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An efficient synthesis of 5-aminoimidazol-2-ones via cyclization reactions of 2-aminoacetonitriles and isocyanates

Benjamin W. Parcher, Derek M. Erion and Qun Dang*

Department of Medicinal Chemistry, Metabasis Therapeutics Inc., 9390 Towne Centre Drive, San Diego, CA 92121, USA

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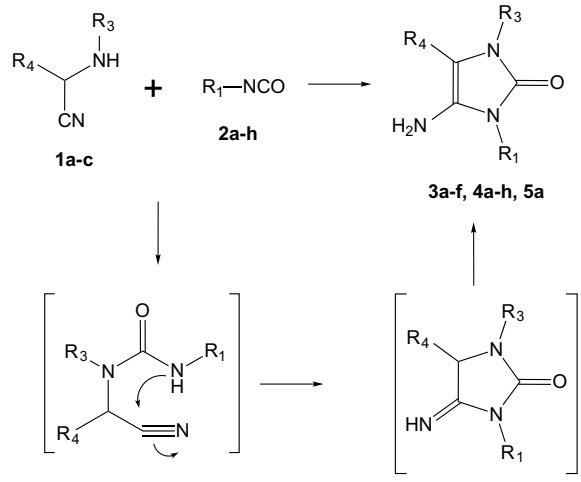
Abstract—The scope of a cyclization reaction between amino-acetonitriles and isocyanates was investigated. The study revealed that this reaction tolerates various functional groups leading to highly functionalized 5-amino-imidazole-2-ones, which are useful intermediates for purine synthesis.

The imidazole moiety frequently appears in biologically active compounds, which are either natural products or generated by medicinal chemistry efforts. Consequently, novel methodologies enabling the efficient construction of imidazole ring systems are always of interest. Although various intramolecular cyclization reactions of amides onto a cyano group have been reported leading to imidazoles,[1] few systematic studies of such reactions have been reported. Therefore, we envisioned that an expansion of this type of reaction as shown in Scheme 1 would allow easy access to 5-amino-imidazole-2-ones,[2] which may be used to prepare heterocyclic libraries. Large numbers of amino-acetonitriles are easily prepared via Strecker reactions, while numerous isocyanates are either commercially available or can be easily prepared. Moreover, these types of imidazole derivatives have been shown to be useful intermediates for the synthesis of purines via either traditional cyclization methods[3] or the recently developed inverse electron-demand Diels–Alder reactions of 1,3,5-triazines.[4] Herein, we report the scope of such cyclization reactions as shown in Scheme 1 and its application to the preparation of potential heteroaromatic dienophiles for 1,3,5-triazine IDA reactions.



Scheme 1. Cyclization reactions of aminoacetonitriles and isocyanates.

2-Phenylglycinonitrile (**1a**, R_4 = phenyl, R_3 = H) was initially chosen to investigate the cyclization reactions depicted in Scheme 1. Treatment of free-based **1a**[5] with phenylisocyanate (**2a**) in refluxing dioxane provided the desired 5-amino-1,4-diphenyl-1,3-dihydro-imidazol-2-one **3a** in good yield (entry 1, Table 1).[6]

The generality of this cyclization reaction was further demonstrated with other isocyanates (**2b–f**). It is evident from Table 1 that the mild reaction conditions tolerate numerous functionalities leading to various N^1-substituted 5-amino-4-phenyl-imidazole-2-ones (**3a–f**). Therefore, imidazoles **3a–f** with R_1 being aryl, alkyl, haloalkyl, arylalkyl, and diethylphosphono groups were prepared in good to high yields in a single step (entries 1–5, Table 1). It is noteworthy that when R_1 is a strong electron-withdrawing group such as an ethoxycarbonyl

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* Corresponding author. Tel.: +1-858-622-5517; fax: +1-858-622-5573; e-mail: dang@mbasis.com

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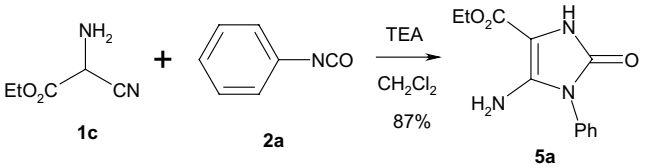
Table 1. Cyclization reactions of aminoacetonitriles (**1a**–**b**, $R_4 = Ph$) and isocyanates (**2a**–**h**) as shown in Scheme 1

Entry	**1a**,**b**	R_3	**2a**–**h**	R_1	Conditions	Products	Yields (%)[a]
1	**1a**	H	**2a**	Ph	Acetonitrile, 80 °C, 2 h	**3a**	68
2	**1a**	H	**2b**	$PhCH_2CH_2$	Dioxane, 100 °C, 2 h	**3b**	59
3	**1a**	H	**2c**	$CH_3CH_2CH_2$	Acetonitrile, 80 °C, 2 h	**3c**	85
4	**1a**	H	**2d**	$ClCH_2CH_2$	Dioxane, 100 °C, 2 h	**3d**	82
5	**1a**	H	**2e**	$(EtO)_2P(O)$	Dioxane, 100 °C, 2 h	**3e**	59
6	**1a**	H	**2f**	EtO_2C	Dioxane, 100 °C, 12 h	**3f**	24
7	**1a**	H	**2f**	EtO_2C	Et_3N (0.1 equiv), $ClCH_2CH_2Cl$, 25 °C, 24 h	**3f**	48
8	**1a**	H	**2f**	EtO_2C	Et_3N (0.1 equiv), $ClCH_2CH_2Cl$, 80 °C, 1 h	**3f**	51[b]
9	**1b**	Bn	**2a**	Ph	Et_3N (0.1 equiv), $ClCH_2CH_2Cl$, 80 °C, 1 h	**4a**	97[b]
10	**1b**	Bn	**2c**	$CH_3CH_2CH_2$	Et_3N (0.1 equiv), $ClCH_2CH_2Cl$, 80 °C, 1 h	**4c**	75[b]
11	**1b**	Bn	**2d**	$ClCH_2CH_2$	Et_3N (0.1 equiv), $ClCH_2CH_2Cl$, 80 °C, 1 h	**4d**	67[b]
12	**1b**	Bn	**2g**	Bz	Et_3N (0.1 equiv), $ClCH_2CH_2Cl$, 80 °C, 1 h	**4g**	71[b]
13	**1b**	Bn	**2h**	4-MeO–Ph	Et_3N (0.1 equiv), $ClCH_2CH_2Cl$, 80 °C, 1 h	**4h**	88[b]

[a] All reactions were conducted under nitrogen using method A unless noted otherwise, yields are based on products isolated via chromatography and all products were characterized by ^1H NMR, MS, and CHN analysis for identity and purity.
[b] Method B was used.

group, then a catalytic amount of a base such as triethylamine has to be used to promote this reaction (entries 6–8, Table 1). This observation may be attributed to the decreased nucleophilicity of the urea intermediate, which may require a base to catalyze the cyclization reaction. The scope of this reaction was further expanded with *N*-benzyl-2-phenylglycinonitrile **1b**, which was readily prepared from benzaldehyde and benzylamine via the Strecker reaction in excellent yield. When **1b** was reacted with **2a** in the presence of a catalytic amount of triethylamine in refluxing dichloroethane for 1 h a highly functionalized imidazole derivative, 5-amino-1-phenyl-3-benzyl-4-phenyl-imidazole-2-one **4a**, was obtained in excellent yield. The scope of this cyclization reaction with **1b** was explored with other selected isocyanates (**2c**–**d**, **2g**–**h**) leading to **4c**–**d** and **4g**–**h** in good to excellent yields (entries 9–13, Table 1). In general, higher yields were obtained with **1b** compared to **1a**, which may be attributed to the increased nucleophilicity of the benzyl substituted amino group in **1b**.

The utility of this reaction is further demonstrated through its application to the synthesis of 5-amino-4-imidazolecarboxylates, which have been shown to efficiently participate in IDA reactions with 1,3,5-triazines for the one-step synthesis of purine analogues.[4]



(1)

Treatment of 2-cyanoglycine ethyl ester (**1c**)[7] with phenylisocyanate (**2a**) in the presence of a catalytic amount of triethylamine provided the desired 5-amino-4-ethoxycarbonyl-1-phenylimidazol-2-one (**5a**) in excellent yield.[8] Imidazole **5a** can be hydrolyzed to give its corresponding carboxylic acid, which should function as aromatic dienophiles in our previously reported tandem decarboxylation-IDA reactions.[4]

In conclusion, the scope of cyclization reactions between aminoacetonitriles and isocyanates was studied, which revealed that the mild reaction conditions tolerate numerous functional groups. Highly functionalized imidazole derivatives are prepared in good to excellent yields in a single step from readily accessible starting materials. This method was also shown to be useful for the synthesis of 5-amino-4-imidazolecarboxylates, which serve as productive dienophiles in 1,3,5-triazine IDA reactions and therefore can be used for preparations of purine analogues.

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5. 2-Phenylglycinonitrile (**1a**) was obtained by free-basing its corresponding hydrogen chloride salt: A solution of **1a** hydrogen chloride salt in methylenechloride was treated with aqueous potassium carbonate (3 equiv) at room temperature for 2 h. Extraction with methylenechloride (3 times) and evaporation gave **1a** as a brown solid.
6. General procedures: Method A. A solution of **1a** (0.77 mmol) and **2a** (0.77 mmol) in anhydrous dioxane (4 mL) was heated to reflux for 2 h. The cooled reaction mixture was evaporated to dryness and the resulting solid was purified by flash chromatography to give 5-amino-1,4-diphenyl-1,3-dihydroimidazol-2-one (**3a**) (132 mg, 68%) as a white solid. Mp 167–169 °C (EtOAc–hexane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.73 (1H, s), 7.58–7.42 (8H, m), 7.30–7.25 (2H, m), 7.00–6.95 (1H, m), 6.05 (1H, d, $J = 7.8$ Hz). Anal. calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.63; H, 5.60; N, 16.83. Method B. A solution of **1a** (1.5 mmol) and **2e** (1.5 mmol) in anhydrous 1,2-dichloroethane (8 mL) was treated with triethylamine (0.15 mmol) at room temperature for 30 min and then heated to reflux for 1 h. The cooled reaction mixture was evaporated to dryness and the resulting solid was purified by flash chromatography (SiO_2, 2×15 cm, 15% EtOAc–CH_2Cl_2) to give 5-amino-1-ethoxycarbonyl-4-phenyl-1,3-dihydro-imidazol-2-one (**3e**) (188 mg, 51%) as a white solid. Mp 141–143 °C (EtOAc–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51 (1H, d, $J = 7.7$ Hz), 7.65 (1H, s), 7.53–7.40 (5H, m), 6.05 (1H, d, $J = 7.7$ Hz), 4.21 (2H, q, $J = 7.2$ Hz), 1.29 (3H, t, $J = 7.2$ Hz). Anal. calcd for $C_{17}H_{13}N_4OCl$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.16; H, 5.68; N, 16.98.
7. 2-Cyanoglycine ethyl ester (**1c**) was prepared according to Heitsch, H.; Wagner, A.; Yadav-Bhatnagar, N.; Griffoul-Marteau, C. *Synthesis* **1996**, *11*, 1325–1330.
8. Preparation of imidazole **5a**: A solution of **1c** (1.56 mmol) and phenylisocyanate (**2a**, 0.78 mmol) in anhydrous 1,2-dichloroethane (4 mL) was treated with triethylamine (0.08 mmol) at 80 °C (reflux) under nitrogen for 1 h. The cooled reaction mixture was evaporated to dryness and the residue was purified by flash chromatography (SiO_2, 2×15 cm, 5% MeOH–CH_2Cl_2) to give **5a** as a white solid (168 mg, 87%). Mp 214–216 °C (EtOH–EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.02 (1H, s), 7.58–7.36 (5H, m), 5.89 (2H, br s), 4.19 (2H, q, $J = 7.2$ Hz), 1.26 (3H, t, $J = 7.2$ Hz). Anal. calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.22; H, 5.60; N, 17.17.