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Practical Synthesis of Functionalized 1,5-Disubstituted 1,2,4-Triazole Derivatives

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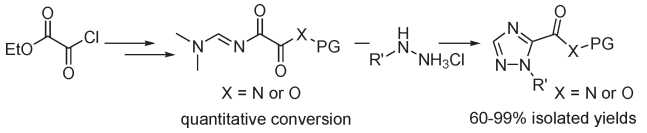

A general approach for the synthesis of 1,5-disubstituted-1,2,4-triazole compounds is described. A series of new oxamide-derived amidine reagents can be accessed in excellent yield with minimal purification necessary. Typically, these amidine reagents are stable crystalline solids and in certain cases were found to exist in a cyclic form as determined by NMR spectroscopy. Under optimized conditions, the direct reaction of these prepared reagents with various hydrazine hydrochloride salts efficiently generates the target triazoles. Both aromatic and aliphatic hydrazines react readily with the amidine reagents under very mild reaction conditions, delivering desired 1,5-disubstituted-1,2,4-triazole derivatives in good yields.

Triazoles and their derivatives constitute heterocyclic subunits that are commonly incorporated into compounds of pharmaceutical interest.[1] In particular, 1,2,4-triazoles are heterocyclic motifs often found in antifungals,[2] anticonvulsants,[3] and oncology compounds.[4] Although the synthesis of 1,2,4-triazoles is well documented in literature,[5–9] effective regiochemical control of the substitution pattern can be difficult to achieve, especially when attempting to elaborate preformed 1,2,4-triazole rings.[10] In support of drug development programs at Merck, we were specifically interested in the preparation of 1,5-disubstituted-1,2,4-triazoles with carboxamide[11] or carboxylate[12] functionalities in the 5-position. In this Note, we report a practical synthetic method to efficiently access 1,2,4-triazoles with protected 5-carboxamide or 5-carboxylate functionality. The proposed strategy is shown in Figure 1, where

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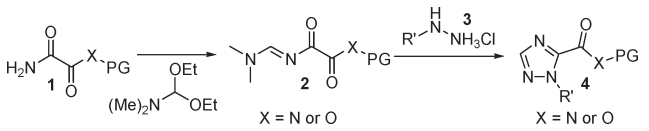
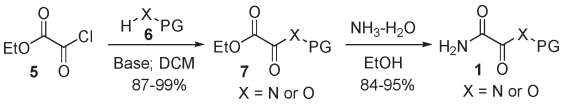


FIGURE 1. Proposed strategy for synthesis of 1,5-disubstituted-1,2,4-triazoles bearing carboxamides or carboxylic esters on the 5-position.

SCHEME 1. Synthesis of Oxamide Derivative 1[a]



[a]Conditions: (1) from **5** to **7**: **6** (1.0 equiv); Et_3N (1.1 equiv); 0 °C−rt; (2) from **7** to **1**: aq NH_3 (14.8 N; 1.2 −10 equiv); 5 volumes of EtOH; 0 °C−rt.

selectively protected oxamide/oxalate derivatives **1** are converted to amidines **2** and then further reacted with aryl- or alkylhydrazine hydrochloride salts **3** to directly generate the target 1,5-disubstituted-1,2,4-triazoles (**4**).

To begin our investigations into the synthesis of 1,5-disubstituted-1,2,4-triazoles we required access to suitably activated oxamide/oxalate reagents **2**. Despite their relative simplicity, inspection of the literature revealed no instances where compounds of this type have been isolated and properly characterized. Nevertheless, we reasoned that standard manipulations on readily available oxalic acid derivatives could lead to the desired reagents and we initiated our studies along these lines. Indeed, synthesis of required precursors **1** was ultimately accomplished in straightforward fashion via reaction of an amine or an alcohol **6** with commercially available ethyl chloroxoacetate **5**. As shown in Scheme 1, using 1.1 equiv of Et_3N as base, amines or alcohols **6** reacted rapidly with **5** in CH_2Cl_2 to give intermediates **7** in almost quantitative yield.[13] Subsequent treatment with aqueous ammonia (14.8 N) smoothly converted intermediates **7** into selectively protected oxamides/oxalates **1** (Scheme 1), although careful control of reaction conditions was necessary for certain substrates.

For substrates bearing an additional amide function (X = N, Scheme 1) treatment with excess aqueous ammonia for several hours at room temperature gave a clean reaction profile. In contrast, for the ester substrate **7** (X = O, Scheme 1), the ammonia stoichiometry was reduced to 1.2 equiv and the reaction temperature was controlled at 0 °C to suppress overreaction and formation of undesired oxamide. In this particular case, since oxamide has low solubility in EtOH while the desired ester **7** (X = O) has high solubility in this solvent, the oxamide byproduct can be easily removed via filtration. Compounds **1** bearing the primary amide functionality are expectedly highly crystalline and can be isolated directly by filtration or filtration after solvent-switch to IPAc and then heptanes. In this fashion, various monoprotected oxamide derivatives **1** were obtained as isolable solids in good yields and high purity without recourse to silica gel chromatography.

For the synthesis of triazoles via reaction with aryl- or alkylhydrazines, the prepared intermediates **1** required activation and installation of an additional carbon atom. To this end we elected to convert the primary amide into a dimethyl amidine group.[14] Initially we used *N*,*N*-dimethylformamide diethylacetal as both the reagent and solvent for this transformation and observed complete conversion within 1 h at 50 °C. It was subsequently established that the stoichiometry of the reagent could be reduced to 1 equiv. Under optimized conditions, heating at 50 °C with EtOAc as solvent gave complete conversion of the starting materials within 5−30 min.

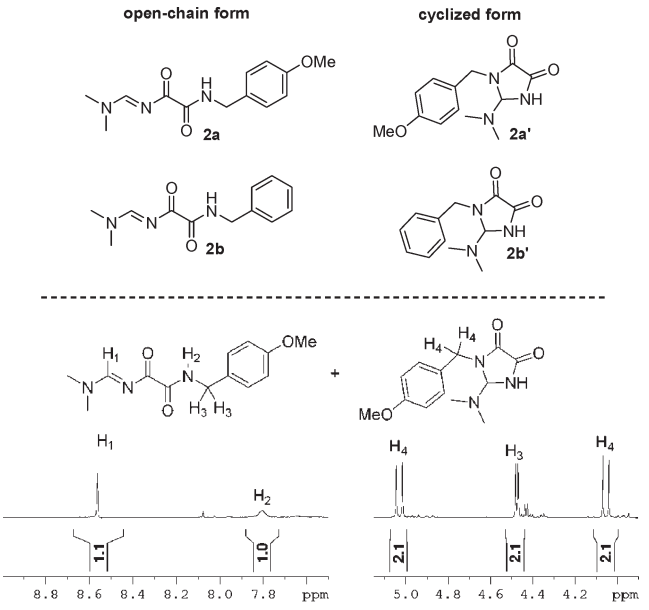


FIGURE 2. Amidines in "open-chain" form (**2a** and **2b**) and cyclized form (**2a′** and **2b′**); partial NMR data for the mixture of **2a** and **2a′** (about 1:2) in $CDCl_3$.

For certain *NH*-amide substrates we observed the amidine products can exist as two different tautomeric structures (in solution), which could be identified by NMR spectroscopic analysis (Figure 2). Taking the conversion of **1a** into **2a** as an example, the initially formed "open-chain" amidine displays the anticipated imine-type methine signal as a singlet at 8.6 ppm and the benzylic methylene as a doublet at 4.5 ppm (from coupling to the adjacent NH). Upon longer reaction time at 50 °C (or even standing at room temperature) the imine methine signal disappeared and the benzylic methylene doublet was replaced by a pair of doublets at 4.1 and 5.1 ppm, indicating conversion to the cyclic 2-dimethylamino-imidazolidine-4,5-dione tautomer. For substrates **2a** and **2b** the cyclic 2-dimethylamino-imidazolidine-4,5-dione (**2a′** and **2b′**) was isolated; however, substrate **2d** containing the *tert*-butylamide was isolated as the open chain form, presumably reflecting the increased steric bulk of this particular compound. Irrespective of the solution structures adopted, these intermediates were usually crystalline solids and performance in the subsequent chemistry was equivalent since interconversion between the structures was facile under the reaction conditions. As shown in Table 1, isolated yields were generally high (>90%) and the amidine compounds were bench stable for periods of months.

With a series of new amidine reagents **2** in hand, we were able to examine conditions for triazole formation via reaction with aryl- and alkylhydrazines. Initial attempts to employ nonpolar solvents such as toluene or MTBE were thwarted by the low solubility of reactants. Indeed, even the more polar DCM or EtOAc did not provide sufficient solubility for these substrates.

(13) In the case of amine substrates, 2.1 equiv of **6** can be used to avoid the use of any additional base.

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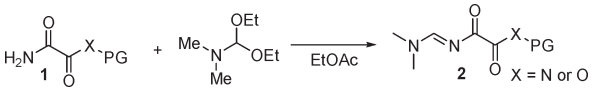
TABLE 1. Synthesis of Amidine Reagents (2)[a,b]



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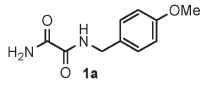
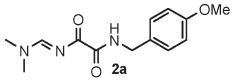
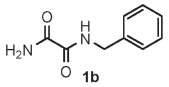
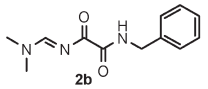
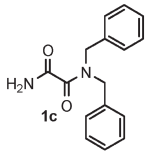
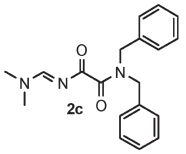
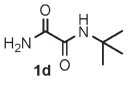
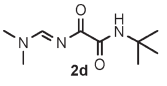
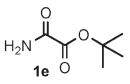
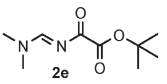
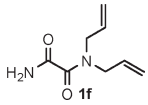
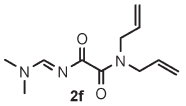
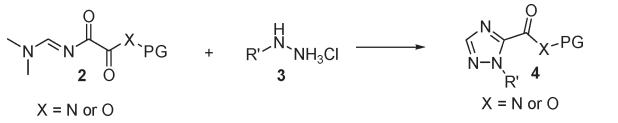
1			96%
2			95%
3			95%
4			99%
5			94%
6			90%

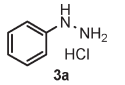
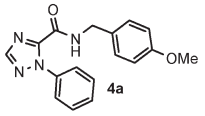
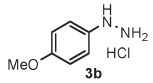
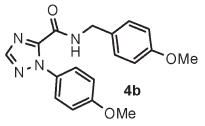
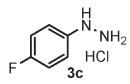
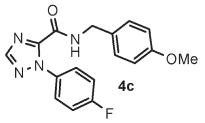
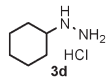
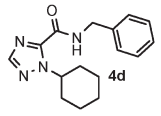
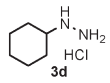
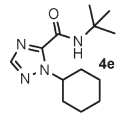
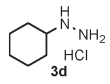
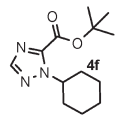
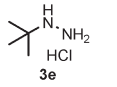
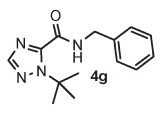
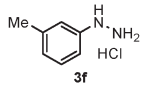
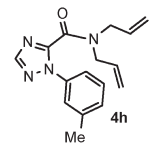
[a]The reaction conditions were carried out at 50 °C with 1.0 equiv of *N*,*N*-dimethylformamide diethyl acetal. [b]Yields of pure, isolated products (characterized by ^{1}H, ^{13}C NMR, and HR-MS).

Consequently, various more polar systems were investigated as media for this reaction, with various common alcohols receiving particular focus. Additionally, it appeared that the desired cyclization process would likely be acid-catalyzed. This prompted extension of the screening experiments to include AcOH as a solvent, which also afforded good solubility for the reactants. When amidine **2** and hydrazine **3** were combined in AcOH, full conversion was observed within 18 h at room temperature. Although this result was encouraging, workup and isolation were slightly complicated by the need to neutralize the excess AcOH. The reaction was also successful in various alcohols (MeOH, EtOH, *i*-PrOH), although slightly elevated temperatures (50 °C) were required to achieve adequate rate of reaction. As a compromise, addition of 2 equiv of AcOH to reactions run in *i*-PrOH was found to provide the optimal balance of reaction rate/purity profile while retaining a relatively uncomplicated workup.[15] In the majority of cases studied, the desired cyclization occurred even in the absence of added AcOH, presumably catalyzed by the slightly acidic pH introduced via the aryl/alkylhydrazine hydrochloride salt. However, with the exception of certain potentially acid sensitive substrates (vide infra), the use of AcOH as an additive serves to increase reaction rate under more mild thermal conditions and is therefore recommended. Having developed an effective procedure for triazole formation,

(15) Reactions in solvents like DMF, DMSO, or NMP gave full conversions within similar reaction time. However, minor loss of desired product in aqueous workup was observed. In addition, a slighly lower assay yield (HPLC) was sometimes obtained in these solvents than in the reaction conducted in IPA.

TABLE 2. Synthesis of 5-Acylated 1,2,4-Triazoles (4) from Hydrazine 3 and Amidine 2[a−e]

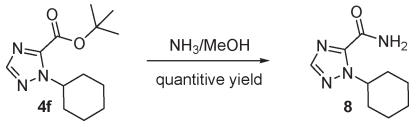


entry	amidine	R'NHNH$_3$Cl	product	yield
1	**2a**			99%[a]
2	**2a**			85%[a,e]
3	**2a**			99%[a]
4	**2b**			90%[b,e]
5	**2d**			74%[c,e]
6	**2e**			72%[c,e]
7	**2b**			60%[b,e]
8	**2f**			90%[b,e]

[a]The reactions were carried out at room temperature with 1.0 equiv of **3** in AcOH. [b]The reactions were carried out at 50 °C with 1.0 equiv of **3** and 2.0 equiv of AcOH in MeOH. [c]The reactions were carried out at 50 °C with 1.0 equiv of **3** in IPA. [d]Reactions were monitored by LC. Yields of pure, isolated products (characterized by ^{1}H, ^{13}C NMR and HR-MS). [e]Additional purification via a silica gel plug was needed.

the conditions were then implemented in the preparation of a series of 1,5-disubstituted-1,2,4-triazoles **4**. Both the amidine and hydrazine components were varied and the results are shown in Table 2. In general, the reactions were relatively clean with no major byproduct and the triazole products were obtained in good yields. Reactions of amidine **2a** with different arylhydrazines (**3a**−**c**) all gave full conversions and good yields of triazoles bearing a PMB-protected carboxamide in the 5-position (entries 1−3, Table 2). Reactions of amidines **2b**,**d**,**e** with cyclohexylhydrazine afforded high yields of triazole products, demonstrating that alkylhydrazine hydrochloride salts can also be employed in this chemistry (entries 4−6, Table 2). In the case of amidine **2e**, the acid-sensitive *tert*-butyl ester function was observed to undergo partial deprotection when subjected to the standard

SCHEME 2. Synthesis of Free 5-Carboxamide 8 from Triazole Compound 4f[a]



[a]Conditions: 10 volumes of 7 N NH_3 in MeOH; 70 °C; 16 h.

AcOH-promoted conditions. To avoid this issue, reaction in *i*-PrOH alone with no AcOH additive was found to give a cleaner reaction profile. Last, the effect of steric encumbrance on the hydrazine component was investigated through reaction of *tert*-butylhydrazine hydrochloride (entry 7, Table 2). The reaction with *tert*-butyl hydrazine (**3e**) was the slowest (18 h at 50 °C) and gave the lowest isolated yield of the examples studied (entry 7: 60% for **4g**, Table 2).

The 5-carboxylate-1-substituted-1,2,4-triazoles obtained from amidine **2e** can be easily converted to corresponding free 5-carboxamide (via reaction with ammonia) triazole derivatives (Scheme 2). Treatment of triazole **4f** with excess of ammonia in MeOH at 70 °C smoothly afforded the desired 5-carboxamide **8** as crystalline solid in quantitively yield.

In summary, we have described an effective method for the regiocontrolled construction of 1,5-disubstituted-1,2,4-triazoles bearing carboxylic esters or carboxamides in the 5-position. A straightforward preparation and characterization of a series of new oxamide/oxalate-derived amidine reagents was a key enabling element in this research. These amidines were generally isolated in high yield and purity as bench stable crystalline solids without need for chromatographic purification. For certain *NH*-amide substrates NMR data indicated a cyclic structure is favored, although reactivity in the subsequent triazole synthesis is equivalent to the open-chain form. The formation of 1,2,4-triazoles via reaction of these reagents with both aryl- and alkylhydrazine hydrochlorides was found to be efficient and completely regioselective to deliver the intended 1,5-ring substitution pattern, with the carboxamide or carboxylic ester at the 5-position. Overall, the developed method is practical and allows facile access to 1,2,4-triazoles bearing protected carboxamides or carboxylic esters that have utility as heterocyclic building blocks for the synthesis of pharmaceutically active compounds.

Experimental Section

Typical Experimental Procedure for Amidine Synthesis from 1a To Afford Amidine 2a′ (entry 1, Table 1): To a slurry of **1a** (1.15 g, 5.52 mmol) in 5 volumes of EtOAc (6 mL) was added 1.0 equiv of *N*,*N*-dimethylformamide diethylacetal (1.00 mL; 5.52 mmol). The mixture was heated at 50 °C for 4 h and then heptanes (20 mL) was added. After the mixture was cooled to rt, the white slurry was filtered and rinsed with heptanes to give product **2a′** as a white crystalline solid (1.40 g, 96% yield). **2a′**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.05 (s, 1H), 7.25 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.23 (s, 1H), 5.03 (d, J = 14.3 Hz, 1H), 4.07 (d, J = 14.3 Hz, 1H), 3.82 (s, 3H), 2.30 (s, 6H); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.97 (br s, 1H), 7.20 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.33 (s, 1H), 4.64 (d, J = 14.7 Hz, 1H), 4.13 (d, J = 14.7 Hz, 1H), 3.73 (s, 3H), 2.13 (s, 6H); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 159.7, 158.7, 158.4, 129.5, 127.9, 113.9, 80.6, 55.0, 42.7, 36.2; exact mass calcd for $[C_{13}H_{17}N_3O_3 + H]^+$ requires m/z 264.1348, found 264.1347 (ESI+).

Typical Experimental Procedure for Triazole Formation from Amidine 2a′ and Hydrazine 3a To Deliver 1,5-Disubstituted 1,2,4-Triazole 4a (entry 1, Table 2): To the mixture of amidine **2a** (0.21 g, 0.80 mmol) and hydrazine **3a** (0.11 g, 0.75 mmol) was added 5 volumes of AcOH (0.6 mL). The slurry was stirred for 2.5 h and LC indicated full conversion of starting materials. The reaction mixture was cooled in an ice bath and EtOAc was added followed by sat. $NaHCO_3$ solution. The organic phase was washed with sat. $NaHCO_3$ solution and water and then concentrated to give **4a** as a light yellow solid (0.23 g; 99%). **4a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (s, 1H), 7.88 (t, J = 6.0 Hz, 1H), 7.50 (m, 5H), 7.23 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 1H), 4.48 (d, J = 6.0 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 159.3, 156.1, 150.3, 146.8, 138.1, 129.6, 129.5, 129.4, 128.8, 125.9, 114.3, 55.4, 43.0; exact mass calcd for $[C_{17}H_{16}N_4O_2 + H]^+$ requires m/z 309.1352, found 309.1363 (ESI+).

Acknowledgment. High resolution mass spectroscopy analysis support from Thomas J. Novak is gratefully acknowledged.

Supporting Information Available: Experimental procedures and analytical data for amidine reagents, intermediates (**1a**−**f**, **2a**−**f**, **7a**−**f**), and triazole compounds (**4a**−**h**, **8**) with copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.