Molecules **2004**, *9*, 894-901

molecules

ISSN 1420-3049

http://www.mdpi.org

Fused Heterocycles: Synthesis of Some New Imidazo[1,2-*a*]-pyridine Derivatives

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Received: 4 August 2004 / Accepted: 13 September 2004 / Published: 30 September 2004

Abstract: Some new thiazolidines and spirothiazolidines derived from hydrazones of 2-methylimidazo[1,2-*a*]pyridine-3-carboxylic acid hydrazide, a bioisosteric derivative of isoniazid, were synthesized and characterized by analytical, IR, ^{1}H- and ^{13}C-NMR and mass spectral data. Some of the newly synthesized compounds were screened for their antimycobacterial activities. None of the tested compounds showed significant *in vitro* antituberculous activity at 6.25 μg/mL (MIC rifampin 0.031 μg/mL).

Keywords: Imidazo[1,2-*a*]pyridine, hydrazones, thiazolidines, spirothiazolidines, antituberculous activity.

Introduction

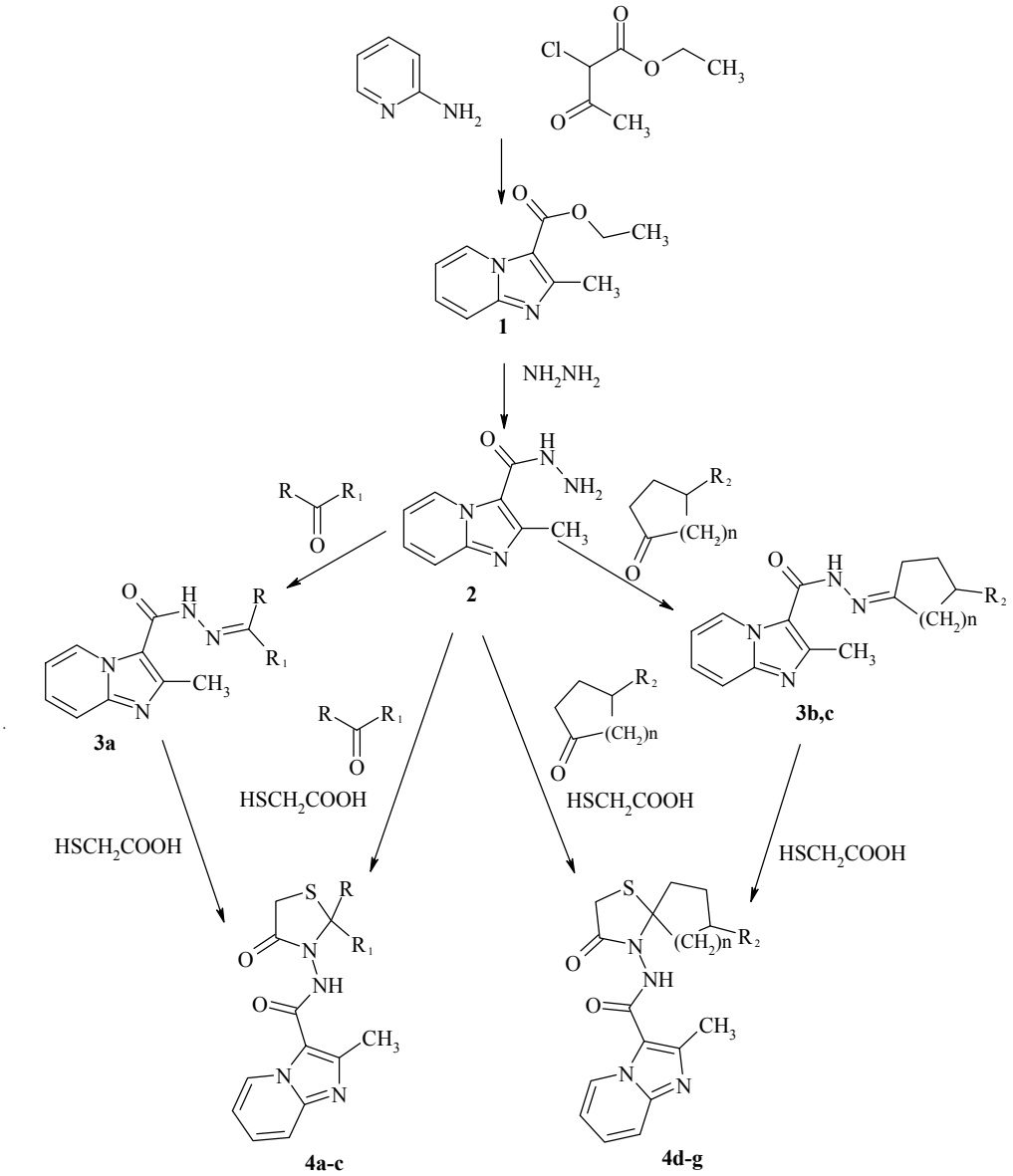
Mycobacterium tuberculosis infects over one-third of the world's population and causes almost three million deaths every year [1]. Isonicotinic acid hydrazide (isonazid) is one of the primary drugs used in combination with ethambutol, rifampin, streptomycin and pyrazinamide to treat tuberculosis, but the treatment of this disease is still a major health problem due to multi-drug resistant bacterial strains and new antimycobacterial agents, different from available first-line drugs, are urgently needed. As part of our studies on imidazo[1,2-*a*]pyridine we have recently reported the synthesis of some imidazo[1,2-*a*]pyridine-3-carboxylic acid hydrazides and related compounds and their antimycobacterial activities [2]. Continuing our search for new antimycobacterial agents we have now

synthesized some new ketone-hydrazones **3a-c**, thiazolidines **4a-c** and spiro compounds **4d-g** incorporating an imidazo[1,2-*a*]pyridine moiety. These compounds were characterized by their elemental and spectral analyses (IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra).

Results and Discussion

The synthetic pathway followed in the preparation of the compounds is outlined in Scheme 1. The starting materials, ethyl 2-methylimidazo[1,2-*a*]pyridine-3-carboxylate (**1**) and 2-methylimidazo[1,2-*a*]pyridine-3-carboxylic acid hydrazide (**2**), were obtained by previously described methods [3,4].

Scheme 1



Condensation of **2** with the appropriate ketones in ethanol yielded the corresponding ketone-hydrazones **3**. The hydrazones were reacted with mercaptoacetic acid in dry benzene (Method A) to give cyclocondensation products **4b,d** and **e** in 69.8-72.3 % yields. On the other hand, refluxing a mixture of **2** and the appropriate ketone together with mercaptoacetic acid in dry benzene (Method B) also produced the target compounds **4** but in higher yields (69.7-99.1 %), except in the case of **4b** (55.5 %). All the compounds were characterized by their physical data and elemental analyses (Table 1), IR, ^{1}H- and ^{13}C-NMR and EI mass spectra.

Table 1. Some physical and analytical data of compounds **3** and **4**

Comp.	R	R_1	R_2	n	M.p. (^{o}C)	Yield %	Formula (molecular weigh)	Analysis (calcd./found)(%)		
								C	H	N
3a	CH_3	C_2H_5	-	-	120-5	75.8	$C_{13}H_{16}N_4O$	63.91	6.60	22.94
							(244.30)	63.81	6.96	22.55
3b	-	-	-	1	162-6	62.1	$C_{14}H_{16}N_4O.1.5H_2O$	59.35	6.76	19.78
							(283.61)	60.84	6.96	19.70
3c	-	-	-	2	76-8	63.8	$C_{15}H_{18}N_4O.2H_2O$	58.81	7.24	18.29
							(306.33)	58.94	7.56	18.21
4a	CH_3	CH_3	-	-	222-5	87.3	$C_{14}H_{16}N_4O_2S.H_2O$	52.16	5.63	17.38
						(Method B)	(322.38)	52.70	6.04	17.30
4b	CH_3	C_2H_5	-	-	138-43	69.8	$C_{15}H_{18}N_4O_2S.H_2O$	53.56	5.99	16.65
						(Method A)	(336.39)	53.45	6.10	16.83
						55.5				
						(Method B)				
4d	-	-	-	1	137-43	75.5	$C_{16}H_{18}N_4O_2S.H_2O$	55.15	5.79	16.08
						(Method A)	(348.42)	55.10	5.82	15.92
						80.0				
						(Method B)				
4e	-	-	-	2	258-65	77.3	$C_{17}H_{20}N_4O_2S$	59.28	5.85	16.27
						(Method A)	(344.43)	58.97	5.77	16.10
						99.1				
						(Method B)				
4f	-	-	CH_3	2	154-6	72.3	$C_{18}H_{22}N_4O_2S.0.5H_2O$	58.85	6.31	15.26
						(Method B)	(367.46)	58.64	7.26	15.42
4g	-	-	C_2H_5	2	142-6	81.7	$C_{19}H_{24}N_4O_2S.2H_2O$	55.86	6.91	13.71
						(Method B)	(408.52)	55.44	6.56	12.09

The IR spectra of the starting materials **3** showed C=O bands in the 1654-1679 cm^{-1} region. A new strong band at 1690-1710 cm^{-1} in the spectra of **4** provided firm support for ring closure. The most significant evidence for the reaction was the presence of two doublets (dd, 2H, *J*=16 Hz) at about 3.61 and 3.68 in the ^{1}H-NMR spectrum of **4b** [6]. In the spectra of **4a,c-g**, the same protons were observed as singlets (2H) at about 3.40-3.72 ppm due to the lack of chirality. ^{13}C-NMR and DEPT (135) spectra of the prototypes (**4b,d** and**, e**) were also studied and are detailed. Signals at about 71.44-76.59 ppm, which are not seen in DEPT spectra, were assigned to the quarternary (spiro) carbon atoms. According to the data obtained from DEPT and HETCOR experiments the signals at about 28.80-29.72 ppm were assigned to the CH_2 group located in the thiazolidine moiety [7]. The mass spectra of all the compounds were relatively simple and showed (except for **4g**) the peaks due to molecular ions.

Antituberculous Activity

Primary screening was conducted at 6.25 μg/mL against *M. tuberculosis* H_{37}Rv. The *M. tuberculosis* H_{37}Rv was grown in a medium containing a radiolabeled substrate. Labeled CO_2 produced was detected and quantitated with a BACTEC 460 automatic radiometric system. Compounds giving inhibitions < 90 % (MIC > 6.25 μg/mL, MIC rifampin 0.031 μg/mL) were not evaluated further [5]. None of the compounds showed antituberculous activity at the tested concentration.

Acknowledgements

We thank Dr. Joseph A. Maddry from the Tuberculosis Antimicrobial Acquisition and Coordination Facility (TAACF), National Institute of Allergy and Infectious Diseases Southern Research Institute, Birmingham, AL (USA) for the *in vitro* evaluation of antituberculous activity. This work was supported by Istanbul University Research Fund Project No. T-452/071197.

Experimental

General

Melting points determined with a Buchi 530 melting point apparatus in open capillaries and are uncorrected. IR (KBr disks) and ^{1}H- and ^{13}C-NMR spectra (DMSO-d_6) were recorded on Perkin Elmer Model 1600 and Bruker AC 200 and DPX 400 instruments, respectively. Microanalyses were carried out on a Carlo Erba 1106 elemental analyzer. All starting materials were purchased E. Merck (Darmstadt, Germany).

Ethyl 2-methyimidazo[1,2-a]pyridine-3-carboxylate (**1**) [3].

2-Aminopyridine (0.01 mol) was heated under reflux with ethyl 2-chloroacetoacetate (0.1 mol) in 96 % C_2H_5OH (25 mL) for 6h and then cooled. Excess C_2H_5OH was evaporated *in vacuo*. The residual red oil was partitioned between ether-water. After drying, the ether extracts were evaporated and the residual oil was allowed to crystallize. M.p. 69 °C, yield 45.05%.

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid hydrazide (**2**) [4].

Ethyl 2-methylimidazo[1,2-*a*]pyridine-3-carboxylate (0.01 mol) was heated under reflux with H_2NNH_2 (0.1 mol) in 96% C_2H_5OH (15 mL) for 5h and then cooled. The crystals formed were washed with H_2O, dried and recrystallized from C_2H_5OH (96 %). M.p.180 °C, yield 27.16 %.

General procedure for preparation of 2-methylimidazo[1,2-a]pyridine-3-carboxylic acid (alkylidene / cycloalkylidene) hydrazides **3a-c**.

2-Methylimidazo[1,2-*a*]pyridine-3-carboxylic acid hydrazide (**2,** 0.01 mol), the appropriate ketone (0.011 mol), a drop of conc. H_2SO_4 and 96 % C_2H_5OH (20 mL) were heated under reflux for 6h. The crude products which precipitated on cooling were filtered and recrystallized from an C_2H_5OH-H_2O mixture.

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid sec-butylidenehydrazide (**3a**)**:** IR: 1654 (C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 1.04 (3H, t, CH_2CH_3), 1.98 (3H, s, CH_3), 2.28 (2H, q, CH_2CH_3), 2.53 (3H, s, 2-CH_3), 7.01 (1H, t, 6-H), 7.38 (1H, t, 7-H), 7.58 (1H, d, 8-H), 8.88 (1H, d, 5-H), 10.03 (1H, s, CONH); EIMS (%) = 244 ($M^{+\cdot}$, 38), 159 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid cyclopentylidenhydrazide (**3b**)**:** IR: 1670 (C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 1.68-1.83 (4H, m, cyclopentylidene-3H,4H), 2.34-2.49 (4H, m, cyclopentylidene-2H,5H), 2.54 (3H, s, 2-CH_3), 7.00 (1H, t, 6-H), 7.40 (1H, t, 7-H), 7.58 (1H, d, 8-H), 8.89 (1H, d, 5-H), 9.91 (1H, s, CONH); EIMS (%) = 256 ($M^{+\cdot}$, 100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid cyclohexylidenhydrazide (**3c**)**:** IR: 1679 (C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 1.4-1.78 (6H, m, cyclohexylidene 3H,4H,5H), 2.21-2.31 (2H, m, cyclohexylidene-2H,6H, axial), 2.33-2.60 (2H, m, cyclohexylidene-2H,6H, equatorial), 2.52 (3H, s, 2-CH_3), 7.01 (1H, t, 6-H), 7.37 (1H, t, 7-H), 7.56 (1H, d, 8-H), 8.86 (1H, d, 5-H), 10.28 (1H, s, CONH); EIMS (%) = 270 ($M^{+\cdot}$, 72), 78 (100).

General procedures for preparation of 2-methylimidazo[1,2-a]pyridine-3-carboxylic acid amides **4 a-g**.

Method A

A mixture of **3a-c** (0.01 mol) and $HSCH_2COOH$ (0.15 mol) was heated under reflux for 6h in dry benzene (30 mL) using a Dean-Stark trap for removal of water of condensation. Excess benzene was evaporated *in vacuo*. The residue was triturated with saturated $NaHCO_3$ until CO_2 evaluation ceased and then allowed to stand overnight. The solid thus obtained was filtered, washed with H_2O and recrystallized from an C_2H_5OH-H_2O mixture.

Method B

The appropriate ketone (0.011 mol) was added to a solution of **2** (0.01 mol) in dry benzene (30 mL) and the mixture was heated under reflux for 1.5h using a Dean-Stark trap. After cooling $HSCH_2COOH$ (0.15 mol) was added dropwise to the solution and the resulting mixture was refluxed for 6h. The compounds were purified using the procedure described under Method A.

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (2,2-dimethyl-4-oxo-1,3-thiazolidin-3-yl)amide (**4a**)**:** IR: 1662 (CONH), 1690 (thiazolidine C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 1.36 (6H, s, -C(CH_3)$_2$), 2.44 (3H, s, 2-CH_3), 3.52 (2H, s, CH_2S), 6.88 (1H, t, 6-H), 7.25 (1H, t, 7-H), 7.42 (1H, d, 8-H), 8.65 (1H, d, 5-H), 9.81 (1H, s, CONH); EIMS (%) = 304 ($M^{+\cdot}$, 3), 156 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (2-ethyl-2-methyl-4-oxo-1,3-thiazolidin-3-yl)amide (**4b**): IR: 1662 (CONH), 1690 (thiazolidine C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.04 (3H, t, CH_2CH_3), 1.66 (3H, s, C-CH_3), 1.76-1.84,1.92-1.99 (1H, 1H, 2m, CH_2CH_3), 2.60 (3H, s, 2-CH_3), 3.61, 3.68 (1H, 1H, dd, J=16 Hz, CH_2S), 6.93 (1H, t, 6-H), 7.34 (1H, t, 7-H), 7.46 (1H, d, 8-H), 9.22 (1H, d, 5-H), 7.93 (1H, s, CONH); ^{13}C-NMR δ(ppm) = 168.67/161.73 (thiazolidine CO and CONH), 148.19/146.57 (imidazopyridine C_2 and C_{8a}), 128.19 (imidazopyridine C_5), 127.80 (imidazopyridine C_7), 117.14 (imidazopyridine C_8), 114.33 (imidazopyridine C_3), 71.44 (thiazolidine C_2), 34.72 ($\underline{C}H_2CH_3$), 29.72 (thiazolidine C_3), 28.32 (CH_3), 16,73 (2-CH_3), 9.53 ($CH_2\underline{C}H_3$); EIMS (%) = 318 ($M^{+\cdot}$,100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (2,2-diethyl-4-oxo-1,3-thiazolidin-3-yl)amide (**4c**)**:** IR: 1662 (CONH), 1690 (thiazolidine C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 0.8 (6H, t, CH_2CH_3), 1.50-1.65 (4H, m, CH_2CH_3), 2.40 (3H, s, 2-CH_3), 3.40 (2H, s, CH_2S), 6.64 (1H, t, 6-H), 7.22 (1H, t, 7-H), 7.40 (1H, d, 8-H), 8.66 (1H, d, 5-H), 9.72 (1H, s, CONH); EIMS (%) = 332 ($M^{+\cdot}$, 4.5), 46 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (3-oxo-1-thia-4-azaspiro[4.4]non-4-yl)amide (**4d**)**:** IR: 1662 (CONH), 1691 (spiro[4.4]nonane C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 1.67-1.97 (4H, m, spiro-7H,8H), 2.15-2.21 (2H, m, spiro-6H,9H axial), 2.23-2.40 (2H, m, spiro-6H,9H equatorial), 2.64 (3H, s, 2-CH_3), 3.72 (2H, s, CH_2S), 7.05 (1H, t, 6-H), 7.46 (1H, t, 7-H), 7.62 (1H, d, 8-H), 8.90 (1H, d, 5-H), 9.98 (1H, s, CONH); ^{13}C-NMR δ (ppm) = 168.67/161.73 (spiro[4.4]nonane C_3 and CONH), 148.05/146.62 (imidazopyridine C_2 and C_{8a}) , 128.25 (imidazopyridine C_5), 127.85 (imidazopyridine C_7), 117.12 (imidazopyridine C_8), 114.74 (imidazopyridine C_3), 114.34 (imidazopyridine C_6), 76.79 (C_5), 39.22 (spiro[4.4]nonane C_6 and C_9), 29.72 (spiro[4.4]nonane C_2), 23.62 (spiro[4.4]nonane C_7 and C_8), 16.75 (2-CH_3); EIMS (%)= 330 ($M^{+\cdot}$, 66.45), 90 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)amide (**4e**)**:** IR: 1673 (CONH), 1709 (spiro[4.5]decane C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 1.05-2.54 (10H, m, spiro-6H,7H,8H,9H,10H), 2.67 (3H, s, 2-CH_3), 3.64 (2H, s, CH_2S), 7.07 (1H, t, 6-H), 7.44 (1H, t, 7-H), 7.62 (1H, d, 8-H), 8.90 (1H, d, 5-H), 9.93 (1H, s, CONH); ^{13}C-NMR δ (ppm) = 168.67/161.73 (spiro[4.5]decane C_3 and CONH), 148.00/146.00 (imidazopyridine C_2 and C_{8a}), 128.29 (imidazo-pyridine C_5), 127.84 (imidazopyridine C_7), 117.11 (imidazopyridine C_8), 114.80 (imidazopyridine C_3), 114.37 (imidazopyridine C_6), 73.04 (spiro[4.5]decane C_5), 28.80 (spiro[4.5]decane C_2), 24.90 (spiro[4.5]decane C_8), 23.76 (spiro[4.5]decane C_6 and C_9), 23.62 (spiro[4.5]decane C_6 and C_{10}), 16.78 (2-CH_3); EIMS (%) = 344 ($M^{+\cdot}$, 92.4), 160 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (8-methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl) amide (**4f**)**:** IR: 1662 (CONH), 1693 (spiro[4.5]decane C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 0.67 (3H, s, CH_3), 1.28-1.63 (9H, m, spiro-6H,7H,8H,9H,10H), 2.43 (3H, s, 2-CH_3), 3.43 (2H, s, CH_2S), 6.85 (1H, t, 6-H), 7.22 (1H, t, 7-H), 7.40 (1H, d, 8-H), 8.67 (1H, d, 5-H), 9.79 (1H, s, CONH); EIMS (%) = 358 ($M^{+\cdot}$, 4), 46 (100).

2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid (8-ethyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl) amide (**4g**)**:** IR: 1672 (CONH), 1710 (spiro[4.5]decane C=O) cm^{-1}; ^{1}H-NMR: δ (ppm) = 0.84 (3H, s, CH_2CH_3), 1.05-1.98 (11H, m, spiro-6H,7H,8H,9H,10H, CH_2CH_3), 2.64 (3H, s, 2-CH_3), 3.64 (2H, s, CH_2S), 6.99 (1H, t, 6-H), 7.37 (1H, t, 7-H), 7.67 (1H, d, 8-H), 8.86 (1H, d, 5-H), 9.99 (1H, s, CONH); EIMS (%) = 46 (100).

In vitro evaluation of antituberculous activity [5]

A primary screen was conducted at 6.25 μg/mL against *M. tuberculosis* $H_{37}R_V$ in BACTEC 12B medium using a BACTEC 460 radiometric system. Compounds **3a-c, 4b,d-e**, chosen as prototypes, did not show *in vitro* antituberculous activity at 6.25 μg/mL (MIC rifampin 0.031 μg/mL).

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Samples Availability: Available from the authors.