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# In Situ Generation of Nitrilimines from Aryldiazonium Salts and Diazo Esters: Synthesis of Fully Substituted Pyrazoles under Room Temperature

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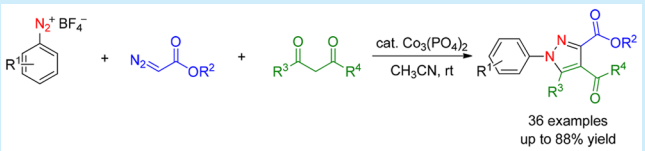
Supporting Information

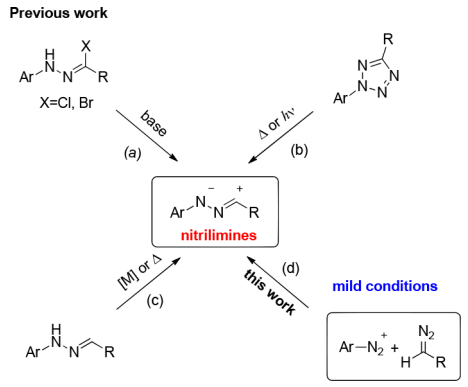
**ABSTRACT:** A novel one-pot synthesis for fully substituted pyrazoles has been well developed via the in situ generation of nitrilimines from aryldiazonium salts and diazo esters and a subsequent cycloaddition with 1,3-dicarbonyl compounds. High yields, mild conditions, wide substrate scope, and operational simplicity are the significant advantages of this methodology.




Pyrazole compounds are ubiquitous in natural products and drug molecules.[1] Due to their unique pharmacological properties and biological activity, they occupy important positions in heterocyclic compounds.[2] Many pesticides, small molecule drugs, and natural products contain the fragment of pyrazoles, such as insecticide Pyrolan,[3a] Fipronil,[3b] anti-inflammatory Celecoxib,[3c] and analgesic Novalgin.[3d] Unfortunately, cyclocondensation of hydrazines with 1,3-dicarbonyl compounds, the classic approach toward pyrazoles, often suffered from poor regioselectivity.[4] Recently, 1,3-dipolar cycloadditions of diazo compounds with alkynes or alkenes has shown excellent regioselectivity to produce pyrazoles.[5] However, in the majority of these methods, the access to fully substituted pyrazoles was usually missed. Recently, Sun and co-workers described an elegant cobalt-catalyzed synthesis of *N*-arylpyrazoles from aryldiazonium salts and vinyl diazoacetates in which the two nitrogen atoms of pyrazoles were derived from the diazo compounds.[6] In general, the development of new and efficient methods for the construction of fully substituted pyrazoles has been both a challenge and a focus of synthetic chemistry.

Notably, nitrilimines as a 1,3-dipole have shown unique potential, which could build diverse fully substituted pyrazoles.[7] The most frequent method for the formation of nitrilimines was the dehydrohalogenation of hydrazonoyl halides (Scheme 1a).[8] However, the difficulties of preparing starting materials and the necessity of bases cannot be underestimated. Apart from the dehydrohalogenation methods, decomposition of tetrazolium[9] or dehydrogenation of hydrazones[10] also have been well explored to generate nitrilimines, which suffered from the requirement of complex raw materials, expensive and toxic catalysts, and harsh conditions (Scheme 1b,c). Herein, we developed a fundamentally different strategy to nitrilimines through the room temperature coupling of aryldiazonium salts and diazo compounds under mild conditions (Scheme 1d), leading to fully substituted pyrazoles after its condensation with 1,3-dicarbonyl compounds.

**Scheme 1. In Situ Generation of Nitrilimines**




We chose acetylacetone **1a**, ethyl diazoacetate **2a**, and 4-bromobenzenediazonium tetrafluoroborate **3a** as model substrates for the formation of fully substituted pyrazole **4a**. After extensive screening of different kinds of transition-metal salts, $Co_3(PO_4)_2$ was found to be the best catalyst and gave the desired product **4a** in 67% yield under room temperature (Table 1, entries 1−7). The choice of solvent was also crucial for this transformation: replacing $CH_3CN$ with other common solvents, such as DCM, DCE, DMF, and *i*-PrOH, decreased the yield of product **4a** significantly (Table 1, entries 8−11). Fortunately, when we increased the amounts of ethyl diazoacetate **2a** and 4-bromobenzenediazonium tetrafluoroborate **3a**, the desired fully substituted pyrazole **4a** was obtained in a high yield of 85%

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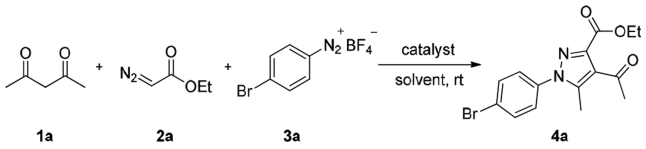
Org. Lett. XXXX, XXX, XXX−XXX

**Table 1. Optimization of the Reaction Conditions**[a]



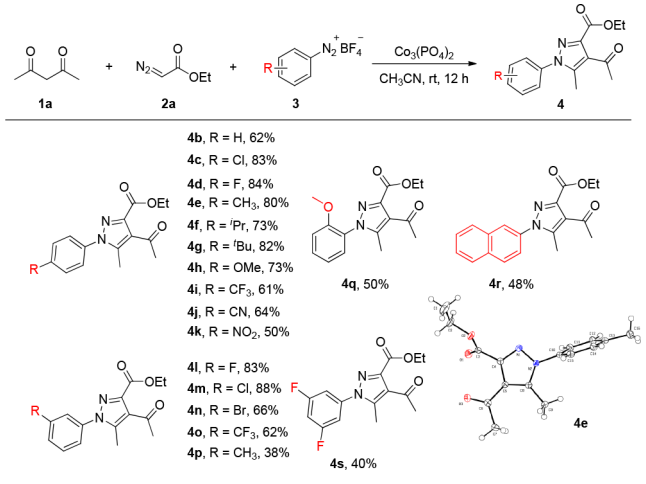

| entry | catalyst | solvent | yield (%)[b] |
|---|---|---|---|
| 1 | $Cu(OAc)_2$ | $CH_3CN$ | 49 |
| 2 | $Fe(OTf)_3$ | $CH_3CN$ | 53 |
| 3 | $MnCl_4{\cdot}4H_2O$ | $CH_3CN$ | 28 |
| 4 | $Co(OAc)_2{\cdot}4H_2O$ | $CH_3CN$ | 54 |
| 5 | $CoI_2$ | $CH_3CN$ | 50 |
| 6 | $Co(ClO_4)_2{\cdot}6H_2O$ | $CH_3CN$ | 45 |
| 7 | $Co_3(PO_4)_2$ | $CH_3CN$ | 67 |
| 8 | $Co_3(PO_4)_2$ | DCM | 42 |
| 9 | $Co_3(PO_4)_2$ | DCE | 45 |
| 10 | $Co_3(PO_4)_2$ | DMF | <5 |
| 11 | $Co_3(PO_4)_2$ | *i*-PrOH | 11 |
| 12[c] | $Co_3(PO_4)_2$ | $CH_3CN$ | 85 |
| 13[c] | | $CH_3CN$ | <5 |

[a]All reactions were carried out with **1a** (0.2 mmol), **2a** (0.8 mmol), **3a** (0.28 mmol), catalyst (0.04 mmol), and solvent (1 mL) at room temperature under air for 12 h unless otherwise noted. [b]Isolated yields. [c]The molar ratio of **1a**/**2a**/**3a** was 1:6:2.

(Table 1, entry 12). The control experiment suggested that transition-metal catalyst was necessary for this pyrazole formation reaction (Table 1, entry 13). For details on optimizing reaction conditions, see Supporting Information.

With the optimized conditions in hand, we next explored the substrate scopes of our reaction by screening different aryldiazonium salts (Scheme 2). Aryldiazonium salts bearing

**Scheme 2. Scope of Aryldiazoium Salts**[ab]

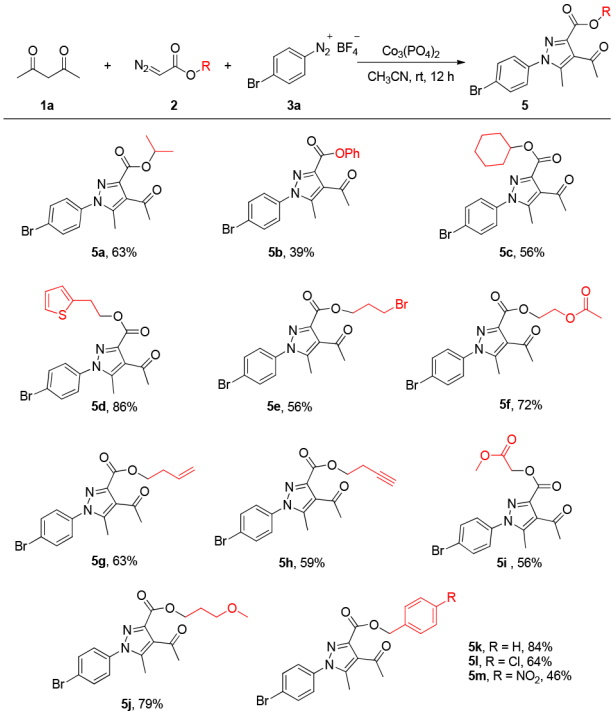



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 mmol), **3** (0.4 mmol), $Co_3(PO_4)_2$ (0.04 mmol, 20 mol %), and $CH_3CN$ (1 mL) for 12 h under air. [b]Isolated products.

either electron-donating groups or electron-withdrawing groups at the *para*-position of the benzene rings produced the corresponding pyrazoles in moderate to excellent yields (**4b**–**4k**). In addition, aryldiazonium salts bearing electron-withdrawing substituents at the *meta*-position of the benzene rings also gave the corresponding products with good yields (**4l**–**4o**). When *ortho*-methoxyl aryldiazonium salt was used as the substrate, the desired product **4q** was obtained in moderate 50% yield. Naphthalene and polysubstituted aryldiazonium salt could deliver the corresponding products **4r** and **4s** in moderate yields, respectively. The exact structure of pyrazole **4e** has been conclusively confirmed by the single-crystal X-ray diffraction.

To further explore the diversity of this transformation, the assessment of various diazo esters was performed, as shown in Scheme 3. A variety of $\alpha$-diazo esters could react well with acetyl-

**Scheme 3. Scope of Diazo Esters**[ab]




[a]Reaction conditions: **1a** (0.2 mmol), **2** (1.2 mmol), **3a** (0.4 mmol), $Co_3(PO_4)_2$ (0.04 mmol, 20 mol %), and $CH_3CN$ (1 mL) for 12 h under air. [b]Isolated products.

acetone **1a** and 4-bromobenzenediazonium tetrafluoroborate **3a**, leading to the corresponding products in moderate to high yields (**5a**–**5m**). Notably, fully substituted pyrazoles bearing an alkenyl or alkynyl group could also be prepared in moderate yields (**5g**–**5h**), which can undergo further synthetic transformations.

Finally, we evaluated the scope of 1,3-dicarbonyl compounds for this transformation (Scheme 4). Symmetrical 1,3-dicarbonyl compounds, such as heptane-3,5-dione and 1,3-diphenylpropane-1,3-dione, delivered the corresponding products **6a** and **6b** in moderate yields. When unsymmetrical 1,3-dicarbonyl compounds, such as 1-phenylbutane-1,3-dione, were used as substrate, two isomers of pyrazoles **6c** and **6c′** were generated with good yields. Notably, the use of 1-phenylbutane-1,3-dione generated the single product **6d** in 40% yield.

Further experiments were conducted to gain insight into the reaction mechanism, as shown in Scheme 5. When $^{15}N$-labeled diazonium salt **3b′** was subjected to the model reaction, the $^{15}N$-labeled product **4b′** was obtained in 61% yield (Scheme 5a). It suggested that the nitrogen atom in the product was derived from diazonium salts, rather than diazo compounds, which was significantly different from Sun's work.[6] The condensation product **7** of 1,3-dicarbonyl compound **1a** and aryldiazoium salt **2a** did not produce compound **4a** under the standard conditions, thus indicating that the condensation/cyclization was not



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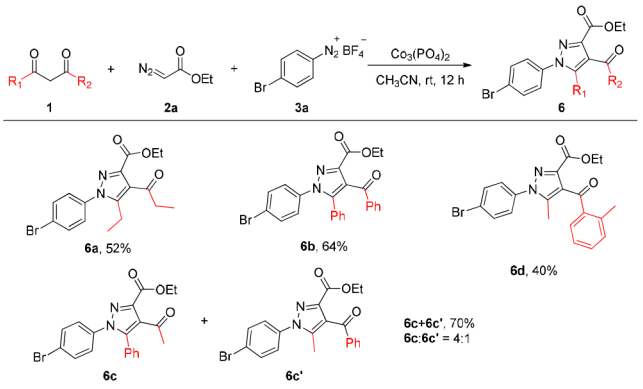
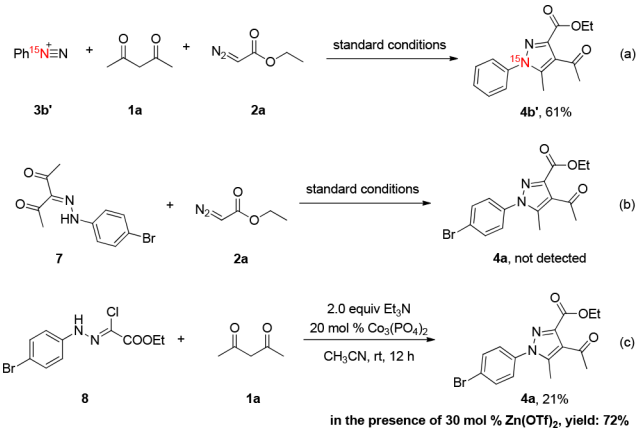
Org. Lett. XXXX, XXX, XXX–XXX

**Scheme 4. Scope of 1,3-Dicarbonyl Compounds**[ab]




[a]Reaction conditions: **1** (0.2 mmol), **2a** (1.2 mmol), **3a** (0.4 mmol), $Co_3(PO_4)_2$ (0.04 mmol, 20 mol %), and $CH_3CN$ (1 mL) for 12 h under air. [b]Isolated products.

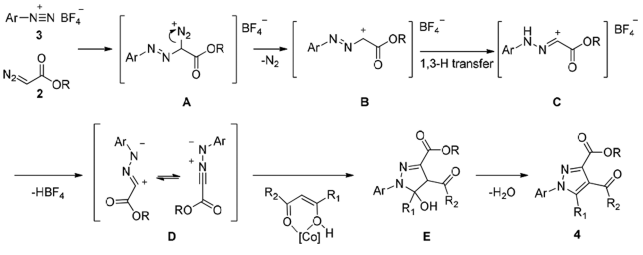
**Scheme 5. Probe for the Possible Mechanism**




involved in this pyrazole formation reaction (Scheme 5b). Notably, the nitrilimine generated *in situ* from hydrazonoyl halide **8** resulted in the desired product **4a** in 21% yield. When Lewis acid $Zn(OTf)_2$ was added to the reaction to promote the enolization of 1,3-dicarbonyl, the product **4a** was obtained in 72% yield (Scheme 5c).

Based upon the above results, and the literature, a plausible catalytic cycle for this transformation was proposed, as shown in Scheme 6. Initially, the reaction between diazo ester **2** and aryldiazonium salt **3** forms intermediate **A**, which then converts to intermediate **B** by releasing one molecule of $N_2$. Next, **B** is converted to a more stable intermediate **C** and then decomposes to the nitrilimines **D** via the loss of $HBF_4$.[11] The 1,3-dipolar cycloaddition between **D** and enol tautomer of 1,3-dicarbonyl compound **1** stabilized by $Co_3(PO_4)_2$ afforded intermediate **E**,

**Scheme 6. Proposed Reaction Mechanism**




which undergoes elimination to afford the desired fully substituted pyrazole product **4**.

In conclusion, we have successfully developed a simple and efficient approach for the synthesis of fully substituted pyrazoles through the *in situ* generation of nitrilimines from aryldiazonium salts and diazo esters and a subsequent 1,3-dipolar cycloaddition with 1,3-dicarbonyl compounds. This reaction allows broad functional group compatibility, mild and neutral reaction conditions, easily available starting materials, and operational simplicity. Further investigations will focus on the discovery of other 1,3-dipolar cycloaddition reaction of nitrilimines generated in situ from diazo compounds and aryldiazonium salts.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00750.

Experimental procedure, characterization data, copies of $^1H$ and $^{13}C$ NMR spectra (PDF)

### Accession Codes

CCDC 1813978 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) For selected examples, see: (a) Mowbray, C. E.; Burt, C.; Corbau, R.; Gayton, S.; Hawes, M.; Perros, M.; Tran, I.; Price, D. A.; Quinton, F. J.; Selby, M. D.; Stupple, P. A.; Webster, R.; Wood, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5857. (b) Chanhan, A.; Sharma, P. K.; Kaushik, N. *Int. J. Chem. Technol. Res.* **2011**, *3*, 11. (c) Kumar, V.; Kaur, K.; Gupta, G. K.; Sharma, A. K. *Eur. J. Med. Chem.* **2013**, *69*, 735. (d) Do, K.; Wilsker, D.; Ji, J.; Zlott, J.; Freshwater, T.; Kinders, R. J.; Collins, J.; Chen, A. P.; Doroshow, J. H.; Kummar, S. *J. Clin. Oncol.* **2015**, *33*, 3409. (e) Indrasena Reddy, K.; Aruna, C.; Manisha, M.; Srihari, K.; Sudhakar Babu, K.; Vijayakumar, V.; Sarveswari, S.; Priya, R.; Amrita, A.; Siva, R. *J. Photochem. Photobiol., B* **2017**, *168*, 89.

(2) For selected books, see: (a) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; John Wiley & Sons, Ltd.: Chichester, 2011; p 1. (b) Ameta, K. L.; Pawar, R. P.; Domb, A. J. *Bioactive Heterocycles: Synthesis and Biological Evaluation*; Nova Science Publishers: New York, 2012; p 217.

(3) (a) El Beit, I. O. D.; Verner Wheelock, J.; Cotton, D. E. *Ecotoxicol. Environ. Saf.* **1981**, *5*, 135. (b) Vidau, C.; Diogon, M.; Aufauvre, J.;



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*Org. Lett.* XXXX, XXX, XXX−XXX

Fontbonne, R.; Viguès, B.; Brunet, J.-L.; Texier, C.; Biron, D. G.; Blot, N.; El Alaoui, H.; Belzunces, L. P.; Delbac, F. *PLoS One* **2011**, *6*, e21550. (c) Nissen, S. E.; Yeomans, N. D.; Solomon, D. H.; Luscher, T. F.; Libby, P.; Husni, M. E.; Graham, D. Y.; Borer, J. S.; Wisniewski, L. M.; Wolski, K. E.; Wang, Q.; Menon, V.; Ruschitzka, F.; Gaffney, M.; Beckerman, B.; Berger, M. F.; Bao, W.; Lincoff, A. M. *N. Engl. J. Med.* **2016**, *375*, 2519. (d) Hearn, L.; Derry, S.; Moore, R. A. *Cochrane Database Syst. Rev.* **2016**, *4*, CD011421.

(4) (a) Sloop, J. C.; Bumgardner, C. L.; Loehle, W. D. *J. Fluorine Chem.* **2002**, *118*, 135. (b) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6737. (c) Wang, Z.-X.; Qin, H.-L. *Green Chem.* **2004**, *6*, 90. (d) Lévai, A.; Silva, A. M. S.; Cavaleiro, J. A. S.; Alkorta, I.; Elguero, J.; Jekő, J. *Eur. J. Org. Chem.* **2006**, *2006*, 2825. (e) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Org. Lett.* **2008**, *10*, 2377. (f) Patil, N. T.; Singh, V. *Chem. Commun.* **2011**, *47*, 11116. (g) Li, D. Y.; Mao, X. F.; Chen, H. J.; Chen, G. R.; Liu, P. N. *Org. Lett.* **2014**, *16*, 3476. (h) Zhang, X.; Kang, J.; Niu, P.; Wu, J.; Yu, W.; Chang, J. *J. Org. Chem.* **2014**, *79*, 10170. (i) Muzalevskiy, V. M.; Rulev, A. Y.; Romanov, A. R.; Kondrashov, E. V.; Ushakov, I. A.; Chertkov, V. A.; Nenajdenko, V. G. *J. Org. Chem.* **2017**, *82*, 7200. (j) Tang, L.; Ma, M.; Zhang, Q.; Luo, H.; Wang, T.; Chai, Y. *Adv. Synth. Catal.* **2017**, *359*, 2610.

(5) (a) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381. (b) Jiang, N.; Li, C. J. *Chem. Commun.* **2004**, 394. (c) Hanamoto, T.; Koga, Y.; Kido, E.; Kawanami, T.; Furuno, H.; Inanaga, J. *Chem. Commun.* **2005**, 2041. (d) Muruganantham, R.; Mobin, S. M.; Namboothiri, N. N. *Org. Lett.* **2007**, *9*, 1125. (e) Qi, X.; Ready, J. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3242. (f) Vuluga, D.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *Green Chem.* **2009**, *11*, 156. (g) Ibad, M. F.; Langer, P.; Reiss, F.; Schulz, A.; Villinger, A. *J. Am. Chem. Soc.* **2012**, *134*, 17757. (h) Wang, H.; Zhao, Y.-L.; Li, L.; Zhang, Z.-W.; Liu, Q. *Adv. Synth. Catal.* **2013**, *355*, 1540. (i) Hu, Y.; Li, C. Y.; Wang, X. M.; Yang, Y. H.; Zhu, H. L. *Chem. Rev.* **2014**, *114*, 5572. (j) Zhang, F. G.; Wei, Y.; Yi, Y. P.; Nie, J.; Ma, J. A. *Org. Lett.* **2014**, *16*, 3122. (k) Shao, Y.; Tong, J.; Zhao, Y.; Zheng, H.; Ma, L.; Ma, M.; Wan, X. *Org. Biomol. Chem.* **2016**, *14*, 8486. (l) Dallinger, D.; Kappe, C. O. *Nat. Protoc.* **2017**, *12*, 2138. (m) Qin, S.; Zheng, Y.; Zhang, F. G.; Ma, J. A. *Org. Lett.* **2017**, *19*, 3406. (n) Baiju, T. V.; Namboothiri, I. N. N. *Chem. Rec.* **2017**, *17*, 939. (o) Chen, Z.; Zheng, Y.; Ma, J. A. *Angew. Chem., Int. Ed.* **2017**, *56*, 4569. (p) Xia, Y.; Wang, J. *Chem. Soc. Rev.* **2017**, *46*, 2306.

(6) Guo, H.; Zhang, D.; Zhu, C.; Li, J.; Xu, G.; Sun, J. *Org. Lett.* **2014**, *16*, 3110.

(7) (a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; J. Wiley and Sons: New York, 1984. (b) Donohue, S. R.; Halldin, C.; Pike, V. W. *Tetrahedron Lett.* **2008**, *49*, 2789. (c) Fustero, S.; Sanchez-Rosello, M.; Barrio, P.; Simon-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (d) Molteni, G.; Ponti, A. *Molecules* **2017**, *22*, 202.

(8) (a) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276. (b) Fuchi, N.; Doi, T.; Takahashi, T. *Chem. Lett.* **2005**, *34*, 438. (c) Abunada, N. M.; Hassaneen, H. M.; Kandile, N. G.; Miqdad, O. A. *Molecules* **2008**, *13*, 1501. (d) Dadiboyena, S.; Valente, E. J.; Hamme, A. T. *Tetrahedron Lett.* **2010**, *51*, 1341. (e) Liu, B.; Cong, H.; Li, X.; Yu, B.; Bao, L.; Cai, W.; Xie, Y.; Lu, X. *Chem. Commun.* **2014**, *50*, 12710.

(9) (a) Croce, P. D.; La Rosa, C.; Zecchi, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, *1*, 2621. (b) Lederhose, P.; Haworth, N. L.; Thomas, K.; Bottle, S. E.; Coote, M. L.; Barner-Kowollik, C.; Blinco, J. P. *J. Org. Chem.* **2015**, *80*, 8009. (c) Lederhose, P.; Wust, K. N.; Barner-Kowollik, C.; Blinco, J. P. *Chem. Commun.* **2016**, *52*, 5928. (d) de Moliner, F.; Kielland, N.; Lavilla, R.; Vendrell, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 3758.

(10) (a) Gladstone, W. A. F.; Aylward, J. B.; Norman, R. O. C. *J. Chem. Soc. C* **1969**, 2587. (b) Noto, R.; Buccheri, F.; Cusmano, G.; Gruttadauria, M.; Werber, G. *J. Heterocycl. Chem.* **1991**, *28*, 1421. (c) Singh, O. V.; George, V. *Synth. Commun.* **1994**, *24*, 2627. (d) Lokanatha Rai, K. M.; Linganna, N. *Synth. Commun.* **1997**, *27*, 3737. (e) Ningaiah, S.; Doddaramappa, S. D.; Chandra; Madegowda, M.; Keshavamurthy, S.; Bhadraiah, U. K. *Synth. Commun.* **2014**, *44*, 2222.

(11) (a) Chattaway, F. D.; Ashworth, D. R. *J. Chem. Soc.* **1933**, 1624. (b) Huisgen, R.; Koch, H. J. *Liebigs Ann. Chem.* **1955**, *591*, 200.



DOI: 10.1021/acs.orglett.8b00750
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