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Three-Component Strategy toward 5-Membered Heterocycles from Isocyanide Dibromides.

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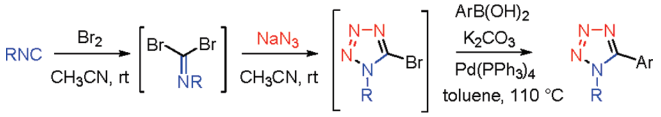
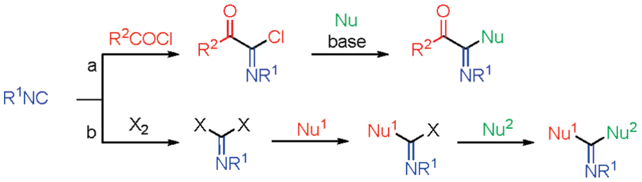
ABSTRACT



A three-component strategy starting from isocyanides allows a straightforward synthesis of five-membered ring heterocycles. New cascades were developed involving the addition of a nitrogenated nucleophile—an azide or a tetrazole—on isocyanide dibromides, an electrocyclization, and a Suzuki coupling, which afford new accesses to tetrazole and triazole scaffolds.

Isocyanides have played a central role in the success of multicomponent reactions.[1] Besides the Ugi reaction, considered as the most powerful four-component coupling, isocyanides have also been used in various three-component couplings such as the Passerini reaction or the less popular Nef reaction.[2] Our research group is involved in extending the scope of the latter by allowing various nucleophiles to trap the intermediate imidoyl chloride (Scheme 1, path a).[3] Among the different possibilities, we envisioned organometallic reagents as the third component. However, when settling such a strategy, deactivation of the catalyst occurs and the reaction fails. Indeed, under basic conditions, the Nef reaction turns out to be reversible and the liberation of isocyanides inhibits the catalytical activity of the metal.[2b,3b]

Scheme 1. 3-CR Involving Imidoyl Halides from Isocyanides



To circumvent these problems, we decided to examine the halogenation of isocyanides as an alternative access to imidoyl derivatives from isocyanides (Scheme 1, path b). Dihalogeno isocyanides are stable derivatives readily formed under the addition of chlorine or bromine onto isocyanides.[3a,4] The presence of the two halogen atoms activates the C=N double bond toward nucleophiles with possible additions in a sequential manner.[5] To the best of our knowledge, these compounds have never been used in three-component reactions involving a palladium-triggered coupling up to now.[6]

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(1) For some reviews, see: (a) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1–140. (b) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144. (c) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53–66. (d) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80. (e) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321–3329. (f) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (g) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(2) The Nef isocyanide reaction stands for the formation of imidoyl halides from acyl halides and isocyanides. If one considers the following additions of nucleophilic reagents to form stable adducts such as pyruvamides after water addition, it represents the first (sequential) three-component coupling of isocyanides. For references, see: (a) Nef, J. U. *Justus Liebigs Ann. Chem.* **1892**, *270*, 267–335. (b) Ugi, I.; Fetzer, U. *Chem. Ber.* **1961**, *94*, 116–1121. (c) Westling, M.; Smith, R.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 1159–1165. (d) Lee, C. H.; Westling, M.; Livinghouse, T.; Williams, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 4089–4095. (e) Livinghouse, T. *Tetrahedron* **1999**, *55*, 9947–9978. (f) Van Wangenen, B. C.; Cardenilla, J. H. *Tetrahedron Lett.* **1989**, *30*, 3605–3608. (g) Adlington, R. M.; Barrett, A. G. M. *Tetrahedron* **1981**, *37*, 3935–3942. (h) El Kaim, L.; Pinot-Périgord, E. *Tetrahedron* **1998**, *54*, 3799–3806. (i) Chen, J. J.; Deshpande, S. V. *Tetrahedron Lett.* **2003**, *44*, 8873–8876.

(3) (a) Coffinier, D.; El Kaim, L.; Grimaud, L. *Org. Lett.* **2009**, *11*, 3799–3806. (b) El Kaim, L.; Grimaud, L.; Wagschal, S *Synlett* **2009**, 1401–1404.

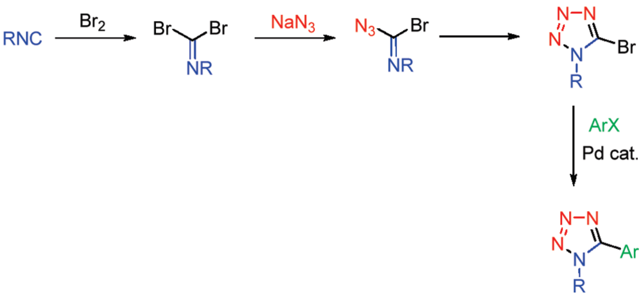
(4) For a review on dihalogenoisocyanides see: Kühle, E.; Anders, B.; Klauke, E.; Tarnow, H.; Zumach, G. *Angew. Chem., Int. Ed.* **1969**, *8*, 20–34.

(5) Schroth, W.; Spitzner, R.; Herrmann, J. *Zeitschrift für Chemie* **1977**, *17*, 172–173. (a) Barreau, M.; Ponsinet, G. *Synthesis* **1987**, 262–265.

10.1021/ol200003u

To limit potential redox processes that would form reduced metal-isocyanide complexes, we decided to perform the organometallic coupling as the last step of the whole sequence.[7] To test the feasibility of such cascades, azide was selected as the first nucleophile as it is known to react with imidoyl halides to form tetrazoles (Scheme 2).[8] Furthermore, the outcome of such an intermediate cyclization would be an increased stability of the final three component adduct toward water, making the process even more appealing.[9]

Scheme 2. 3-Component Tetrazole Formation



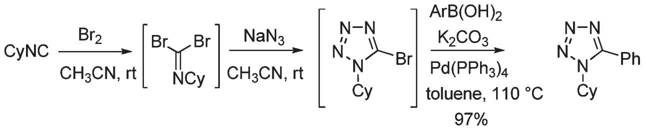
The optimization of each step of the sequence was done separately. The cyclohexyl isocyanide was chosen as a model input for starting material. When treated with 1 equivalent of bromine in dichloromethane at room temperature, the cyclohexyl isocyanide was totally transformed to the corresponding dibromide. We examined next various conditions for the tetrazole formation. First trials were performed using trimethylsilyl azide. The addition of a slight excess of TMSN$_3$ to the former solution failed to give any coupling adduct. Various acid catalysts were then tested. The addition of a few drops of methanol did not give desired products although the use of a catalytic amount of silver salts resulted in isolation of the bromo tetrazole. Indeed, the addition of silver perchlorate (40 mol %) gave about 50% of the product while the use of silver acetate (10 mol %) afforded the bromo tetrazole in quantitative yield after 3 days. Considering this long reaction time and the need of a Lewis acid as catalyst, we investigated other azide sources. Quantitative results were also obtained using sodium azide in acetonitrile in only 1 h (Scheme 3).

Scheme 3. Optimization of the Tetrazole Formation

conditions	yields
TMSN$_3$, CH_2Cl_2, rt	-
TMSN$_3$, CH_2Cl_2, MeOH (cat.), rt	-
TMSN$_3$, CH_2Cl_2, $AgClO_4$ (40 mol %), 18 h, rt	54%
TMSN$_3$, CH_2Cl_2, AgOAc (10 mol %), 3 d, rt	100%
NaN$_3$, CH_3CN, rt	100%

Next we examined the final Suzuki coupling. Unfortunately, it failed in acetonitrile, which leds us to change the solvent of the last reaction step. After completion of the reaction, the acetonitrile was removed and toluene was added to adjust the concentration to 0.5 M concentration. The boronic acid (3 equiv), potassium carbonate (3 equiv) and a catalytic amount of tetrakis(triphenylphosphine) palladium (5 mol %) were added and the resulting mixture was refluxed for 18 h to give the desired aryl tetrazole in 90% yield. The amount of boronic acid could be decreased to 1.5 equiv without any change. Finally, the desired aryl tetrazole was obtained in three steps in a 90% overall yield. We surmised that considering the efficiency of each step, the whole sequence could be performed in the same pot with an intermediate change of solvent. Thus, we performed the bromination-addition of the azide-electrocylization in acetonitrile as solvent. The resulting mixture was then evaporated and diluted with toluene to perform the pallado-catalyzed coupling. Under these conditions, the desired aryl tetrazole was isolated in an optimized 97% yield (Scheme 4).

Scheme 4. One-Pot Tetrazole Formation



The scope of such a sequence was next examined varying the isocyanide and the boronic acid partners as depicted in Table 1. When varying the isocyanide, the electrocyclization step turned out to be poorly efficient unless increasing the temperature up to 65 °C. In all the cases, the corresponding aryl tetrazoles were obtained according to a sequential one-pot procedure in moderate to good yields. This method constitutes a straightforward and convenient access to aryl tetrazoles.

To extend the scope even more of this synthetic path, we further examined other nucleophiles in the second step. Indeed, as part of our ongoing interest in 1,2,4-triazoles

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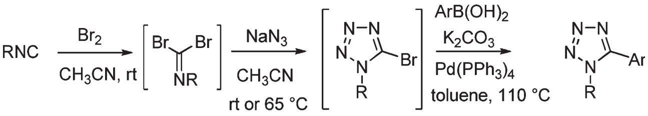
(6) An isocyanide dihalogenide conversion to chloropyridines followed by a palladium coupling has been reported in a synthesis of variolin analogues. However, with the low yields obtained in the first step, a one-pot multicomponent strategy may be very difficult to settle: Baeza, A.; Burgos, C.; Alvarez-Builla, J.; Vaquero, J. J. *Tetrahedron Lett*. **2007**, *48*, 2597–2601. For an additional cascade involving the cyclization of an isocyanide followed by a Suzuki coupling see:Liu, L.; Wang, Y.; Wang, H.; Peng, C.; Zhao, J.; Zhu, Q. *Tetrahedron Lett*. **2009**, *50*, 6715–6719.

(7) For reduction of isocyanide dichloride under pallado-catalyzed Grignard addition see: Ito, Y.; Inouye, M.; Murakami, M. *Tetrahedron. Lett*. **1988**, *29*, 181–192.

(8) For tetrazole formation from isocyanide dichlorides see: (a) Cristiano, M.; Lurdes, S.; Johnstone, R. A. W. J. *Chem. Research, Synopses* **1997**, *3*, 164–165. (b) Alves, J. A.; Johnstone, R. A. W. *Synth. Commun*. **1997**, *27*, 2645–2650. (c) Mloston, G.; Galindo, A.; Bartnik, R.; Marchand, A. P.; Rajagopal, D. J. *Het. Chem*. **1996**, *33*, 93–96. (d) Quast, H.; Bieber, L. *Chem. Ber*. **1981**, *114*, 3253–3272. For an alternative three-component palladium catalyzed preparation of tetrazole using a Tsuji-Trost reaction see:Kamijo, S.; Jin, T.; Huo, Z.; Young Soo, G.; Shim, J-G; Yamamoto, Y. *Mol. Div*. **2003**, *6*, 181–192. For tetrazole formation from isocyanide and $X-N_3$, see: Fowler, F. W.; Hassner, A.; Levy, L. A. *J. Am. Chem. Soc*. **1967**, *89*, 2077–2082. Collibee, W. L.; Nakajima, M.; Anselme, J. −P. *J. Org. Chem*. **1995**, *60*, 468–469.

(9) Without such a cyclization, sequential nucleophilic additions lead to imines prone to hydrolytic cleavage unless engaged in further reactions.

Table 1. One-Pot Three-Step Aryl Tetrazole Formation



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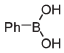
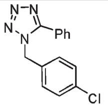
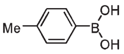
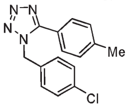
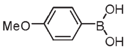
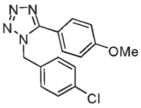
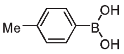
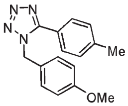
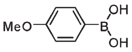
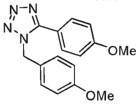
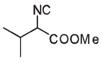
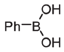
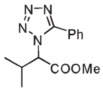
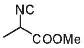
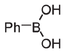
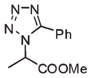
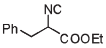
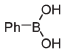
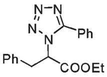
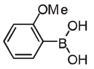
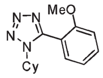
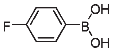
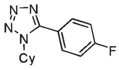
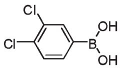
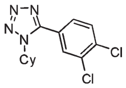
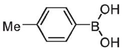
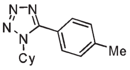
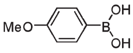
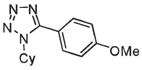
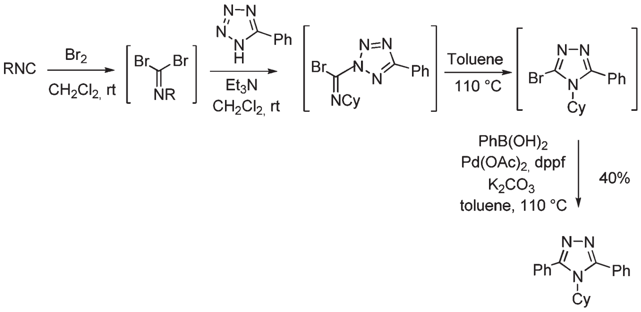
1	*p*-ClBnNC			64
2	*p*-ClBnNC			86
3	*p*-ClBnNC			70
4	*p*-MeOBnNC			82
5	*p*-MeOBnNC			41
6				62
7				67
8				36
9	CyNC			70
10	CyNC			41
11	CyNC			23
12	CyNC			98
13	CyNC			90

and their synthesis via isocyanide-based chemistry, we speculated that tetrazoles should react with the dibromo isocyanide and the resulting adduct should evolve via a Huisgen rearrangement to give the corresponding bromo triazole.[3b,10] Indeed, the dibromo isocyanide was treated with a stoichiometric amount of phenyl tetrazole in dichloromethane which was then evaporated; the resulting mixture was diluted with toluene and heated up to 110 °C for 2.5 h to give the corresponding bromo triazole which is submitted to subsequent Suzuki coupling. Therefore, we isolated the desired 1,2,4-triazole according to a one-pot four-step synthesis in a 40% yield (Scheme 5).

Scheme 5. 3-Component 1,2,4-Triazole Synthesis



During the last 20 years, in the field of isocyanide chemistry, the prominent use of the Ugi and Passerini couplings[1] has masked the potential of earlier work for the development of new isocyanide-based multicomponent reactions (IMCRs). This is the case for isocyanide dihalides.[4] Known for more than a century, the interest for the chemistry of these compounds peaked in the 1950s, well before the development of organometallic couplings. As shown by the tetrazole and triazole syntheses reported herein, isocyanide dihalides together with palladium chemistry have a high potential for multicomponent formation of five-membered ring heterocycles. In a way, isocyanide dihalides may be considered as isocyanide surrogates suitable for transition metal catalyzed couplings.[11] Further work is under study to extend this work to oxazole, imidazole and thiazole formations.

Acknowledgment. We thank the ANR program CP2D (Muse project) and the ENSTA for financial support.

Supporting Information Available. Detailed experimental procedures and spectral data for aryl heterocycles. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Huisgen, R.; Sauer, J.; Sturm, H. J. *Angew. Chem.* **1958**, *70*, 272–273. (b) Huisgen, R.; Sauer, J.; Seidel, M. *Chem. Ber.* **1960**, *93*, 2885–2891. (c) Huisgen, R.; Sturm, H. J.; Seidel, M. *Chem. Ber.* **1961**, *94*, 1555–1562. (d) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 947–1034. (e) Boyd, G. V.; Cobb, J.; Lindley, P. F.; Mitchell, J. C.; Nicolaou, G. A. *J. Chem. Soc., Chem. Commun.* **1987**, 99–101.

(11) Due to the high complexing properties of isocyanides towards transition metals, catalyzed processes are difficult to settle unless using sterically hindered isocyanides: (a) Yamamoto, Y.; Yamazaki, H. *Coord. Chem. Rev.* **1972**, *8*, 225–239. For some representative examples see: (b) Saluste, C. G.; Whitby, R. J.; Furber, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4156–4158. (c) Ito, Y.; Matsuura, T.; Murakami, M. *J. Am. Chem. Soc.* **1988**, *110*, 3692–3693.