ORGANIC LETTERS

2013
Vol. 15, No. 17
4620–4623

Multicomponent Reactions Involving Arynes, Quinolines, and Aldehydes

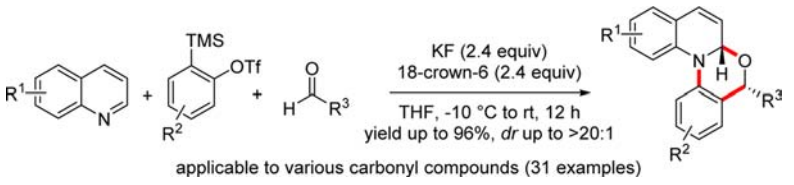
Anup Bhunia,[†] Digvijay Porwal,[†] Rajesh G. Gonnade,[‡] and Akkattu T. Biju*[,†]

Organic Chemistry Division, and Center for Materials Characterization, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune – 411008, India

at.biju@ncl.res.in

Received August 13, 2013

ABSTRACT



The multicomponent reaction involving arynes, quinolines, and aldehydes leading to the diastereoselective synthesis of benzoxazino quinoline derivatives in good yields proceeding via 1,4-zwitterionic intermediates is reported. In addition, the synthetic potential of various carbonyl compounds in this reaction as well as the utility of isoquinoline as the nucleophilic trigger has been examined.

Multicomponent Reactions (MCRs) are one-pot reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product.[1] Speed, diversity, efficiency, atom economy, and environmental friendliness are some of the notable features of this class of reactions.[2] The most important MCRs are the isocyanide-based reactions such as the Passerini three-component reaction[3] and the Ugi four-component reaction.[4] Moreover, a variety of heterocycles can be constructed using the MCR strategy, where zwitterionic intermediates are generated by the addition of a nucleophile to activated C–C multiple bonds followed by their interception with a third component.[5]

The synthetic utility of arynes in MCRs has been recently significant, as this method allows a straightforward access to various multisubstituted arenes of structural complexity and diversity.[6,7] The initial reports on aryne MCRs utilize the anionic nucleophiles as the nucleophilic trigger.[8] However, in 2004, Yoshida, Kunai and co-workers employed isocyanides as the neutral nucleophile source and they reported an efficient MCR involving arynes, isocyanides, and aldehydes leading to the formation of benzannulated

[†] Organic Chemistry Division.
[‡] Center for Materials Characterization.

(1) For recent reviews on multicomponent reactions, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) *Multicomponent Reaction*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (d) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234. (e) Graaff, C. de.; Ruijter, E.; Orru, R. V. A. *Chem Soc. Rev.* **2012**, *41*, 3969. (f) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083.

(2) Ruijter, E.; Orru, R. V. A. *Drug Discovery Today: Technologies* **2013**, *10*, e15.

(3) (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126. (b) Passerini, M. *Gazz. Chim. Ital.* **1922**, *52*, 432. For a review, see: (c) Banfi, L.; Riva, R. In *Organic Reactions*; Charette, A. B., Ed.; Wiley: New York, 2005; Vol. 65, pp 1–140.

(4) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267.

(5) For an account, see: Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899.

(6) For recent reviews on arynes, see: (a) Wu, C.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116. (b) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191. (c) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (d) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766. (e) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (f) Okuma, K. *Heterocycles* **2012**, *85*, 515. (g) Yoshida, H.; Takaki, K. *Synlett* **2012**, *23*, 1725. (h) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199. (i) Chen, Y.; Larock, R. C. Arylation reactions involving the formation of arynes. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2009; p 401. (j) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215. (k) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502. (l) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701.

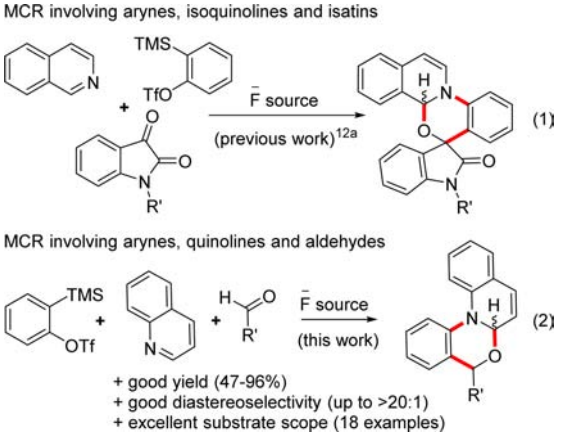
(7) For a recent highlight on transition-metal-free aryne MCRs, see: Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520. For selected recent reports, see: (b) Sha, F.; Huang, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 3458. (c) Allan, K. M.; Gilmore, C. D.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4488. (d) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638. (e) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2010**, *12*, 1956. (f) Yoshida, H.; Ito, Y.; Ohshita, J. *Chem. Commun.* **2011**, *47*, 8512. (g) Yoshida, H.; Asatsu, Y.; Mimura, Y.; Ito, Y.; Ohshita, J.; Takaki, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 9676.

(8) (a) Meyers, A. I.; Pansegrau, P. D. *Tetrahedron Lett.* **1983**, *24*, 4935. (b) Meyers, A. I.; Pansegrau, P. D. *J. Chem. Soc., Chem. Commun.* **1985**, 690. (c) Tripathy, S.; LeBlanc, R.; Durst, T. *Org. Lett.* **1999**, *1*, 1973.

10.1021/ol4023134
Published on Web 08/28/2013

iminofuran derivatives.[9,10] Interestingly, however, the synthetic utility of N-heterocycles as nucleophiles in aryne MCRs has received only limited attention.[11] We have recently reported a unique MCR involving arynes, N-heterocycles, and isatins.[12] With isoquinoline as the nucleophilic trigger, the reaction afforded the spirooxazino isoquinoline derivatives proceeding via 1,4-dipolar intermediates (Scheme 1, eq 1). In addition, the use of pyridine as a nucleophile furnished indolin 2-one derivatives and the reaction is likely to proceed through a pyridylidene intermediate.

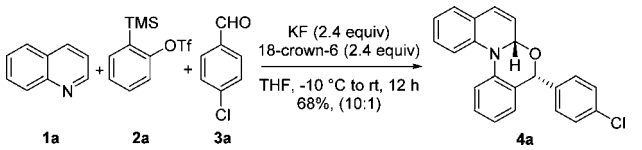
Scheme 1. N-Heterocycle Triggered MCRs of Arynes with Electrophiles



However, the reaction was limited to isatins as the electrophilic coupling partner. Herein, we report the general MCR involving quinolines, arynes, and various carbonyl compounds, leading to a diastereoselective synthesis of oxazinoquinoline derivatives, and the reaction proceeds through a 1,4-dipolar intermediate (eq 2).

The present study commenced by treating quinoline **1a** and 4-chlorobenzaldehyde **3a** with the aryne generated in situ from 2-(trimethylsilyl)aryl triflate **2a**[13] using KF and 18-crown-6. A facile reaction occurred resulting in the formation of the benzoxazino quinoline derivatives as an inseparable mixture of diastereomers in 68% yield and 10:1 diastereomeric ratio (Scheme 2).[14] The optimization studies revealed that the use of other fluoride sources such as tetrabutylammonium fluoride (TBAF) and CsF were not beneficial, and reactions carried out above −10 °C were not efficient.

Scheme 2. MCR Involving Quinoline, Aryne, and 4-Chlorobenzaldehyde



The major diastereomer **4a** was separated by crystallization, and its structure and stereochemistry were unequivocally confirmed by single-crystal X-ray analysis (Figure 1).[15] Notably, some oxazinoquinoline derivatives are known to exhibit antimalarial activity and a few of them are possibly antitumor agents.[16]

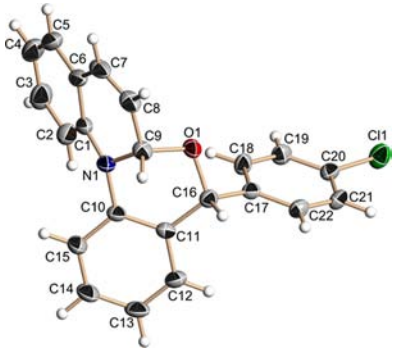


Figure 1. Crystal structure of **4a** (thermal ellipsoids are shown with 30% probability).

With the new reaction conditions in hand, we then examined the substrate scope of this quinoline initiated aryne MCR (Scheme 3). First, we evaluated various aldehydes. Benzaldehyde worked well and electron-releasing or -withdrawing group at the 4-position of the aromatic ring was well tolerated, leading to benzoxazino quinoline derivatives in good yields and excellent diastereoselectivity (**4b**−**4d**). Moreover, substitution is tolerated at the 3- and 2-position of the aromatic ring of **3** resulting in the smooth conversion to the product in excellent diastereoselectivity (**4e, 4f**). Furthermore, disubstituted aldehyde as well as

(9) (a) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3935. (b) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2004**, *45*, 8659. (c) Yoshida, H.; Fukushima, H.; Morishita, T.; Ohshita, J.; Kunai, A. *Tetrahedron* **2007**, *63*, 4793.

(10) (a) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040. (b) Yoshida, H.; Morishita, T.; Ohshita, J. *Org. Lett.* **2008**, *10*, 3845. (c) Yoshida, H.; Morishita, T.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2007**, *9*, 3367. (d) Morishita, T.; Fukushima, H.; Yoshida, H.; Ohshita, J.; Kunai, A. *J. Org. Chem.* **2008**, *73*, 5452.

(11) (a) Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2006**, 2454. (b) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Chem.—Asian J.* **2010**, *5*, 153.

(12) (a) Bhunia, A.; Roy, T.; Pachfule, P.; Rajamohanan, P. R.; Biju, A. T. *Angew. Chem., Int. Ed.* **2013**, *52*, DOI:10.1002/anie.201304278. For recent reports on aryne chemistry from our lab, see: (b) Kaicharla, T.; Bhojgude, S. S.; Biju, A. T. *Org. Lett.* **2012**, *14*, 6238. (c) Bhojgude, S. S.; Kaicharla, T.; Bhunia, A.; Biju, A. T. *Org. Lett.* **2012**, *14*, 4098.

(13) For the generation of arynes from 2-(trimethylsilyl)aryl triflates, see: (a) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211. For a modified procedure for the synthesis of the triflate, see: (b) Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, 1454.

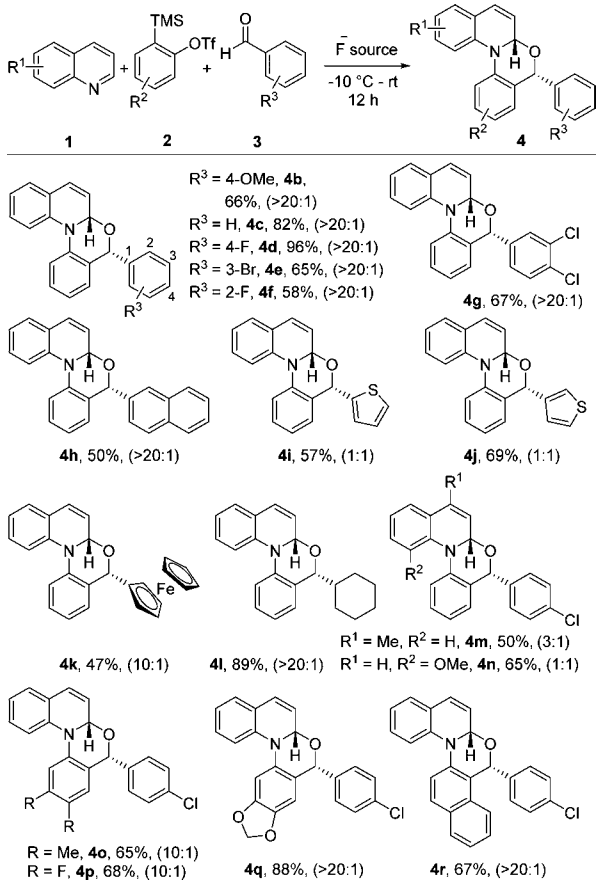
(14) For details, see the Supporting Information.

(15) CCDC-954832 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

(16) March, L. C.; Romanchick, W. A.; Bajwa, G. S.; Joullié, M. M. *J. Med. Chem.* **1973**, *16*, 337. (b) Nasr, M.; Abbasi, M. M.; Nabih, I. *J. Pharm. Sci.* **1974**, *63*, 1314.

2-naphthaldehyde worked well (**4g, 4h**). Additionally, heterocyclic aldehydes furnished moderate to good yields of the desired products, in a 1:1 diastereomeric ratio, further expanding the scope of this aryne MCR (**4i**, **4j**). Gratifyingly, challenging aldehydes such as ferrocenecarboxaldehyde as well as aliphatic aldehyde also furnished moderate to good yields of the desired products, in excellent diastereoselectivity (**4k**, **4l**). Besides, this unique MCR is not limited to quinoline. 4-Methylquinoline as well as 8-methoxyquinoline worked well leading to the formation of the desired products in moderate to good yields thus demonstrating the versatility of the present reaction (**4m**, **4n**).

Scheme 3. Substrate Scope of the MCR Involving Quinoline, Aryne, and Aldehyde[a]

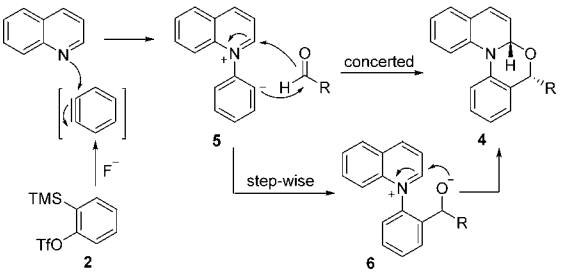


[a] General conditions: **1** (0.5 mmol), **2** (0.6 mmol), **3** (0.75 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), −10 °C to rt, 12 h. Total yields of both diastereomers are given, and the major diastereomer is shown. The diastereomeric ratio is given in parentheses and was determined by ^{1}H NMR analysis of the crude reaction mixture.

We next examined the effect of varying the substituents on the aryne precursor **2**. Electronically dissimilar 4,5-disubstituted symmetrical aryne precursors readily furnished the benzoxazino quinoline derivatives in good yields and diastereoselectivities (**4o**−**4q**). Interestingly, the unsymmetrical naphthalyne underwent efficient MCR to deliver a single regioisomer, arising from the addition of quinoline to the less hindered position of naphthalyne, in 67% yield and an excellent diastereoselectivity of >20:1 (**4r**).

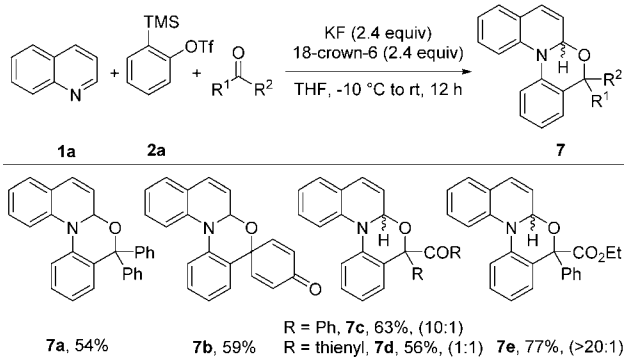
The mechanistic rationale for this aryne MCR may be advanced as follows (Scheme 4). The reaction proceeds via the initial generation of the 1,4-dipolar intermediate **5** from quinoline and aryne (generated from **2**).[17] The zwitterion **5** can add to the electrophilic aldehyde in a concerted 1,4-dipolar cycloaddition reaction leading to the formation of **4**. On the other hand, in a stepwise pathway, **5** can add to aldehyde generating the tetrahedral intermediate **6**, which undergoes cyclization leading to **4**.

Scheme 4. Plausible Reaction Mechanism



In view of these interesting results, we next evaluated the effect of varying the aldehyde component of this reaction (Scheme 5). Delightfully, benzophenone underwent efficient cyclization with quinoline and aryne leading to the formation of the 5,5-diphenyl benzoxazino quinoline derivative **7a** in 54% yield. Moreover, *p*-benzoquinone can be used as an effective carbonyl surrogate in this reaction, and the reaction afforded the spirobenzooxazino quinoline derivative **7b** in 59% yield. Additionally, di(hetero)aryl 1,2-diones including benzil and 2,2′-thenil as well as ethylphenyl glyoxylate can also be used as the third component in this MCR furnishing the desired products as a mixture of diastereomers in moderate yield (**7c**−**7e**).

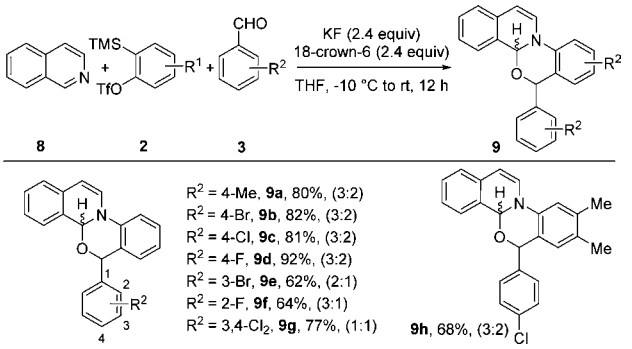
Scheme 5. MCR Involving Quinoline, Aryne, and Ketones[a]



[a] General conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), ketone (0.75 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), −10 °C to rt, 12 h. The diastereomeric ratio is given in parentheses and was determined by ^{1}H NMR analysis of the crude reaction mixture.

Encouraged by the interesting results using quinoline as the nucleophile, we then focused our attention on isoquinoline as the nucleophile for the aryne MCRs anticipating

Scheme 6. Scope of the MCR Involving Isoquinoline, Aryne, and Aldehyde[a]



[a] General conditions: **8** (0.5 mmol), **2** (0.6 mmol), **3** (0.75 mmol), KF (1.2 mmol), 18-crown-6 (1.2 mmol), THF (2.0 mL), −10 °C to rt, 12 h. The total yields of the mixture of diastereomers are given. The diastereomeric ratio is given in parentheses and was determined by ^{1}H NMR analysis of the crude reaction mixture.

that the reaction affords the analogous benzoxazino isoquinoline derivatives. In an initial experiment, treatment of isoquinoline **8** and *p*-tolualdehyde with aryne precursor **2a** in the presence of the fluoride source afforded the benzoxazino isoquinoline derivatives as an inseparable mixture of diastereomers in 80% yield and a 3:2 diastereomeric ratio (Scheme 6).[18] A variety of aromatic aldehydes with electron-releasing and -withdrawing groups on the aromatic ring were well tolerated, leading to the desired heterocycle in good yields (**9a**−**9g**) and a diastereoselectivity up to 3:1. Moreover, a symmetrical aryne precursor also worked well leading to the desired product in 68% yield.[19]

In conclusion, we have developed a new MCR involving arynes, quinolines, and aldehydes leading to the formation of benzoxazino quinoline derivatives and the reaction proceeds via 1,4-dipolar intermediates. The desired product was formed in moderate to good yields with good diastereoselectivity. In addition, the reaction works well with various carbonyl compounds as the third component as well as isoquinoline as the nucleophilic trigger. Efforts to further expand the scope of aryne MCRs are ongoing in our laboratory.

Acknowledgment. Generous financial support from CSIR-New Delhi (Network project ORIGIN, CSC0108) is gratefully acknowledged. A.B. thanks CSIR-New Delhi for the award of the Junior Research Fellowship, and D.P. thanks DST for the award of the KVPY fellowship. We thank Dr. P. R. Rajamohanan (CSIR-NCL) for the NMR spectra.

Supporting Information Available. Detailed experimental procedures, single crystal X-ray data of **4a**, and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) For selected reports on the generation of 1,4-dipolar intermediates from quinoline and activated C−C triple bonds and its interception with electrophiles, see: (a) Nair, V.; Devipriya, S.; Suresh, E. *Tetrahedron* **2008**, *64*, 3567. (b) Nair, V.; Devipriya, S.; Suresh, E. *Tetrahedron Lett*. **2007**, *48*, 3667.

(18) Initial attempts to separate the diastereomers by crystallization failed.

(19) For selected reports on the generation of 1,4-dipolar intermediates from isoquinoline and activated C−C triple bonds and their interception with electrophiles, see: (a) Nair, V.; Sreekanth, A. R.; Abhilash, N.; Bhadbhade, M. M.; Gonnade, R. C. *Org. Lett*. **2002**, *4*, 3575. (b) Nair, V.; Sreekanth, A. R.; Biju, A. T.; Rath, N. P. *Tetrahedron Lett*. **2003**, *44*, 729. (c) Nair, V.; Remadevi, R.; Varma, L. *Tetrahedron Lett*. **2005**, *46*, 5333.

The authors declare no competing financial interest.