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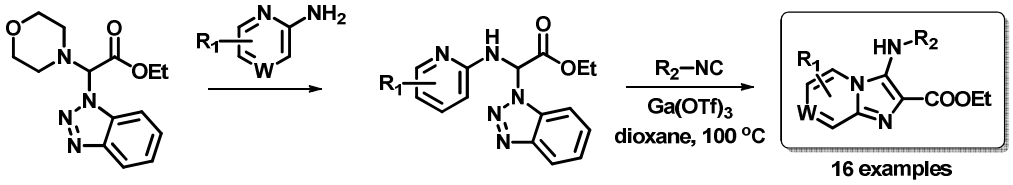

Synthesis of functionalized 2-carbonyl-imidazo[1,2-a]pyridines derived from ethyl α-benzotriazolyl-α-morpholinoacetate

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$Ga(OTf)_3$ Promoted Synthesis of Functionalized 2-Carbonyl-imidazo[1,2-a]pyridines Derived from Ethyl α-Benzotriazolyl-α-morpholinoacetate

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An efficient route to the synthesis of 3-amino-2-ethoxycarbonyl imidazo[1,2-*a*]pyridine derivatives starting from ethyl α-benzotriazolyl-α-morpholinoacetate has been developed. By mentions of reaction with primary heterocyclic amidines and isocyanides catalyzed by $Ga(OTf)_3$, target compounds were obtained in moderate to good yields. This in turn will set the stage for a wide application of this useful reaction for the synthesis of 3-amino-2-carbonylimidazo[1,2-*a*]pyridines based on imidazo[1,2-*a*]pyridine privileged structure.

As a structural component of key bioactive molecules, a fused imidazo[1,2-*a*]heterocycles moiety was widely incorporated in the design of multiple biologically active agents.[1] Consequently, imidazopyridines, imdazopyrazines, and imidazopyrimidines in particular have been the focus of pharmaceutical investigations across a broad range of therapeutic areas.[2] The efficient synthesis of 3-amino-imidazo[1,2-*a*]azines *via* a reaction between a 2-aminoazine, an aldehyde and an isocyanide known as the Groebke-Blackburn-Bienaymé multicomponent reaction (GBB Reaction),[3] has triggered numerous efforts to develop libraries based on this drug-like core.[1a] Analysis of the recent patent literature reveals that 3-amino-imidazo[1,2-*a*]azines manifested themselves as ubiquitin ligase inhibitors (**A**),[4] histone deacetylase inhibitors (**B**),[5] skeletal muscle myosin modulators (**C**),[6] potential antidiabetic SGLT1 inhibitors (**D**),[7] angiogenesis inhibitors (**E**),[8] modulators of sodium channels (**F**),[9] as well as ligands for G-protein coupled receptors (e.g., PAR2, **G**) [10] (Figure 1).

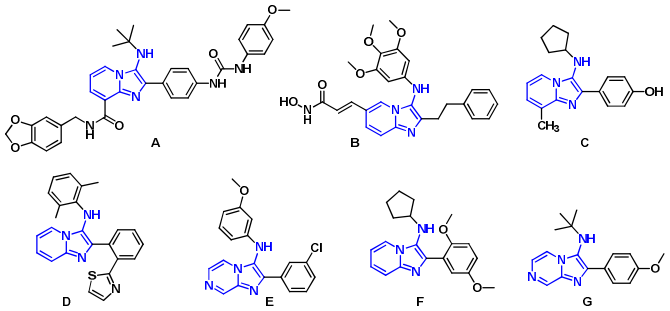
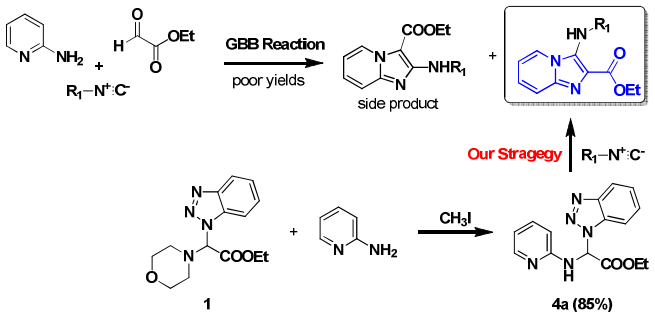


Figure 1. Therapeutic agents based on 3-amino-imidazo[1,2-*a*]azines

As a part of our continuing efforts on discovery of novel heterocycles as antitumor agents based on imidazo[1,2-*a*]pyridine ring system,[11] which may be regarded as a privileged structure.[12] Following this strategy, our next challenge was the introduction of an additional 2-carboxy ester and 3-amino functionalities in the imidazo[1,2-*a*]pyridine framework as shown in Scheme **1**. 3-Amino-2-ethoxycarbonyl imidazo[1,2-*a*]pyridines and related compounds have also been described as potential antibacterial agents,[2e] and constitute valuable intermediates for the synthesis of purine derivatives.[13] Groebke reaction was first proposed to prepare this type of compound, in this case, glyoxylic acid or ethyl glyoxalate could be used as the carbonyl component, reacted with 2-aminopyridine and isocyanides to afford the target products. However, several papers have revealed that by utilizing glyoxylic acid as a source of aldehyde in Ugi-type MCR to only afford the decarboxylic 2-unsubstituted 3-amino imidazoazine.[12a,14] Nenajdenko et al. also reported by using ethyl glyoxalate as the carbonyl component of the Groebke reaction, reacted with 2-aminopyridines and isocyanides to afford the target product in around 30% yield, and with ethyl 2-aminoimidazo[1,2-*a*]pyridine-3-carboxylate isomer as the by-product (Scheme 1). [15]

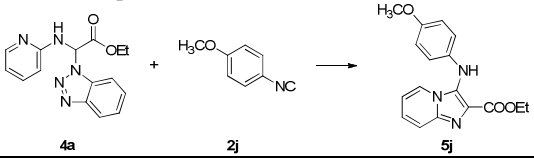


Scheme 1. Proposed synthetic approach to 3-amino-2-ethoxycarbonyl imidazo[1,2-*a*]pyridines

Ethyl α-Benzotriazolyl-α-morpholinoacetate (**1**) was reported as a valuable synthon capable of reacting with different nucleophiles to form 3-amino imidazo heterocycle.[16] Some preliminary studies of Bourguignon[16], Risch[17] and Katritzky[18,19] have been very helpful for our purposes. Mannich condensations of benzotriazole and ethyl glyoxalate with morpholine give adduct ethyl α-benzotriazolyl-α-morpholinoacetate, which upon nucleophilic displacement of primary heterocyclic amidines (such as 2-aminopyridine) resulted in the reactive intermediate (**4a**). We supposed this intermediate (**4a**) could react with isocyanides, might lead directly to 3-amino-2-ethoxycarbonyl imidazo[1,2-*a*]pyridines (Scheme 1).

The investigation was initiated with ethyl α-benzotriazolyl-α-morpholinoacetate (**1**) reacted with 2-aminopyridine in presence of MeI to afford aminopyridine substituted α-benzotriazolyl acetate **4a** in good yield (85%). Subsequently, **4a** was used to react with 4-methoxyphenyl isocyanide (**2j**) as the model substrate to optimize reaction conditions (Scheme 2). The experiments are conducted to find the best conditions in terms of different catalysts, temperature and various solvents, and the results are summarized in Table 1. No reaction occurred in the absence of catalysts (Table 1, entry 1); the same is true for TsOH or acetic acid as the catalysts (Table 1, entries 2-3). There is a moderate enhancement in the yield when triflic acid is used (Table 1, entry 4). Further catalyst screening indicates that $Ga(OTf)_3$ displayed the highest catalytic activity toward the formation of **5a** with an 78% yield (Table 1, entries 5-10). Furthermore, changing solvents from THF to dioxane under 100 °C condition increases the yield up to 89% (Table 1, entries 11-14).

Table 1. Optimization of the reaction conditions.[a]

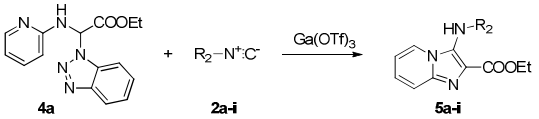


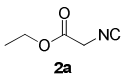
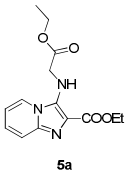
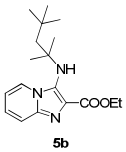
entry	Catalyst	Solvent	T (°C)	Time (h)	Yield (%)[b]
1	-	THF	65	10	0
2	TsOH	THF	65	5	Trace
3	HOAc	THF	65	7	Trace
4	TfOH (3 mol%)	THF	65	3	35
5	$Cu(OTf)_2$	THF	65	3	28
6	$Sc(OTf)_3$	THF	65	3	60
7	$Yb(OTf)_3$	THF	65	3	64
8	$Ga(OTf)_3$	THF	65	3	78
9	$InCl_3$	THF	65	5	40
10	$ZnCl_2$	THF	65	5	35
11	$Ga(OTf)_3$	EtOH	80	3	72
12	$Ga(OTf)_3$	toluene	100	4	60
13	$Ga(OTf)_3$	CH_3CN	80	4	65
14	$Ga(OTf)_3$	dioxane	100	2	89

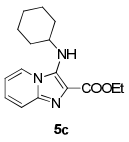
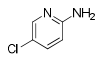
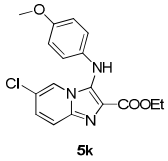
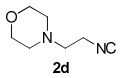
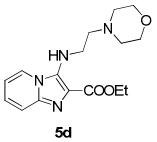
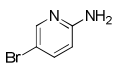
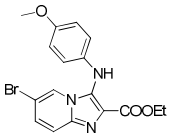
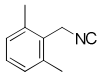
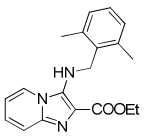
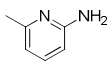
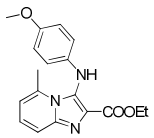
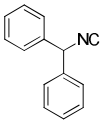
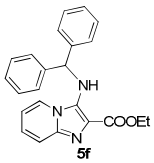
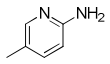
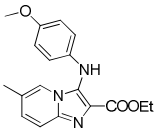
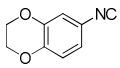
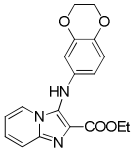
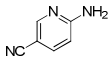
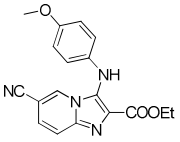
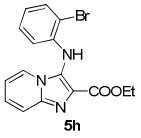
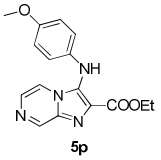
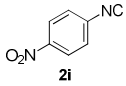
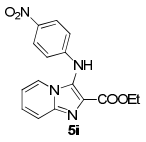
[a] *Reaction conditions*: **4a** (1 mmol), **2j** (1.2 mmol), catalyst (1 mol%), solvent (3.0 mL), 65 to 100 °C.
[b] Isolated yields.

With the optimal conditions established, we then examined a series of isocyanides and substrate **4a** to establish the scope and limitations of this process. The simplicity of this procedure is perfectly amenable to automation for combinatorial synthesis. Likewise, all the syntheses were performed on a parallel synthesizer (Radleys Discovery Technology, Carousel 12 Place Reaction Station) to give corresponding products. Aliphatic (even sterically encumbered, Table 2, entries 1-6), aromatic (electron-rich or electron-poor, Table 2, entries 7-9) gave the corresponding products in moderate to good yields (ranging from 65-87%) (Table 2). Consequently, we also examined the reactions of various 2-aminopyridines (**3b-f**) and 2-aminopyrazine (**3g**) with ethyl α-benzotriazolyl-α-morpholinoacetate, which proceeded smoothly and efficiently to produce the corresponding intermediates (**4b-g**) in excellent yields (step i, Table 3). Followed by reaction with 4-methoxyphenyl isocyanide (**2a**) to give the correspondingly products (**5k-p**) in good yields (step ii, Table 3).

Table 2. Synthesis of **5a-i** under optimized conditions[a]

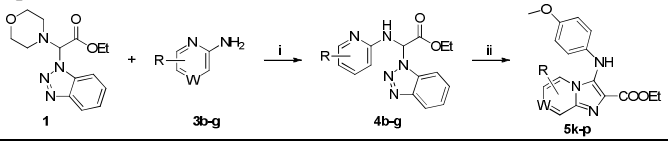


entry	Isocyanides	Products	Yields (%)[b]
1	 2a	 5a	82
2	 2b	 5b	85

3	 2c	 5c	78	1	 3b	 5k	79	80
4	 2d	 5d	87	2	 3c	 5l	82	81
5	 2e	 5e	87	3	 3d	 5m	85	83
6	 2f	 5f	65	4	 3e	 5n	87	82
7	 2g	 5g	85	5	 3f	 5o	75	77
8	 2h	 5h	76	6	 3g	 5p	80	68
9	 2i	 5i	79					

[a] *Reaction condition:* **4a** (1.0 mmol), **2a-i** (1.2 mmol), $Ga(OTf)_3$ (1 mol%), dioxane (3.0 mL), 100 °C, 2 h.
[b] Isolated yields.

Table 3. Synthesis of substrates **4b-g** and products **5k-p** under optimized conditions[a]

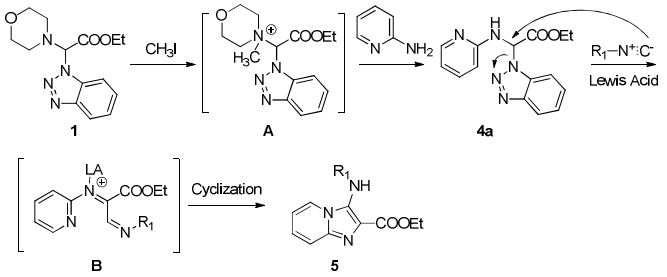


1 3b-g 4b-g 5k-p

Entry	Substrates	Products	Yield of Step	
			i [b]	ii [b]

[a] *Reaction conditions:* (i) **1** (1.0 mmol), **3b-g** (1.0 mmol), CH_3I (1.2 mmol), THF (3.0 mL); (ii) **4b-g** (1.0 mmol), **2j** (1.2 mmol), $Ga(OTf)_3$ (1 mol%), dioxane (3.0 mL), 100 °C, 2 h.
[b] Isolated yields.

On the basis of these preliminary results, the mechanism of these transformations was hypothesized as shown in Scheme 2. Ethyl α-benzotriazolyl-α-morpholinoacetate (**1**) was methylated *in situ* to form the methyl morpholinium **A**, N-methylmorpholinium group was replaced by 2-aminopyridine to afford substrate **4a**, followed by attacking by isocyanide to form intermediate **B**. A subsequent prototropic shift gives the final aromatic fused 3-aminoimidazole **5** (Scheme 2).



Scheme 3. Proposed reaction mechanism for the formation of 3-amino-2-ethoxycarbonyl imidazo[1,2-*a*]pyridines

In summary, we provide a simple and straightforward synthesis of 3-amino-2-ethoxycarbonyl imidazo[1,2-*a*]pyridine related compounds starting from ethyl α-benzotriazolyl-α-morpholinoacetate by mentions of reaction with primary heterocyclic amidines and isocyanides catalyzed by $Ga(OTf)_3$. The protocol uses readily available starting materials, and the corresponding target products are obtained in moderate to good yields. Imidazo[1,2-*a*]pyridines are well-known as biologically and pharmaceutically active molecules, therefore, the present method will be of wide application in organic and medicinal chemistry.

Experimental Section

General. The ^{1}H-NMR (400 MHz) spectra were recorded using High Performance Digital FT-NMR with TMS as internal standard, and the ^{13}C NMR (125 MHz) spectra were recorded using High Performance Digital FT-NMR. LR-MS and HR-MS were obtained by ESI (positive ion mode) on TOF mass analyzer. Purity was recorded on high-performance liquid chromatography (HPLC) Conditions were as follows: ACN/H_2O eluent at 2 mL/min flow (containing 0.05% TFA) at 40 °C, 5 min, gradient 5% ACN to 95% ACN, monitored by UV absorption at both 214 and 254 nm. TLC was carried out with glass pre-coated silica gel plates. TLC spots were visualized under UV light. All the solvents and reagents were used directly as obtained commercially unless otherwise noted.

Typical Procedure for the Synthesis of Ethyl 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-2-(pyridin-2-ylamino)acetate (4a)

Methyl iodide (117 mg, 0.83 mmol) was added to a solution of ethyl 2-(benzotriazol-l-yl)-2-morpholinoacetate (**1**, 200 mg, 0.69 mmol) in dry THF. The mixture was stirred at 20 °C for 10 min and then 2-aminopyridine (**3a**, 65 mg, 0.69 mmol) was added. The mixture was refluxed for 3 h, cooled at 20 °C and left for 16 h. The heterogeneous solution was filtered and the resulting solution was evaporated in vacuum. The residue was purified by flash chromatography (petroleum ether-ethyl acetate 3:1) to give titled compound **4a** as a white solid; yield 174 mg (85%); mp 110-120 °C. 1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 4.9 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.51 (dd, J = 16.1, 8.0 Hz, 2H), 7.38 (dt, J = 15.4, 7.1 Hz, 2H), 6.69-6.64 (m, 1H), 6.61 (d, J = 8.3 Hz, 1H), 6.41 (d, J = 7.8 Hz, 1H), 4.30-4.23 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H). LRMS(ESI): calcd for $C_{15}H_{16}N_5O_2$ (M+H): 298.12, found 298.15.

Typical Procedure for the Synthesis of Ethyl 3-((4-methoxyphenyl)amino)imidazo[1,2-*a*]pyridine-2-carboxylate (5j)

To a solution of ethyl 2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-2-(pyridin-2-ylamino)acetate (**4a**, 100 mg, 0.34 mmol), 4-methoxyphenyl isocyanate (**2j**, 54 mg, 0.4 mmol) in dioxane was added $Ga(OTf)_3$ (35 mg, 0.07 mmol). The mixture was stirred at 100 °C for about 2 h. TLC showed the starting materials were completely consumed. The reaction mixture was cooled to room temperature and concentrated under vacuum. The reaction mixture was poured onto a mixture of dichloromethane (50 mL) and H_2O (25 mL). The organic layer was washed with water (2 x 25 mL), dried, and concentrated in vacuum. The residue was purified by flash chromatography (SiO_2, petroleum ether-ethyl acetate 1:1) to give **5j** as pale yellow solid; yield: 93 mg (89%); HPLC purity: 98%; mp 153-155 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 9.4 Hz, 1H), 7.52 (d, J = 7.0 Hz, 1H), 7.19 (dd, J = 9.3, 6.8, 1.3 Hz, 1H), 7.10 (s, 1H), 6.84-6.79 (m, 2H), 6.72 (t, J = 6.9 Hz, 1H), 6.67-6.62 (m, 2H), 4.45 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.23, 155.55, 140.42, 134.83, 132.35, 126.13, 124.22 (2×C), 119.70 (2×C), 118.87, 114.90 (2×C), 113.04, 61.23, 55.60, 14.45. HRMS(ESI) *m/z* calcd for $C_{17}H_{18}N_3O_3$ (M+H): 312.1348, found 312.1349.

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