Efficient Syntheses of 1-Amido-3-aryl- and 1-Amido-3-alkylimidazo[1,5-*a*]pyridines

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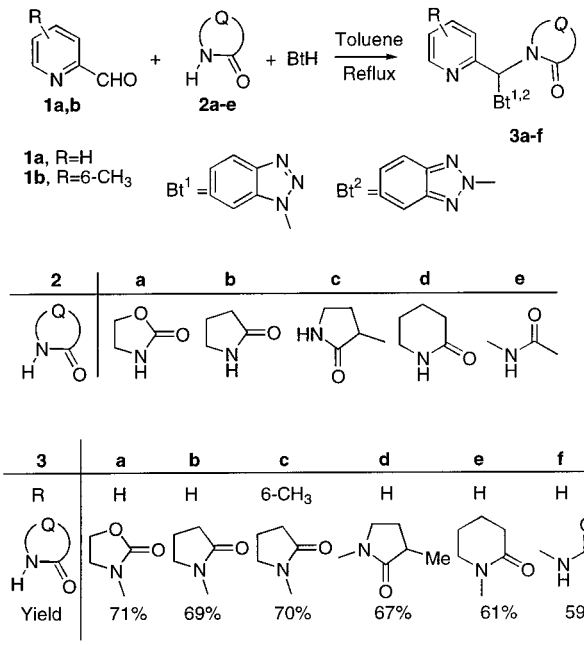
Imidazo[1,5-*a*]pyridines have been screened as selective inhibitors of aromatase estrogen production suppressors,[1a,b] as potential positive inotropic agents,[2] and platelet aggregation and thromboxane synthetase inhibitors.[3a,b] These imidazopyridines also undergo nitration,[4] acylation,[5] formylation,[6] and other transformations[7a,b] to afford valuable intermediates in the construction of heterocyclic compounds.

Syntheses of imidazo[1,5-*a*]pyridines are well documented.[8] Most routes involve reaction of a 2-aminomethylpyridine with a "one-carbon unit": (i) acylation followed by cyclization with phosphorus oxychloride[1b,9a] or polyphosphoric acid;[9b] (ii) thioacylation followed by ring closure using dicyclohexylcarbodiimide (DCC)[9c] or mercuric salts.[9d] Imidazo[1,5-*a*]pyridines were also obtained from 2-cyanopyridine by Vilsmeier reaction,[10a] or by reaction with a phosphazene followed by an aza-Wittig reaction.[10b] Other methods have utilized diverse starting materials, including imidazoles,[11a] α-pyridylglycine,[11b] *N*-benzyl-2-pyridinecarboxamide,[11c] and α-pyridylketimines.[11d]

However, the only method for the synthesis of a 1-amidoimidazo[1,5-*a*]pyridine[4] reported so far involved the nitration of 3-methylimidazo[1,5-*a*]pyridine followed by reduction with zinc dust−acetic acid to the corresponding amine, and final acetylation to 1-acetamidoimidazo[1,5-*a*]pyridine. The overall yield was about 21%. We have recently used benzotriazole methodology to synthesize indolizines,[12a] imidazo[1,2-*a*]pyridines,[12b] octahydroimidazo[1,2-*a*]pyridines,[12c] and pyrido[1,2-*a*]pyridinium salts.[12d] We now report a novel and effective strategy for the preparation of a variety of 1-amido-3-aryl- and 1-amino-3-alkylimidazo[1,5-*a*]pyridines **5** from readily available 1-[amido(2-pyridinyl)methyl]benzotriazoles **3**.

Scheme 1



Results and Discussion

Syntheses of 1-[Amido(2-pyridinyl)methyl]benzotriazoles 3a−f. Reactions of 2-pyridinecarboxaldehydes **1** and benzotriazole with 2-oxazolidinone **2a** or 2-pyrrolidinones **2b**,**c** generated corresponding Mannich adducts **3a**−**d** according to the literature procedure (Scheme 1).[13] Products **3a**,**b** and **3d** were obtained essentially pure after filtration and were advantageously used directly in the next step without further purification. Examination of the ^{1}H and ^{13}C NMR spectra of derivatives **3a**,**b** and **3d** shows that the recrystallization from ethyl acetate gave exclusively Bt-1 isomers. Presumably, the corresponding Bt-2 isomers are either not formed at all or formed in smaller amounts and remain in solution. Compound **3d**, which contains two chiral centers, is formed as a mixture of diasteoreomers (ratio of 6:4) according to ^{1}H and ^{13}C NMR spectra.

However, 1-[amido(2-pyridinyl)methyl]benzotriazole **3c** was obtained after the column chromatography as a mixture of Bt-1 and Bt-2 isomers in the ratio of 95 to 5. As both isomers have the same reactivity, this mixture was used in subsequent reactions without the isomer separation. 1-[α-Benzotriazol-1-yl(2-pyridinyl)methyl]tetrahydro-2(1*H*)-pyridinone (**3e**) and *N*-[α-benzotriazol-1-yl(2-pyridinyl)methyl]-*N*-methylacetamide (**3f**) were pre-

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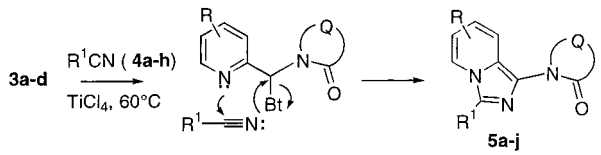
Scheme 2



4	a	b	c	d	e
R^1	C_5H_{11}	C_6H_5	Allyl	*p*-Me-C_6H_4	C_2H_5

4	f	g	h
R^1	*p*-MeO-$C_6H_4CH_2$	1-Cyclohexenyl	$BrCH_2CH_2CH_2$

pared using the same procedure, but starting from *δ*-valerolactam (**2d**) and *N*-methylacetamide (**2e**), respectively. Structures of compounds **3a**−**f** were all supported by their analytical and spectral data.

Preparation of 1-Amido-3-aryl- and 1-Amino-3-alkylimidazo[1,5-*a*]pyridines 5. Transformation of compounds **3a**−**d** into 1-amido-3-aryl- and 1-amino-3-alkyl-imidazo[1,5-*a*]pyridines **5a**−**j** was achieved in excellent yields by treatment of the pyridin-2-yl intermediates **3** with aliphatic, aromatic, and functionalized aliphatic cyanides at 60 °C in the presence of $TiCl_4$ (Scheme 2). Compounds **5a**−**j** are all novel; their structures are fully supported by the NMR data and CHN analyses, and are in good accordance with their analogues.[10a] For the compound **5c**, a doublet of doublets at ca. 5.15 ppm with the coupling constants 19.5 and 11.4 Hz and a multiplet at 5.88−6.04 ppm in the ^{1}H NMR spectrum are characteristic for the terminal CH_2 and the methylene CH of the allyl group, respectively. It shows that the procedure described in this paper is well applicable for the introduction of a variety of substituents, including alkyl, aryl, halogenated alkyl, allyl, vinyl, benzyl, at the 3-position of imidazo[1,5-*a*]pyridines **5**.

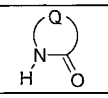
As illustrated in Scheme 2, removal of the benzotriazole group (facilitated by the coordination of the Lewis acid) leads to a cation and the formation of imidazo[1,5-*a*]pyridines proceeds via the nucleophilic attack of the lone pair of the cyano nitrogen at this cation with subsequent cyclization and aromatization. Yields and melting points of the products **5** are presented in Table 1. Unfortunately, attempts to prepare compounds **5** with an amido group at the 1-position other than part of a five-membered heterocycles, failed. The intermediates **3e** and **3f** were readily synthesized from the six-membered ring amide **2d** and the acyclic amide **2e**, respectively, by procedures similar to that used for **3a**−**d**. However, no expected imidazo[1,5-*a*]pyridine **5** was obtained by the reaction of **3e** or **3f** with cyanides, possibly because of increased steric reasons.

In summary, 1-amido-3-aryl- and -alkylimidazo[1,5-*a*]-pyridines **5a**−**j** can be readily prepared from cyanides **4** and easily available benzotriazole intermediates **3**. This method possesses the advantages of a simple procedure, mild conditions, easy availability of starting materials, and excellent yields.

Experimental Section

Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Gemini 300 NMR spectrometer in chloroform-*d* solution (with tetramethylsilane for ^{1}H and chloroform-*d* for ^{13}C as the internal references), unless otherwise stated. Column chromatography was performed on silica gel. Elemental analyses were performed on a Carlo Erba-1106 instrument.

Table 1. Preparation of Imidazo[1,5-*a*]pyridines 5a−j

5	R		R^1	Yield[a] (%)	mp(°C)
a	H		C_5H_{11}	91	—
b	H		C_6H_5	89	155-156
c	H		Allyl	81	—
d	H		4-CH_3-C_6H_4	92	104-105
e	H			84	—
f	H		$BrCH_2CH_2CH_2$	81	—
g	5-CH_3		C_6H_5	82	168-169
h	5-CH_3		C_2H_5	84	123-124
i	H		C_6H_5	87	—
j	H		4-MeO-$C_6H_4CH_2$	83	116-117

[a] Isolated yield based on **3a**−**d**.

General Procedure for the Preparation of 1-[Amido(2-pyridinyl)methyl]benzotriazoles 3a−f. A mixture of an appropriate 2-pyridinecarboxaldehyde (10 mmol), a 2-pyrrolidinone or 2-oxazolidinone (10 mmol), and benzotriazole (10 mmol) in toluene (50 mL) was heated at reflux with a Dean−Stark trap in the presence of *p*-toluenesulfonic acid (1 mmol) under nitrogen for 12 h. After cooling to room temperature, the precipitate was filtered off and washed with ethyl acetate to give pure **3a**,**b**. For compounds **3c**−**f**, the cooled mixture was washed with 2 N aqueous NaOH solution, and then with water, extracted with EtOAc and dried over anhyd Na_2SO_4. After removal of the solvent in vacuo, **3d** was obtained as a solid. The compounds **3a**,**b** and **3d** were obtained as colorless crystals after recrystallization from EtOAc for the elemental analysis purpose. Compounds **3c** and **3e**,**f** were purified by column chromatography (silica gel) with the eluent of hexane/EtOAc (1:3−9) as a mixture of Bt-1 and Bt-2 isomers in the ratio of 95/5.

3-[α-Benzotriazol-1-yl(2-pyridinyl)methyl]-1,3-oxazol-2-one (3a): off-white prisms; mp 166.0−167.0 °C (ethanol/ethyl acetate); ^{1}H NMR (DMSO-d_6) *δ* 3.52−3.64 (m, 1H), 3.79−3.90 (m, 1H), 4.34−4.48 (m, 2H), 7.43−7.52 (m, 3H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.93 (td, *J* = 7.8, 1.5 Hz, 1H), 8.05 (s, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 8.61 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR (DMSO) *δ* 41.9, 62.8, 68.7, 110.8, 119.3, 122.7, 124.2, 124.4, 127.9, 132.8, 137.6, 144.9, 149.4, 152.5, 157.6. Anal. Calcd for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 60.86; H, 4.38; N, 23.68.

1-[α-Benzotriazol-1-yl(2-pyridinyl)methyl]-2-pyrrolidinone (3b): colorless prisms; mp 143.0−144.0 °C (ethanol/ethyl acetate); ^{1}H NMR (DMSO-d_6) *δ* 1.88−2.12 (m, 2H), 2.30−2.52

(m, 2H), 3.26−3.38 (m, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.56 (t, J = 6.9 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.91 (td, J = 7.8 Hz, 1H), 8.14 (d, J = 9.9 Hz, 1H), 8.15 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H); ^{13}C NMR (DMSO) δ 17.7, 29.9, 44.2, 66.5, 110.7, 119.4, 122.4, 124.0, 124.4, 127.9, 132.8, 137.6, 144.9, 149.5, 153.0, 175.4. Anal. Calcd for $C_{16}H_{15}N_5O$: C, 65.52; H, 5.15; N, 23.88. Found: C, 65.18; H, 5.08; N, 23.89.

1-[α-Benzotriazol-1-yl(6-methyl-2-pyridinyl)methyl]-2-pyrrolidinone (3c): colorless prisms; mp 98.0−99.0 °C (ethyl acetate); ^{1}H NMR δ 1.95−2.10 (m, 2H), 2.40−2.60 (m, 2H), 2.55 (s, 3H), 3.46−3.56 (m, 1H), 3.70−3.80 (m, 1H), 6.90 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 18.1, 24.4, 30.5, 44.4, 66.5, 109.9, 119.2, 119.7, 123.2, 124.2, 127.8, 133.2, 137.0, 145.4, 152.3, 158.7, 176.0. Anal. Calcd for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.57; N, 22.79. Found: C, 66.28; H, 5.64; N, 22.80.

1-[1*H*-1,2,3-Benzotriazol-1-yl(2-pyridinyl)methyl]-3-methyl-2-pyrrolidinone (3d): Obtained as diastereoisomers in the ratio 6:4 (minor isomer in the parentheses): colorless prisms; mp 128−129 °C (ethyl acetate); ^{1}H NMR δ 1.17 (d, J = 7.2 Hz, 1.2H), 1.30 (d, J = 7.2 Hz, 1.8H), 1.56−1.68 (m, 0.4H), 1.68−1.84 (m, 0.6H), 2.16−2.26 (m, 1H), 2.40−2.54 (m, 0.6H), 2.62−2.74 (m, 0.4H), 3.26−3.38 (m, 0.6H), 3.50−3.64 (m, 1.4H), 7.09 (d, J = 8.1 Hz, 0.4H), 7.16 (d, J = 7.8 Hz, 0.6H), 7.27−7.36 (m, 1H), 7.40 (t, J = 6.9 Hz, 1H), 7.50 (t, J = 8.1 Hz, 1H), 7.60−7.76 (m, 2H), 8.06−8.16 (m, 2H), 8.66 (d, J = 3.6 Hz, 1H); ^{13}C NMR δ 15.7 (15.6), 27.3 (27.1), 36.5 (36.2), 24.5, 66.4 (66.7), 109.8, 119.8, 122.2 (122.3), 123.6, 124.3, 127.9, 133.3 (133.1), 136.9, 145.3, 149.7 (149.6), 153.1, 178.5 (178.3). Anal. Calcd for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.57; N, 22.79. Found: C, 66.45; H, 5.97; N, 22.95.

General Procedure for the Preparation of 1-Amido-3-aryl- and -alkylimidazo[1,5-*a*]pyridines 5a−j. To a mixture of **3** (1 mmol) and cyanide **4** (2 mmol) under nitrogen was added $TiCl_4$ in CH_2Cl_2 (1.2 mL, 1.2 mmol) at 60 °C, and the mixture was stirred for 4−8 h. The mixture was washed with 2 N aqueous NaOH solution (2 × 5 mL) and H_2O (5 mL), and the combined aqueous phase was extracted with EtOAc. The combined organic layers were dried over anhyd Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by column chromatography (silica gel) with hexane/EtOAc (1:1−2) as an eluent to afford **5a**−**j**.

1-(2-Oxo-1,3-oxazol-3-yl)-3-pentylimidazo[1,5-*a*]pyridine (5a): light yellow oil; ^{1}H NMR δ 0.91 (t, J = 7.1 Hz, 3H), 1.32−1.46 (m, 4H), 1.52−1.70 (m, 2H), 2.90 (t, J = 7.8 Hz, 2H), 4.21 (t, J = 8.8 Hz, 2H), 4.55 (t, J = 7.6 Hz, 2H), 6.51 (t, J = 6.3 Hz, 1H), 6.62 (dd, J = 9.3, 6.3 Hz, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ 13.8, 22.2, 26.3, 26.6, 31.4, 46.3, 62.5, 112.6, 117.2, 118.8, 119.9, 120.9, 124.3, 135.6, 155.9. Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.89; H, 7.31; N, 15.68.

1-(2-Oxo-1,3-oxazol-3-yl)-3-allylimidazo[1,5-*a*]pyridine (5c): light yellow oil; ^{1}H NMR δ 3.75 (d, J = 6.3 Hz, 2H), 4.22 (t, J = 8.4 Hz, 2H), 4.55 (t, J = 7.5 Hz, 2H), 5.15 (dd, J = 19.5, 11.4 Hz, 2H), 5.88−6.04 (m, 1H), 6.53 (t, J = 6.9 Hz, 1H), 6.66 (t, J = 7.8 Hz, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 31.3, 46.2, 62.6, 112.7, 117.4, 117.5, 118.9, 120.2, 121.2, 124.6, 131.7, 132.6, 155.9. Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.85; H, 5.59; N, 17.42.

1-(2-Oxo-1-pyrrolidinyl)-3-(4-methylphenyl)imidazo[1,5-*a*]pyridine (5d): light green flakes; mp 104−105 °C (ethyl acetate/hexane); ^{1}H NMR δ 2.20−2.32 (m, 2H), 2.41 (s, 3H), 2.64 (t, J = 8.1 Hz, 2H), 4.09 (t, J = 7.2 Hz, 2H), 6.51 (t, J = 6.6 Hz, 1H), 6.66 (dd, J = 9.0, 6.6 Hz, 1H), 7.30 (d, J = 7.8 Hz, 2H), 7.61 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 9.0 Hz, 1H), 8.09 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ 18.7, 21.3, 31.8, 49.3, 113.4, 117.8, 120.1, 120.9, 122.2, 126.9, 127.6, 127.9, 129.6, 134.9, 138.7, 173.6. Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.43; H, 5.86; N, 14.71.

1-(2-Oxo-1-pyrrolidinyl)-3-(1-cyclohexen-1-yl)imidazo[1,5-*a*]pyridine (5e): light yellow oil; ^{1}H NMR δ 1.68−1.88 (m, 4H), 2.18−2.33 (m, 4H), 2.48−2.58 (m, 2H), 2.61 (t, J = 8.1 Hz, 2H), 4.03 (t, J = 7.2 Hz, 2H), 6.39−6.49 (m, 1H), 6.46 (t, J = 6.3 Hz, 1H), 6.59 (dd, J = 8.7, 6.6 Hz, 1H), 7.53 (d, J = 9.3 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 18.5, 21.7, 22.3, 25.2, 27.7, 31.6, 49.1, 112.6, 117.3, 119.6, 121.5, 121.7, 126.4, 127.9, 129.1, 136.2, 173.4. HRMS Calcd for $C_{17}H_{20}N_3O$ 282.1606 (M + 1), found 282.1605.

1-(2-Oxo-1-pyrrolidinyl)-3-phenyl-5-methylimidazo[1,5-*a*]pyridine (5g): pale yellow prisms; mp 168.0−169.0 °C (CH_2Cl_2/hexane); ^{1}H NMR δ 2.05 (s, 3H), 2.18−2.32 (m, 2H), 2.63 (t, J = 7.8 Hz, 2H), 4.06 (t, J = 6.9 Hz, 2H), 6.28 (d, J = 6.3 Hz, 1H), 6.65 (dd, J = 9.0, 6.6 Hz, 1H), 7.38−7.52 (m, 6H); ^{13}C NMR δ 18.6, 21.6, 31.6, 49.3, 114.1, 117.3, 118.3, 123.5, 126.2, 127.2, 128.7, 130.8, 132.4, 133.1, 135.5, 173.7. Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.17; H, 5.92; N, 14.36.

1-(3-Methyl-2-oxo-1-pyrrolidinyl)-3-phenylimidazo[1,5-*a*]pyridine (5i): light yellow oil; ^{1}H NMR δ 1.34 (d, J = 7.2 Hz, 3H), 1.80−1.97 (m, 1H), 2.39−2.50 (m, 1H), 2.69−2.80 (m, 1H), 3.98−4.08 (m, 2H), 6.5 (td, J = 6.3, 0.9 Hz, 1H), 6.65 (dd, J = 9.0, 6.6 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.66−7.75 (m, 3H), 8.11 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ 16.2, 27.7, 37.4, 47.0, 113.5, 117.7, 120.3, 120.6, 122.0, 127.9, 128.1, 128.5, 128.8, 129.7, 134.5, 175.9. Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.05; H, 5.98; N, 14.43.

1-(3-Methyl-2-oxo-1-pyrrolidinyl)-3-(4-methoxybenzyl)-imidazo[1,5-*a*]pyridine (5j): colorless plates; mp 116−117 °C (ethyl acetate/CH_2Cl_2); ^{1}H NMR δ 1.33 (d, J = 7.2 Hz, 3H), 1.80−1.95 (m, 1H), 2.38−2.50 (m, 1H), 2.66−2.80 (m, 1H), 3.75 (s, 3H), 3.95−4.04 (m, 2H), 4.30 (s, 2H), 6.39 (t, J = 6.6 Hz, 1H), 6.56 (dd, 6.3 Hz, 1H), 6.80 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 9.3 Hz, 1H); ^{13}C NMR δ 16.3, 27.8, 32.4, 37.4, 47.1, 55.1, 112.7, 114.0, 116.8, 120.2, 120.3, 121.1, 126.4, 127.9, 129.1, 133.6, 158.3, 175.7. Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.55; H, 6.46; N, 12.52.

Supporting Information Available: Characterization data for compounds **3e**−**f**, **5b**, **5f**, and **5h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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