A Facile One-Pot Synthesis of 3-Imidazolyl 1,2,4-Triazoles and 1,2,4-Oxadiazolones

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Abstract: 5-(5-Aminoimidazol-4-yl)-1,2,4-triazol-3-ones were obtained under mild experimental conditions from 5-amino-4-(*N*-ethoxycarbonyl) cyanoformimidoyl imidazoles and hydrazine in a rapid one-pot reaction. When hydroxylamine hydrochloride was used, in the presence of base, the corresponding 1,2,4-oxadiazol-5-ones were isolated. An equally fast reaction occurred when 5-amino-4-(*N*-acetyl/benzoyl) cyanoformimidoyl imidazoles were combined with hydrazine to give 5-(5-aminoimidazol-4-yl)-1,2,4-triazoles.

Key words: heterocycles, cyclization, ring closure, imidazole, 1,2,4-triazole, 1,2,4-oxadiazole

Azole heterocycles are present in a wide range of biologically active molecules. The growing number of patents describing 1,2,4-triazole derivatives with biological properties reveals the importance of this heterocycle.[1] The biological activities displayed by 1,2,4-triazoles and 1,2,4-triazolones include antibacterial,[2] antifungal,[3] antitumor,[4] anti-inflammatory,[5] and adenosine receptor antagonist effects.[6] 1,2,4-Oxadiazoles have also been well documented throughout the literature due to their pharmacological importance. Indeed, the 1,2,4-oxadiazole nucleus can be found in potent agonist or antagonist receptor ligands and in enzyme inhibitors.[7] Additionally, both triazole and oxadiazole moieties have often been used as amide and ester bioisosteres in order to improve the bioavailability of the parent bioactive molecules. The use of these surrogates is particularly important for peptide chemistry and for the development of peptidomimetics.[6,8] The synthesis of 1,2,4-triazoles was recently reviewed.[1] The most used method to synthesize 1,2,4-triazoles and 1,2,4-oxadiazoles involves a cylodehydration of *N*-acylamidrazone or *O*-acylamidoxime, respectively, at high temperatures.[1] These intermediates have been preferably obtained from activated amide or nitrile derivatives such as imidate and thioamide precursors. In general, these procedures require high temperature and/or long reaction times and usually result in low yields of the product.[1,9a–c] Some reactions were performed at room temperature in the presence of mercury(II) acetate,[1] and more recently, silver benzoate.[9d] More specific methods were also reported.[10]

To the best of our knowledge there are only three reports on the synthesis of 5-(5-aminoimidazolyl)-1,2,4-triazoles. An indirect synthesis involving ring opening of triazolo[3,4-*i*]purines or triazolo[5,1-*i*]purines, which were obtained upon treatment of 6-hydrazinopurine and 6-(1-benzylhydrazino)purine with dimethoxymethyl acetate and, more recently, from the reaction of 5-amino-4-cyanoimidazoles with triethylorthoformate followed by condensation with hydrazines and acylhydrazines at high temperature.[11]

In our research group, 5-amino-4-cyanoformimidoyl imidazoles **1** have been used as versatile precursors for nitrogen heterocycles linked or fused with the imidazole ring.[12]

In previous work, imidazoles **1** were reacted with ethyl chloroformate. The acylation occurs on the imine nitrogen leading to the formation of compounds **2**[12g,13] (Table 1).

These compounds were combined with methyl and benzylamine under mild conditions and a fast nucleophilic attack occurred at the imine carbon atom with substitution of the cyano group.[13] As an extension of this work, we now present the results of the reaction of intermediates **2** with hydrazine and hydroxylamine.

When hydrazine monohydrate was added to a suspension of **2** in DMF or ethanol, the bright yellow color of the starting material disappeared instantly leading to a white solid which was identified as the imidazolyl 1,2,4-triazolone **3**. Most of the products **3** were isolated in excellent yield after 5–40 minutes of reaction.[14] This one-pot formation of the 1,2,4-triazolone ring can only be rationalized on the basis of a two-steps reaction sequence: the elimination of HCN followed by the elimination of ethanol (Scheme 1).

These results prompted us to investigate the reaction of intermediates **2** with hydroxylamine. For this purpose, hydroxylamine hydrochloride was neutralized in situ with an aqueous 1 M KOH solution, and the resulting mixture was added to a suspension of imidazole **2** in dichloromethane. A slow reaction occurred at room temperature leading to the 1,2,4-oxadiazolone **4a** after 29 hours, which was isolated as a light yellow solid in an excellent yield. Attempts to reproduce this procedure with differently substituted imidazoles **2** failed. Alternatively, triethylamine was added to a suspension of hydroxylamine hydrochloride in acetonitrile giving the desired products after two days at room temperature in moderate yields.[15] The assignment of

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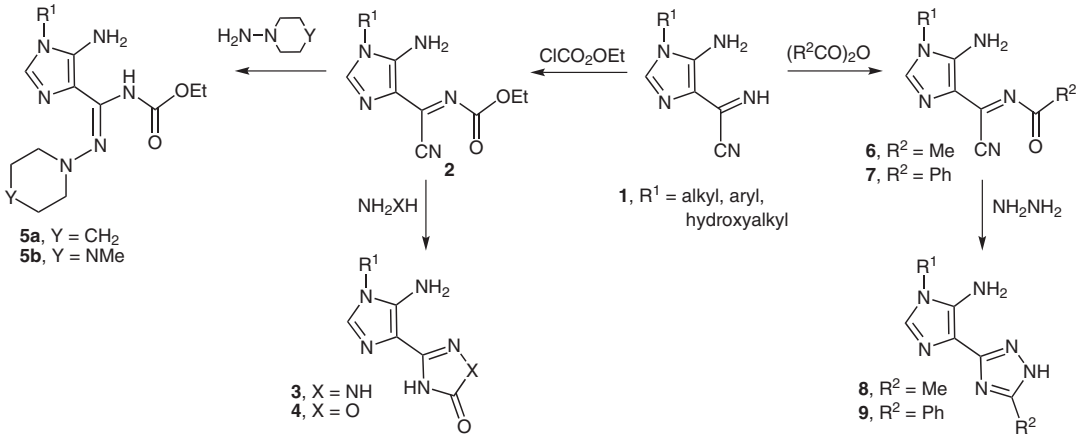
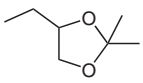
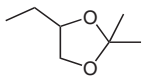
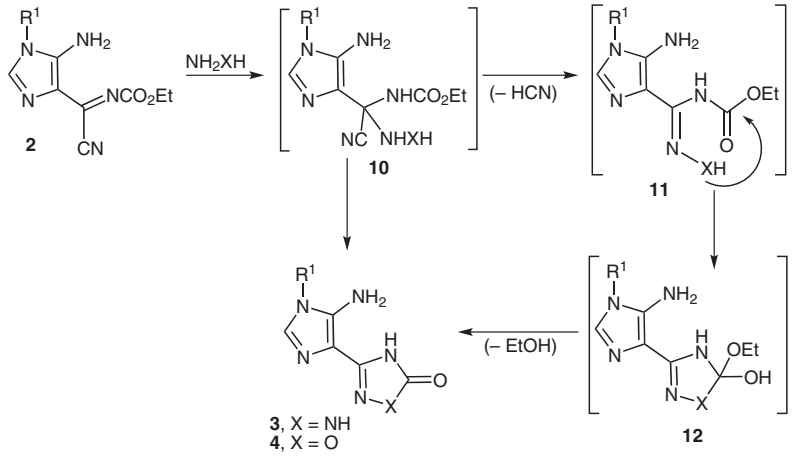
Table 1 Synthesis of Compounds **3**–**5**, **8**, and **9**



Compound	R^1	X/Y/R^2	NHXH (equiv)	Reaction conditions	Yield (%)
3a	4-$MeOC_6H_4$	NH	2.0	DMF, 5 min, r.t.	99
3b	4-CNC_6H_4	NH	2.0	DMF, 30 min, r.t.	83
3c	4-FC_6H	NH	2.0	EtOH, 40 min, 0 °C	98
3d	Me	NH	2.0	EtOH, 30 min, r.t.	37
3e	CH_2CH_2OH	NH	2.0	EtOH, 30min, r.t.	92
3f		NH	2.0	EtOH, 5 min, 0 °C	78
4a	4-$MeOC_6H_4$	O	3.0	KOH (aq) 1 M (3 equiv), CH_2Cl_2, 29 h, r.t.	99
4b	4-FC_6H_4	O	2.0	Et_3N (3 equiv), MeCN, 2 d, r.t.	50
4c	CH_2CH_2OH	O	1.2	Et_3N (3 equiv), MeCN, 2 d, r.t.	58
4d		O	2.0	Et_3N (3 equiv), MeCN, 2 d, r.t.	17
5a	4-$MeOC_6H_4$	CH_2	1.2	CH_2Cl_2, 15 min, r.t.	66
5b	4-$MeOC_6H_4$	NMe	1.3	EtOH, 15 min, r.t.	65
8a	4-$MeOC_6H_4$	Me	2.0	EtOH, 5 min, 0 °C	61
8b	Ph	Me	1.2	EtOH, 5 min, 0 °C	85
8c	Me	Me	1.2	EtOH, 5 min, 0 °C	82
8d	CH_2CH_2OH	Me	1.2	EtOH, 5 min, 0 °C	82
8e	$CH_2CHOHCH_2OH$	Me	2.0	EtOH, 5 min, 0 °C	56
9a	4-$MeOC_6H_4$	Ph	2.0	EtOH, 5 min, 0 °C	66
9b	4-FC_6H_4	Ph	1.2	EtOH, 5 min, 0 °C	76
9c	Ph	Ph	1.2	EtOH, 5 min, 0 °C	63
9d	Me	Ph	1.2	EtOH, 5 min, 0 °C	79

structure **4** was well supported by their IR spectra showing a carbonyl band at ca. 1780 cm^{-1}. This result was consistent with the presence of a urethane unit in a five-membered ring. For the 1,2,4-triazolones **3** the corresponding carbonyl stretching vibration was observed at 1715 cm^{-1} as was expected for a cyclic urea.

Imidazoles **2** were also combined with N,N-disubstituted hydrazines, in order to establish the reaction mechanism. When aminopiperidine and 1-amino-4-methylpiperazine



Scheme 1 Proposed mechanism for the one-pot formation of 1,2,4-triazolones **3** and 1,2,4-oxadiazolones **4**

were reacted with imidazole **2**, only products **5** were formed, after 45–50 minutes at room temperature.[16]

These results agree with previous studies on the reactivity of the imidazoles **2** with primary amines,[13] supporting the postulated mechanism outlined in Scheme 1. The reaction is initiated by a nucleophilic attack of the amino group in the hydrazine/hydroxylamine to the imine carbon atom. A tetrahedral intermediate **10** must be formed and evolves to the amidrazone **11** by elimination of HCN. The free hydrazine amino group is still a strong nucleophile and an easy and prompt intramolecular cyclization occurs, upon attack to the carbonyl carbon atom. The triazolone ring is formed by elimination of ethanol from the cyclic intermediate **12**.

The amidoxime unit, with a less reactive hydroxy group at an equivalent position, requires basic medium to be converted on the target 1,2,4-oxadiazolone ring through a similar pathway.

The same synthetic sequence must be followed for the preparation of 1,2,4-triazoles **8** and **9** starting from the corresponding acetylated and benzoylated imidazole precursors **6** and **7**. Imidazoles **6** were prepared by a previously reported method involving acetylation of imidazoles **1** with acetic anhydride under mild experimental conditions.[12g] Benzoylation of **1** was carried out under similar experimental conditions. Acetonitrile was used as solvent and the products **7** were obtained after two to four hours at room temperature or 0 °C in good to excellent yields.[17] Treatment of precursors **6** and **7** with a slight excess of hydrazine monohydrate (2.0–1.2 equiv) resulted in an equally facile and fast one-pot, two-steps reaction, providing the desired 1,2,4-tiazoles **8** and **9** after five minutes at 0 °C. The products were isolated as off-white solids in good to very good yields.[18] The higher electron-withdrawing effect of the acetyl and benzoyl groups when compared to the oxycarbonyl counterpart may be responsible for the faster and milder reaction conditions. The intramolecular cyclization will also be facilitated due to the higher electrophilicity of the amide group.

In conclusion, a general and efficient one-pot reaction was developed to prepare imidazolyl 1,2,4-triazolones **3** and 1,2,4-triazoles **8** and **9**. These compounds were formed at room temperature or 0 °C from the easily accessible acylated imidazole (**2**, **6**, and **7**) and hydrazine. An equally simple method was developed for the synthesis of the corresponding 3-imidazolyl 1,2,4-oxadiazolones starting from the same precursor **2** upon reaction with hydroxylamine. The acylated imidazoles **2**, **6**, and **7** were obtained in very good yields from the versatile imidazoles **1** and anhydrides or ethyl chloroformate. These compounds are not easy to prepare by other methods.

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(14) **General Procedure for the Synthesis of 1,2,4-Triazolones 3**
Hydrazine monohydrate (2.0 equiv) was added to a suspension of imidazole **2** (0.52–1.95 mmol) in DMF (for **3a** and **3b**, 2.0 mL) or EtOH (for **3c**–**f**, 1.0–5.0 mL). The mixture was stirred at r.t. for 5–30 min (for **3a**,**b** and **3d**–**e**), and at 0 °C for 40 min (for **3c** and **3f**). The resulting suspension was filtered and washed with EtOH and Et_2O to give compounds **3** (78–99%). The structure of the products was confirmed by elemental analysis, ^1H NMR and ^{13}C NMR spectroscopy.
5-[5-Amino-1-(4-methoxyphenyl)-1*H*-imidazol-4-yl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3a)
Mp >316 °C (dec.). ^1H NMR (300 MHz, DMSO-d_6): δ = 11.20 (s, 1 H), 7.42 (d, *J* = 8.7 Hz, 2 H), 7.39 (s, 1 H), 7.09 (d, *J* = 8.7 Hz, 2 H), 5.22 (s, 2 H), 3.81 (s, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.98, 155.64, 144.33, 137.91, 130.96, 127.36, 126.31, 114.85, 108.10, 55.52. Anal. Calcd for $C_{12}H_{12}N_6O_2$: C, 52.94; H, 4.44; N, 30.87. Found: C, 52.75; H, 4.60; N, 30.88. IR (mull): 3428, 3331, 3102, 1715 (CO), 1634 cm^{-1}.

(15) **General Procedure for the Synthesis of 1,2,4-Oxadiazolones 4**
A yellow suspension of **2** (0.29–1.85 mmol) in CH_2Cl_2 (for **4a**, 15.0 mL) or in MeCN (for **4b**–**d**, 3.0–5.0 mL) was added to a solution of hydroxylamine hydrochloride (for **4a**, 3.0 equiv; for **4b**–**d**, 2.0 equiv; for **4c**, 1.2 equiv) in aq 1 M KOH (for **4a**, 3.0 equiv) or to a solution of Et_3N (for **4b**–**d**, 3.0 equiv) in MeCN. The mixture was stirred at r.t., and after 29–72 h the starting material was totally consumed. The light yellow solid was filtered and washed with EtOH, MeCN, and Et_2O to give compounds **4** in 17–99% yield. The structure of the products was confirmed by elemental analysis, ^1H NMR and ^{13}C NMR spectroscopy.
3-[5-Amino-1-(4-methoxyphenyl)-1*H*-imidazol-4-yl]-1,2,4-oxadiazol-5 (4*H*)-one (4a)
Mp 261–264 °C. ^1H NMR (300 MHz, DMSO-d_6): δ = 13.00–10.00 (br s, 1 H), 7.49 (s, 1 H), 7.42 (d, *J* = 8.7 Hz, 2 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 5.46 (s, 2 H), 3.81 (s, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.54, 159.30, 155.30, 140.73, 132.66, 126.78, 126.75, 114.96, 103.15, 55.56. Anal. Calcd for $C_{12}H_{11}N_5O_3$: C, 52.75; H, 4.06; N, 25.63. Found: C, 52.85; H, 4.13; N, 25.57. IR (mull): 3414, 3317, 3128, 1787 (CO), 1633 cm^{-1}.

(16) **General Procedure for the Synthesis of 5**
A suspension of aminopiperidine or 1-amino-4-metilpiperazine (1.2–1.3 equiv) and imidazole **2** (0.98–1.20 mmol) in CH_2Cl_2 (0.5 mL) or EtOH (2.0 mL) was stirred at r.t.. After 45–50 min the yellow suspension evolved to a white solid precipitate that was filtered and washed with EtOH and Et_2O. The structure of the products obtained was confirmed by elemental analysis, ^1H NMR and ^{13}C NMR spectroscopy.
Ethyl [5-Amino-1-(4-methoxyphenyl)-1*H*-imidazol-4-yl](piperidin-1-ylimino)methylcarbamate (5a)
Mp 165–166 °C. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.06 (s, 1 H), 7.38 (d, *J* = 8.7 Hz, 2 H) 7.38 (s, 1 H), 7.10 (d, *J* = 8.7 Hz, 2 H), 5.69 (br s, 2 H), 3.81 (s, 3 H), 3.98 (q, *J* = 7.2 Hz, 2 H), 2.50–3.50 (br s, 4 H), 1.50 (br s, 6 H), 1.20 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.35, 159.04, 149.28, 141.60, 130.05, 59.95, 55.55, 55.03, 26.69, 25.27, 14.28. Anal. Calcd for $C_{19}H_{26}N_6O_3$: C, 59.05; H, 6.78; N, 21.75. Found: C, 59.08; H, 6.68; N, 21.69. IR (mull): 3359, 3287, 3162, 3112, 3066, 1698 (CO), 1618, 1571 cm^{-1}.

(17) **General Procedure for the Synthesis of 6 and 7**
Acetic or benzoic anhydride (2.0 equiv) was added to a suspension of **1** (1.0–4.0 mmol) in MeCN (1.0–5.0 mL) at 0 °C, and the mixture was stirred at r.t. until the starting material was totally consumed (2–4 h). The bright yellow/orange solid was filtered and washed with MeCN and Et_2O to give compounds **6** and **7** in 13–99% yields. The structure of the products was confirmed by elemental analysis, ^1H NMR and ^{13}C NMR spectroscopy.
5-Amino-1-(4′-fluorophenyl)-4-[(*N*-benzoyl)cyanoformimidoyl]-1*H*-imidazole (7, R^1 = 4-FC_6H_4, R^2 = Ph)
Mp 167–168 °C. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.34 (br s, 2 H), 8.08 (d, *J* = 7.2 Hz, 2 H), 7.77 (s, 1 H), 7.64 (t, *J* = 7.2 Hz, 1 H), 7.55 (dd, *J* = 9.0, 4.8 Hz, 2 H), 7.54 (t, *J* = 7.2 Hz, 2 H), 7.44 (t, *J* = 9.0 Hz, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 174.93, 160.06 (d, *J* = 243 Hz), 151.23, 138.60, 135.38, 134.74, 132.81, 131.57 (d, *J* = 3 Hz), 129.41, 128.51, 125.08 (d, *J* = 8 Hz), 122.51, 116.31 (d, *J* = 22 Hz), 112.14. Anal. Calcd for $C_{12}H_{11}N_5O_3 \cdot 0.1H_2O$: C, 64.51; H, 3.67; N, 20.90. Found: C, 64.40; H, 3.81; N, 20.86. IR (mull): 3342, 2232 (CN), 1629, 1603, 1529 cm^{-1}.

(18) **General Procedure for the Synthesis of 8 and 9**
Hydrazine monohydrate (2.0 or 1.2 equiv) was added to a

suspension of imidazole **6** (0.78–1.36 mmol) or **7** in EtOH (1.5–2.0 mL) at 0 °C leading to a homogeneous solution. After 5 min a white solid precipitated out of solution and was filtered and washed with EtOH and Et_2O. The structure of the products was confirmed by elemental analysis, ^1H NMR and ^{13}C NMR spectroscopy.

Characterization of 1-Methyl-4-(5-methyl-4*H*-1,2,4-triazol-3-yl)-1*H*-imidazol-5-amine (8c)

Mp >233 °C (dec.). ^1H NMR (300 MHz, DMSO-d_6): δ = 13.15 (br s, 1 H), 7.20 (s, 1 H), 5.51 (br s, 2 H), 3.44 (s, 3 H), 2.23 (s, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.43, 152.03, 139.21, 141.98, 139.87, 131.61, 108.53, 29.76, 13.76. Anal. Calcd for $C_8H_9N_5O{\cdot}0.1H_2O$: C, 46.71; H, 5.71; N, 46.69. Found: C, 46.65; H, 5.86; N, 46.25. IR (mull): 3354, 3276, 3170, 3104, 2725, 1616, 1571 cm^{-1}.

1-(4-Fluorophenyl)-4-(5-phenyl-4*H*-1,2,4-triazol-3-yl)-1*H*-imidazol-5-amine (9b)

Mp >250 °C (dec.). ^1H NMR (300 MHz, DMSO-d_6): δ = 13.94 (br s, 1 H), 8.06 (dt, *J* = 6.6, 1.5 Hz, 2 H), 7.64 (dd, *J* = 9.0, 4.8 Hz, 2 H), 7.55 (s, 1 H) 7.43 (t, *J* = 9.0 Hz, 2 H), 7.48–7.40 (m, 3 H), 5.75 (br s, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.48 (d, *J* = 244 Hz), 160.16, 152.27, 138.98, 131.58, 131.15, 128.65, 128.58, 127.11 (d, *J* = 9 Hz), 125.76, 116.58 (d, *J* = 23 Hz), 108.89. Anal. Calcd for $C_{17}H_{13}N_6F{\cdot}0.1H_2O$: C, 63.39; H, 4.13; N, 26.08. Found: C, 63.26; H, 4.18; N, 26.01. IR (mull): 3407, 3276, 3318, 3127, 1634, 1603, 1518 cm^{-1}.