5119. (k) Li, F. H.; Cai, Z. J.; Yin, L.; Li, J.; Wang, S. Y.; Ji, S. J. *Org. Lett*. **2017**, *19*, 1662.

[5] Oliver, M. A.; Gandour, R. D. *J. Org. Chem*. **1984**, *49*, 558.

[6] (a) Yao, T.; Larock, R. C. *J. Org. Chem*. **2003**, *68*, 5936. (b) Yao, T.; Larock, R. C. *Tetrahedron Lett*. **2002**, *43*, 7401. (c) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem*. **2009**, *74*, 1141. (d) Peuchmaur, M.; Lisowski, V.; Gandreuil, C.; Maillard, L. T.; Martinez, J.; Hernandez, J.-F. *J. Org. Chem*. **2009**, *74*, 4158. (e) Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem*. **2010**, *75*, 7691. (f) Verma, A. K.; Aggarwal, T.; Rustagi, V.; Larock, R. *C. Chem. Commun*. **2010**, *46*, 4064. (g) Barluenga, J.; Llavona, L.; Yus, M.; Concellon, J. M. *Tetrahedron Lett*. **1991**, *47*, 7875.

[7] Husain, H.; Green, I. R.; Ahmed, I. *Chem. Rev*. **2013**, *113*, 3329.

[8] (a) Sakthivel, K.; Srinivasan, K. *Eur. J. Org. Chem*. **2013**, *16*, 3386. (b) Yuan, S.-T.; Zhou, H.; Zhang, L.; Qiu, G.; Liu, J.-B. *Org. Biomol. Chem*., **2017**, *15*, 4867. (c) Qiu, G.; Li, Y.; Ma, L.; Zhou, H. *Org. Chem. Front*. **2017**, *4*, 1069. (d) V. V. K. M. Kandepi, N. Narender, *Synthesis* **2012**, *44*, 15. (e) Wang, H.; Zhu, M.; Ye, S.; Wu, J. *RSC Adv*. **2013**, *3*, 13626.