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Rapid Synthesis of 1,3,5-Substituted 1,2,4-Triazoles from Carboxylic Acids, Amidines, and Hydrazines

Georgette M. Castanedo,* Pamela S. Seng, Nicole Blaquiere, Sean Trapp, and Steven T. Staben*

Discovery Chemistry Group, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, United States

castanedo.georgette@gene.com; staben.steven@gene.com

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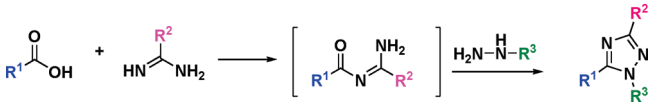


A general method for the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles has been developed from reaction of carboxylic acids, primary amidines, and monosubstituted hydrazines. This highly regioselective and one-pot process provides rapid access to highly diverse triazoles.

1,2,4-Triazoles are an important class of heterocycles that are found in a variety of pharmaceutically active molecules.[1] Although a variety of methods exist for reliable and regioselective synthesis of 3,4,5-substituted 1,2,4-triazoles,[2] direct access to nonsymmetrical 1,3,5-substituted regioisomers remains difficult as limits to substituent identity and regioselectivity exist.[3] Meckler's method[4] involves reaction of primary hydrazides with primary amidines to form *1H*-1,2,4-triazoles. However, subsequent alkylation is not regioselective, giving mixtures of 3,4,5 and 1,3,5 isomers, creating purification and structural charaterization difficulties.[5] 3-Methyl-1,5-substituted triazoles can be obtained by reaction of a primary amide with dimethylacetamide dimethylacetal (DMA-DMA) followed by reaction with a monosubstituted hydrazine.[6] Unfortunately, this rapid and highly regioselective synthesis is constrained by the lack of commercially available orthoaminals.[7,8]

SCHEME 1. Carbonylative and Noncarbonylative Access to Primary Acylamidines en route to 1,2,4-Triazoles

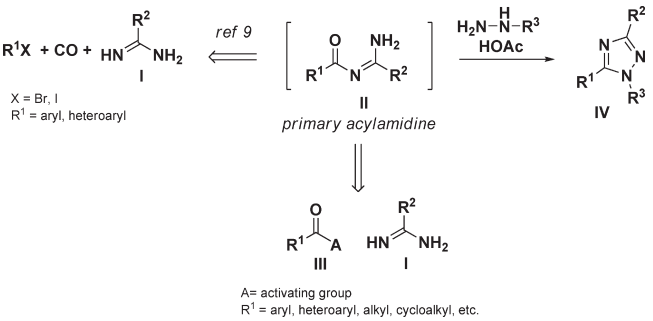
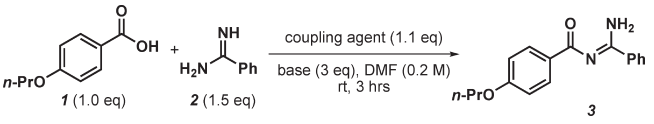


TABLE 1. Coupling Reagent and Base Screen for Acylamidine Formation



entry	coupling agent	base	% conversion[a]	% formation of *3*
1[b]	HATU	DIPEA	**> 99**	**> 99**
2	HATU/HOBt	DIPEA	97	90
3[c]	HATU	DIPEA	> 99	91
4[c]	HATU/HOBt	DIPEA	> 99	86
5	EDC	DIPEA	53	4[d]
6	EDC/HOBt	DIPEA	75	59
7	HBTU	DIPEA	> 99	97
8	TFFH	DIPEA	92	89
9	CD	DIPEA	33	0
10[e]	PYBOP	DIPEA	97	85
11	HATU	NMM	94	71[f]
12	HATU	Cs_2CO_3	94	96
13[b]	HATU	K_2CO_3	91	91
14	HATU	Na_2CO_3	96	87
15	HATU	$NaHCO_3$	97	48[g]

[a]Percent conversions determined by LC-MS integration (254 nm) against an anthracene-9-carbonitrile internal standard. [b]Average of three runs on a similar scale. [c]Preactivation of the carboxylate before amidine addition. [d]No other discernible byproduct observed by LC-MS. [e]Significant pyrrolidine amide formation observed by LC-MS. [f]Seventeen percent formation of 4-propyloxybenzamide. [g]Forty-four percent formation of 4-propyloxybenzamide.

Our group recently reported (Scheme 1) a four-component synthesis of fully substituted 5-aryl-1,2,4 triazoles by carbonylative heterocyclization of aryl halides.[9] This method allows regioselective access to a 5-triazolyl heterobiaryl linkage without generation of organometallic reagents and proceeds through reactive acyl amidine intermediates **II**. An alternative and experimentally convenient strategy to access

(1) For a review, see: Al-Masoudi, A.; Al-Soud, Y. A.; Al-Salihi, N. J.; Al-Masoudi, N. A. *Chem. Heterocycl. Compd.* **2006**, *42*, 1377.
(2) For a recent one-pot method, see: (a) Stocks, M. J.; Cheshire, D. R.; Reynolds, R. *Org. Lett.* **2004**, *6*, 2969. For a comprehensive review, see: (b) Moulin, A.; Bibian, M.; Blayo, A.-L.; Habnouni, S. E.; Martinez, J.; Fehrentz, J.-A. *Chem. Rev.* **2010**, *110*, 1809.
(3) (a) Temple, C., Jr. *The Chemistry of Heterocyclic Compounds*, Vol. 37; Montgomery, J. A., Ed.; Wiley-Interscience: New York, 1981; pp 62−95. (b) Potts, K. T. *Chem. Rev.* **1961**, *61*, 87.
(4) (a) Francis, J. E.; Gorczyca, L. A.; Mazzeuga, G. C.; Meckler, H. *Tetrahedron Lett.* **1987**, *28*, 5133. One-pot primary hydrazide and triazole formation: (b) Funabiki, K.; Noma, N.; Kuzuya, G.; Matsui, M.; Shibata, K. *J. Chem. Res.* (*S*) **1999**, 300. Using imidoyl benzotriazoles: (c) Katritzky, A. R.; Khashab, N. M.; Kirichenko, N.; Singh, A. *J. Org. Chem.* **2006**, *71*, 9051.
(5) Katritzky, A. R.; Qi, M.; Feng, D.; Zhang, G.; Griffith, M. C.; Watson, K. *Org. Lett.* **1999**, *1*, 1189.
(6) Lin, Y.; Lang, S. A.; Lovell, M. F.; Perkinson, N. A. *J. Org. Chem.* **1979**, *44*, 4160.
(7) DMF-DMA and DMA-DMA are the only commercially available orthoaminals allowing only access to 3-H and 3-Me 1,2,4 triazoles. Alternatively, multistep synthesis of an acylimidate is a viable intermediate: Pérez, M. A.; Dorado, C. A.; Soto, J. L. *Synthesis* **1983**, 483.
(8) For a recent synthesis of 5-carboxyl-3H-1,2,4-triazoles, see: Xu, Y.; McLaughlin, M.; Bolton, E. N.; Reamer, R. A. *J. Org. Chem.* **2010**, *75*, 8666.
(9) Staben, S. T.; Blaquiere, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 325.

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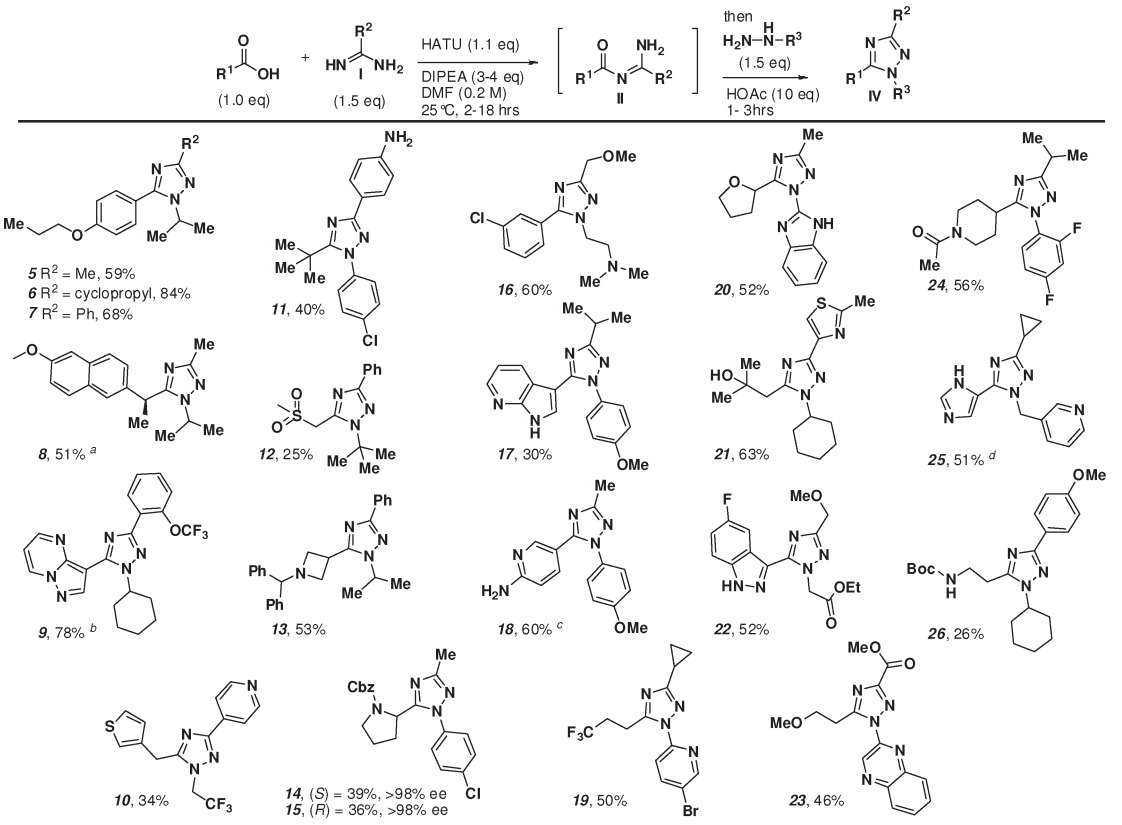
TABLE 2. Substrate scope



[a]Yields reported in this table are isolated yields after silica gel chromatography or reverse phase HPLC.1,3,5- substituted regioisomers were confirmed by ^{15}N HMBC and/or ^{1}H nOe measurements for compounds **8**, **16**, **17** and **18**; the remainder of products were assigned by analogy. Hydrazines and amidines generally added as HCl salts. Product was not analyzed for potential racemization. [b]Yield of ~90% pure **9**, an analytical sample for characterization was obtained on repurification. [c]Due to poor solubility of carboxylic acid, preactivation with HATU was necessary. [d]Potassium carbonate was used instead of DIPEA.

acyl amidines **II** would be reaction of primary amidines (**I**) with activated carboxylic acids (**III**) that would obviate the need for using carbon monoxide and also allow synthesis of triazoles with nonaryl 5-substitution. Herein we report reaction optimization and substrate scope studies for this one-pot heterocycle synthesis.

Using 4-propyloxybenzoic acid and benzamidine as test substrates,[10] we began with optimization for formation of the acylamidine intermediate through a screen of standard peptide coupling reagents[11] using diisopropylethylamine (DIPEA) as a base and DMF as the reaction solvent. The coupling reactions were monitored over 3 h by LC-MS for the percent consumption of acid **1** and conversion to acylamidine intermediate **3** as determined by comparison to an internal standard. The results (Table 1) indicate that a variety of coupling agents worked well in the formation of acylamidine **3**.[12] HATU (2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) was selected for further evaluation based on availability and ease of removal of coupling byproducts. While screening alternative bases, we noticed a trend that bases with lower pK_a values such as *N*-methylmorpholine and sodium bicarbonate lead to formation of the primary amide byproduct, presumably due to hydrolysis of protonated acylamidine intermediate.[13] Thus, HATU/DIPEA (entry 1) was selected as a standard condition for substrate scope studies.

As reported in our previous communication, after addition of isopropylhydrazine (1.5 equiv) and acetic acid (10 equiv) to the crude solution of acyl amidine **3**, cyclization was complete after 3 h at 80 °C to give triazole **7** (Table 2). On the basis of these optimized reaction conditions, we commenced exploration of our substrate scope. Results are summarized in Table 2. In addition to incorporation of aryl and heteroaryl substitutents at the 5-position (**5**−**7**, **9**, **16**−**18**, **22**, **25**), substituted alkyl (**8**, **10**−**12**, **19**, **21**, **26**), and heterocycloalkyl (**13**−**15**, **20**, **24**) carboxylic acids are viable substrates for this one-pot process. We were pleased to see that the presence of less nucleophilic nitrogen and oxygen atoms on the reactants are not a problem in triazole formation (**11**, **17**, **18**, **21**, **22**, **25**, **26**).

Notable is the synthesis of **18**, demonstrating selective reaction of a nonaromatic amidine over an aminopyridine substructure. Importantly, clean synthesis of antipodes **14** and **15** demonstrate that the reaction conditions are mild enough to avoid racemization of enantiomerically pure amino

(10) To the best of our knowledge, a systematic study for the acylation of amidines has not been reported, see: (a) Baker, P. L.; Gendler, P. L.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2455. (b) Gupta, S.; Agarwal, P. K.; Kundu, B. *Tetrahedron Lett.* **2010**, *51*, 1887.

(11) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827.

(12) In contrast, reaction of 4-propyloxybenzoyl chloride with benzamidine gave a complex mixture of products.

(13) MoKa estimated pK_a of the conjugate acid of **3** = 7.13.

acids. As noted in our previous report,[9] acylamidines created from alkyl, aryl and heteroaryl amidines react cleanly with widely varied hydrazines. Interestingly, ester functionality is also tolerated as amidine and hydrazine substituents, as in the synthesis of **22** and **23**. Yields were generally low when bulky carboxylic acids and/or hydrazines were used (i.e., PivOH for **11** and ^{t}BuNHNH$_2$ for **12**).[14]

In summary, we have developed an efficient and experimentally convenient synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from carboxylic acids. This synthesis allows greater diversity at the 5-position compared to our previously reported palladium-catalyzed carbonylative route. Yields range from 25−84%, or 63−94% per bond for this one pot reaction. The wide-substrate scope and high functional group compatibility allows generation of considerable diversity.[15] The speed, experimental ease and regioselectivity of this process are improvements on existing methods for access to this important substructure.

Experimental Section

Representative procedure for the synthesis of **7**: DMF (10 mL) and DIPEA (1.45 mL, 8.3 mmol) were added to 4-propyloxybenzoic acid **1** (0.500 g, 2.8 mmol, 1.0 equiv), benzamidine **2** (500 mg, 4.2 mmol, 1.5 equiv) and HATU (1.16 g, 3.1 mmol, 1.1 equiv) in a flask. The reaction was stirred at room temperature and monitored by LC-MS for consumption of acid **1** and formation of acylamidine intermediate **3**. After 3 h, isopropylhydrazine hydrochloride (0.460 g, 4.2 mmol, 1.5 equiv) then acetic acid (1.58 mL, 27.7 mmol, 10 equiv) were added and the reaction mixture was heated to 80 °C and monitored for consumption of acylamidine intermediate. After 3 h, the reaction was cooled to room temperature, diluted with 200 mL EtOAc and extracted once with a saturated $NaHCO_3$ (200 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash column chromatography (0−100% EtOAc in heptanes) to afford pure compound **7** as a colorless crystalline solid (68% yield).

^{1}H NMR (500 MHz, DMSO) δ 8.05 (d, J = 7.0 Hz, 2H), 7.62 (d, J = 7.7 Hz, 2H), 7.51−7.40 (m, 3H), 7.13 (d, J = 8.8 Hz, 2H), 4.68 (dt, J = 13.1, 6.5 Hz, 1H), 4.02 (t, J = 6.5 Hz, 2H), 1.82 − 1.73 (m, 2H), 1.48 (d, J = 6.6 Hz, 6H), 1.01 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 159.9, 159.8, 154.2, 131.2, 130.3, 129.0, 128.7, 125.7, 120.0, 114.8, 69.1, 50.3, 22.6, 21.9, 10.4.

HREIMS calcd for $C_{20}H_{24}N_3O$: 322.1919, found 322.2159.

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Supporting Information Available: Experimental procedures, tabulated spectroscopic data, images of ^{1}H and ^{13}C NMR spectra and HREIMS data for all final products. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) Common byproduct observed by LC-MS include primary amide formation, reaction of HATU with amidine to form guanidinyl by-product, acid/amidine dimer and reaction of hydrazine with carboxylic acid (indicating incomplete formation of acylamidine intermediate). Isolated yields seem highly dependent on the solubility of the triazole products.

(15) Notably, all reagents utilized in this publication are commercially available.