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Multicomponent Synthesis of 1-Aryl 1,2,4-Triazoles

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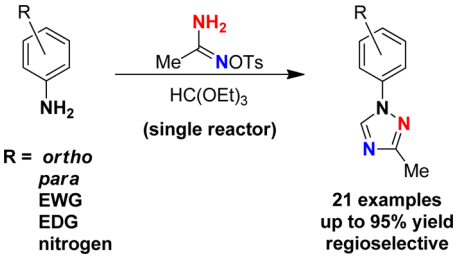
ABSTRACT



A multicomponent (single reactor) process for the synthesis of 1-aryl 1,2,4-triazoles was explored and developed. This transformation prepared the 1,2,4-triazole directly from anilines, amino pyridines, and pyrimidines. The reaction scope was explored with 21 different substrates, and the position of the nitrogen atoms in the newly formed ring was established by ^{15}N labeling and NMR spectroscopy.

1,2,4-Triazoles are a class of heterocycles found in a wide range of biologically active molecules encompassing several therapeutic areas, and as subunits of coordination polymers.[1,3d]

Several methodologies to prepare this important motif have been reported and reviewed in the literature.[2,3d] Common methods to access aryl 1,2,4-triazoles include the formation and condensation of a hydrazine derivative,[3] transition metal mediated C−N bond coupling,[4,5] and S_NAr-type chemistry of a halogenated arene with a 1,2,4-triazole nucleophile.[6] Some limitation of these approaches include multiple steps to generate and activate the hydrazine for cyclization, or in the case of S_NAr chemistry, a mixture of *N*-regioisomers can be formed.[6,7] General

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(3) For an elegant synthesis of fully substituted 1,2,4-triazoles with hydrazines, see: (a) Staben, S. T.; Blaquiere, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 325–328. (b) Castanedo, G. M.; Seng, P. S.; Blaquiere, N.; Trapp, S.; Staben, S. T. *J. Org. Chem.* **2011**, *76*, 1177–1179. (c) An elegant copper catalyzed approach to 1,2,4-triazoles: Xu, H.; Jiang, Y.; Fu, H. *Synlett* **2013**, *24*, 125–129. (d) Guru, M. M.; Punniyamurthy, T. *J. Org. Chem.* **2012**, *77*, 5063–5073 and references therein. (e) Terauchi, J.; Koike, T.; Honda, E.; Nakamura, M.; Kajita, Y.; Hoashi, Y.; Morimoto, S.; Fujimoto, T. Preparation of Piperazines and Related Compounds for Inhibiting Amyloid-β Production. PCT Int. Appl., 2011002067.

(4) For an example of C-N coupling metal-mediated synthesis of fused 1,2,4-triazoles from amino pyridines, see: Ueda, S.; Nagasawa, H. *J. Am. Chem. Soc.* **2009**, *131*, 15080–15081.

(5) For examples of metal-mediated C−N bond coupling with symmetrical 1,2,4-triazole and aryl halides, see: (a) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578–5587. (b) Yang, K.; Qiu, Y.; Zheng, Li, Z.; Wang, Z.; Jiang, S. *J. Org. Chem.* **2011**, *76*, 3151–3159. (c) Albrecht, B. K.; Gehling, V. S.; Hewitt, M. C.; Taylor, A. M.; Harmange, J.-C. Preparation of 4H-Benzo[b][1,2,4]Triazolo[4,3-d][1,4]Diazepine Derivatives as Bromodomain Inhibitors. PCT Int. Appl., 2012151512. (d) Aspnes, G. E.; Didiuk, M. T.; Filipski, K. J.; Guzman-Perez, A.; Lee, E. C. Y.; Pfefferkorn, J. A.; Stevens, B. D.; Tu, M. M. Preparation of 3-[4-(Heterocyclyl-Substituted)-Benzamido]Propanoic Acids as Glucagon Receptor Modulators. U.S. Pat. Appl., 20120202834.

(6) S_NAr: (a) De Cleyn, M. A. J.; Van Brandt, S. F. A.; Gijsen, H. J. M.; Berthelot, D. J-C.; Oehlrich, D. Triazole Derivatives as Gamma-Secretase Modulators and Their Preparation and Use for the Treatment of Diseases. PCT Int. Appl. WO 2011086098 A1. (b) Kamenecka, T. M.; Jiang, R.; Song, X.; Lograsso, P.; Cameron, M. D. Preparation of Phenylaminopyrimidine Derivatives and Analogs as Protein Kinase Inhibitors. PCT Int. Appl. WO 2009032861. (c) Naidu, B. N.; Connolly, T. P.; Ueda, Y. Cyclic Pyrimidinone Derivatives as HIV Integrase Inhibitors and Their Preparation, Pharmaceutical Compositions and Use in the Treatment of HIV Infections. U.S. Patent, 7419969.

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examples of methodologies used to prepare 1-aryl 1,2,4-triazoles are depicted in Figure 1.

We envisioned that building the 1,2,4-triazole ring directly from an aniline would provide an efficient method to prepare 1,2,4-triazoles and hypothesized that this could be effected as outlined in Scheme 1. Formation of an imidate (**3**) from the condensation of an aniline (**1**) with triethylorthoformate is known to be a facile process.[8] We postulated that in the presence of a third component, such as tosylamidoxime **5**,[9] imidate **3** could condense first and then undergo a N−N bond-forming cyclization reaction to generate aryl 1,2,4-triazole **6**.[10,11] However, it is known that, in the absence of excess orthoester, imidate **3** will react with a second equivalent of aniline to form a less reactive amidine product (**4**).[12] Although this undesired condensation could occur before the aniline is entirely consumed, imidate **3** can slowly regenerate under the reaction conditions.[12] We were encouraged to investigate this process because the 1,2,4-triazole would be forged directly from an aniline (convergently), efficiently (in one step) and without the application of transition metal catalysts.

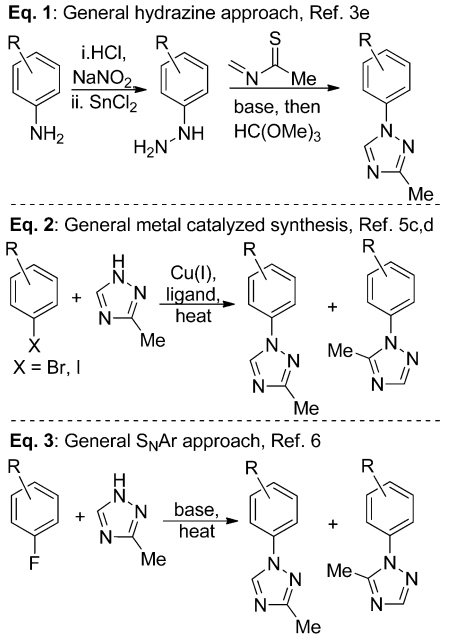
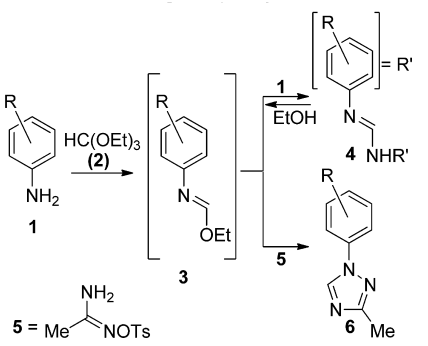


Figure 1. General synthetic routes to 1-aryl 1,2,4-triazoles.

To begin this investigation, *para*-chloroaniline was chosen as a model substrate (Table 1, entry 1).[13] A mixture of *para*-chloroaniline (**1a**), triethylorthoformate ($HC(OEt)_3$), and tosylamidoxime **5** in THF was heated to 60 °C for 24 h to produce the desired triazole **6a** as a minor product. The major components of the crude reaction mixture were observed to be amidine **4a** and imidate **3a**. Aniline **1a** was completely consumed, and tosylamidoxime **5**, which was added in slight excess, was still present. Continued heating was not beneficial, as it mainly led to the decomposition of **5**, generated other side products, and consumed amidine **4a**. As previously reported, a protic environment assists in the conversion of amidines such as **4a** back to the corresponding imidate.[12] We hypothesized that by introducing an acid catalyst and facilitating this equilibrium, greater conversion could be achieved. We were gratified to discover that addition of ethanesulfonic acid ($EtSO_3H$, 10 mol %) to a mixture of tosylamidoxime **5**, aniline **1a**, $HC(OEt)_3$, THF and heating at 60 °C for 24 h afforded facile consumption of both amidine **4a** and imidate **3a** with an excellent conversion to triazole **6a**, in 93% isolated yield.

Scheme 1. Reaction Pathway Design



The efficiency of this methodology was tested with a series of anilines, and the outcomes are summarized in Table 1. For substrates containing electron-withdrawing groups, the desired 1,2,4-triazole products were generated in very good to excellent yields (80−95%, Table 1 entries 1−6, 14). Not surprisingly the electronic nature of the ring substituents impacts the time required for reaction completion. For example, *para*-nitro aniline (Table 1, entry 2) reached completion after 4 h whereas substrates that possess a less electronegative group (entries 3−6) required ~6 h. Continued heating after most of the amidine had been consumed led to decomposition of the 1,2,4-triazole and a diminished product yield (54% after 24 h vs 93% after 4 h; Table 1, entry 2). Thus, in order to maximize product recovery, cooling the reaction mixture after reaching completion is paramount.

(7) For a discussion on the regioselectivity of 1,2,4-triazole alkylation: Bulger, P. G.; Cottrell, I. F.; Cowden, C. J.; Davies, A. J.; Dolling, U.-H. *Tetrahedron Lett*. **2000**, *41*, 1297–1301.

(8) Roberts, R. M. *J. Am. Chem. Soc*. **1949**, *71*, 3848–3849 and references therein.

(9) Preparation of tosyl amidoxime **5**: Inagaki, T.; Kurita, Y.; Hirakata, K.; Mizutani, A.; Kondo, M. Preparation of Alkoximino-5-Amino-1,2,4-thiadiazole-3-Acetates. Eur. Pat. Appl. EP 0795551 A1.

(10) For a review on the structure and chemistry of hydroxylamidoximes, see: Katritzky, A. R.; Huang, L.; Chahar, M.; Sakhuja, R.; Hall, C. D. *Chem. Rev*. **2012**, *112*, 1633–1649.

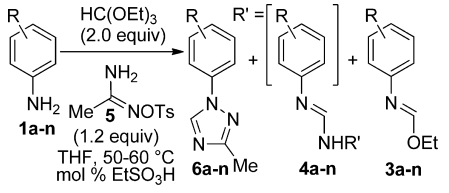
(11) For an example illustrating a N−N bond forming cyclization reaction using a mesylated oxime, see: Wray, B. C.; Stambuli, J. P. *Org. Lett*. **2010**, *12*, 4576–4579.

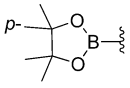
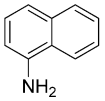
(12) Roberts, R. M.; DeWolfe, R. H. *J. Am. Chem. Soc*. **1954**, *76*, 2411–2414 and references therein.

(13) LCMS analysis of the reaction mixture can easily differentiate impurities related to the chloro aniline (m/z = M and M+2), or those arising from amidoxime decomposition (m/z = M).

In the case of electron-rich aniline substrates (**1g**–**l**) the corresponding amidine intermediates (**4g**–**l**) were, as expected, more resistant to undergo the productive exchange reaction, and a full equivalent of $EtSO_3H$ was necessary to achieve high conversion to the 1,2,4-triazole products (**6g**–**l**). In the *ortho*-substituted substrate series, which include a sterically demanding 2,6-diisopropyl aniline, diminished formation of the amidine was observed and the 1,2,4-triazoles were furnished in good yields (76–87%) after 6 h at 60 °C (Table 1, entries 9–12). For the *para*-substituted series, the reaction conditions were further modified to minimize amidine formation (Table 1, entries 7–8). This was achieved by slow addition of a dilute THF solution of the aniline to a mixture of **5**, $EtSO_3H$, triethylorthoformate, and THF at 50 °C. Again, the triazole products were generated in good yields (70–75%) even with the electron-rich anisidine substrate (entry 7). Lastly, a unique *p*-pinacol boronate ester 1,2,4-triazole product (Table 1, entry 13) was prepared using these reaction conditions in moderate yield, 56%.

Table 1. 1-Aryl 1,2,4-Triazole Synthesis Substrate Scope with Anilines

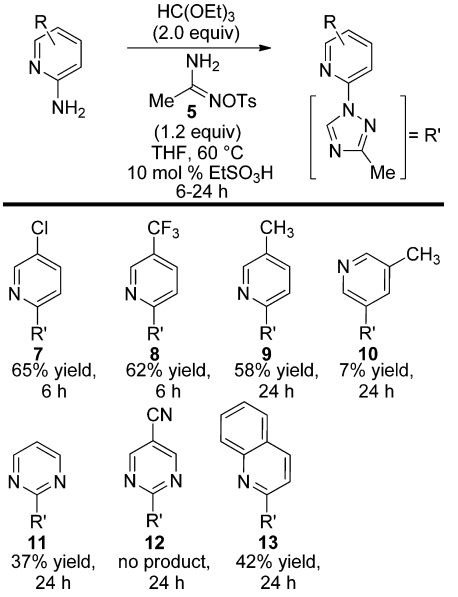


entry	R =	time (h)	product	yield[a]
1[b,e,i]	*p*-Cl	24	6a	93
2[b,f]	*p*-NO_2	4	6b	95
3[b]	*p*-F	6	6c	80
4[b]	*p*-CO_2Et	6	6d	84
5[b]	*p*-CN	6	6e	89
6[b]	*p*-CF_3	6	6f	92
7[c,d,g]	*p*-MeO	24	6g	75
8[c,d]	*p*-Me	24	6h	70
9[c,d,h]	*o*-Me	24	6i	84
10[c]	*o*-*t*-Bu	24	6j	83
11[c]	*o*-isopropyl	24	6k	87
12[c]	2,6-diisopropyl	24	6l	76
13[c,d]	*p*- 	24	6m	56
14[b]		8	6n	92

[a] Solution yields obtained by QNMR analysis. [b] Reaction conditions A: 10 mol % $EtSO_3H$, THF, 60 °C. [c] Reaction conditions B: 100 mol % $EtSO_3H$, 50 or 60 °C. [d] Slow addition of aniline [e] 93% isolated yield. [f] 93% isolated yield of triazole after 4 h, 54% isolated yield after 24 h at 60 °C. [g] 65% isolated yield of triazole. [h] 76% solution yield of triazole product without slow addition of aniline. [i] Without $EtSO_3H$: **6a:4a:3a** ratio is 1:1:2. With $EtSO_3H$: **6a:4a:3a** ratio is > 50:1:not detected.

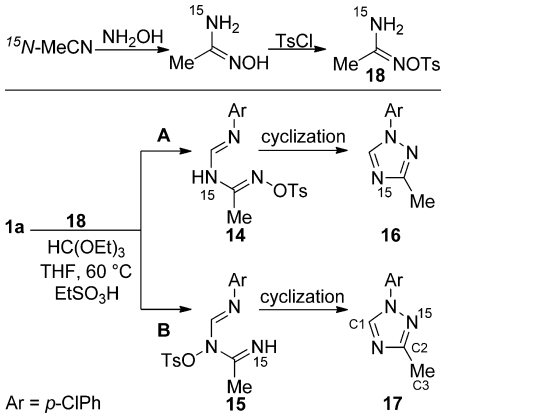
The scope of this transformation was expanded to include heterocycles such as pyridines and pyrimidines (Scheme 2). For substrates containing electron-withdrawing groups, formation of the 1,2,4-triazole products (Scheme 2, structures **7** and **8**) occurred in moderate yield (~60%). After 6 h at 60 °C, the reactions stalled, amidine side products were only present in trace amounts, and unconsumed aminopyridine starting materials (~10% for **7** and ~20% for **8**) were observed. The position of the amino group relative to the ring nitrogen atom also impacted the reaction efficiency. Formation of the 1,2,4-triazole product **10** (Scheme 2) from 3-amino-5-methylpyridine occurred in low yield (7%). The major components of this reaction were identified by LCMS as the ethoxy-imidate intermediate and aminopyridine starting material. Yields of the 1,2,4-triazoles prepared from pyrimidines were also modest (37%, **11**), or in the case of 5-cyanopyrimidine, the triazole product was not observed (**12**). In both experiments, mostly starting material was present after 24 h. Further modifications of the reaction conditions were not explored.

Scheme 2. Multicomponent Synthesis of 1-Aryl 1,2,4-Triazoles from Aminopyridines and Pyrimidines



The mechanism of cyclization that forms the 1,2,4-triazole can occur through two pathways as depicted in Scheme 3. Isolation of condensation intermediates (such as **14** and **15**) was not possible and their molecular mass was not observed by LCMS, indicating that the cyclization is virtually instantaneous. To identify the operative reaction pathway, an experiment with ^{15}N-labeled tosylamidoxime was carried out, and the results are summarized in Scheme 3. In Pathway A, if the less substituted ^{15}N labeled amino group in tosylamidoxime **18** condenses with the imidate and then undergoes cyclization, triazole product **16** would be observed. Conversely in Pathway B, if the more substituted unlabeled-nitrogen atom (N-OTs) is first

Scheme 3. Condensation Pathways and ^{15}N-Labeled Triazole Experiment



to react with the imidate and undergo electrocyclic cyclization and loss of TsOH, triazole product **17** would form. The position of the ^{15}N atom in the 1,2,4-triazole product would indicate if either of these two pathways is preferred.

The labeled tosylamidoxime **18** was prepared in two steps from the reaction of ^{15}N-labeled acetonitrile with hydroxylamine and subsequent tosylation of the *N*-hydroxylacetamide (Scheme 3). After subjecting this material to the triazole reaction conditions, the ^{15}N-position in the triazole product was determined by 1-D and 2-D NMR spectroscopy. The C1 triazole carbon gave a ^{13}C singlet at 142.5 ppm whereas splitting of ^{13}C resonances at C2 (d, 161.1 ppm, $J = 4.6$ Hz) and C3 (d, 13.6 ppm, $J = 7.3$ Hz), due to $^{15}N-C$ coupling, was observed. The results clearly indicate that product **17** was formed in >98% selectivity and that Pathway B is in operation. This 1,2,4-triazole synthesis takes place with complete regiochemical control of the nitrogen atoms in the newly formed triazole ring.[14]

(14) Only the ^{13}C resonances of product **17** were observed in the NMR spectrum. Small ^{13}C signals related to the unlabeled triazole product were also present, which originates from the commercial ^{15}N-MeCN used for this experiment having an isotopic enrichment of 98%.

In conclusion, a multicomponent synthesis of 1-aryl 1,2,4-triazoles was described and its scope evaluated using several substituted aryl amines. For anilines, the key step was determined to be the consumption of an amidine intermediate where the presence of electron-withdrawing groups or *ortho* substitution in the aryl ring led to a more efficient triazole reaction. The addition of an acid promoted reaction throughput by facilitating the breakdown of the amidine intermediate. Electron-donating groups stabilized the amidine intermediate, and controlled addition of the aniline to the reaction mixture was required to achieve efficient triazole synthesis. The behavior of heterocycles, such as pyridines and pyrimidines, was more unpredictable. For this substrate series, the ring substituents influenced whether the limiting step was consumption of amidine, ethoxy-imidate or if the substrate was unreactive. Through the preparation of a ^{15}N-labeled 1,2,4-triazole, the mode in which the tosylamidoxime reacts with the intermediate imidate was elucidated. This multicomponent N–N bond forming reaction is exceptionally regioselective with respect to the position of the nitrogen atoms in the 1,2,4-triazole ring. Overall, an efficient multicomponent process for the preparation of 1-aryl 1,2,4-triazoles has been defined.

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Supporting Information Available. Experimental procedures, ^{1}H, ^{13}C, and 2D NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.