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PREPARATION OF DIFFERENTIATED DIAMIDES OF 4,5,6,7-TETRAHYDROPYRAZOLO[1,5-*a*]PYRIDINE-2,6- AND -3,6-DICARBOXYLIC ACIDS SUITABLE FOR PARALLEL SYNTHESIS

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1,3-Dipolar cycloaddition of a bicyclic sydnone to a propargylic acid amide affords 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-2,6- and -3,6-dicarboxylic acid monoamides which are further converted to corresponding differentiated diamides.

Keywords: sydnones, 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridines, 1,3-dipolar cycloaddition.

The pyrazole core represents an important class of nitrogen-containing heterocycles since it is a stuctural element of natural products [1] and pharmaceutically active compounds [2–4]. The bicyclic pyrazole motif is a fragment of numerous biologically active compounds [5–8]. The partially saturated bicyclic pyrazole system, 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine, has found use as a scaffold in drug research [9, 10] and agrochemicals [11].

Within the medicinal chemistry program in our laboratories, we considered a diversity-oriented library synthesis around this scaffold, specifically, the synthesis of differentiated diamides of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-2,6-dicarboxylic acid **1a** and 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-3,6-dicarboxylic acid **1b**. The literature search revealed that only few structural modifications of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine [12], the corresponding 2-carboxylic acid derivatives [13, 14], and boranes [14] are known. Furthermore, 6-substituted 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine derivatives have not been reported.

Two principally distinct synthetic routes towards 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine derivatives have been reported. Route A is based on the hydrogenation of pyrazolo[1,5-a]pyridines 3a,b [9, 10], and route B – on the pyrazole ring closure by 1,3-dipolar cycloaddition of bicyclic sydnone 6 to propargylic acid derivatives. Retrosynthetic analysis of target compounds showed that for route A, an intermediate pyrazolo[1,5-*a*]pyridine-2- or -3-carboxylic acid derivatives 4a,b would be required. Pyrazolo[1,5-*a*]pyridine-2-carboxylic acid derivatives 4a are synthesized by 1,3-dipolar cycloaddition of 1-aminopyridinium species 5 to acetylene dicarboxylic acid esters and subsequent monodecarboxylation [15], whereas the corresponding

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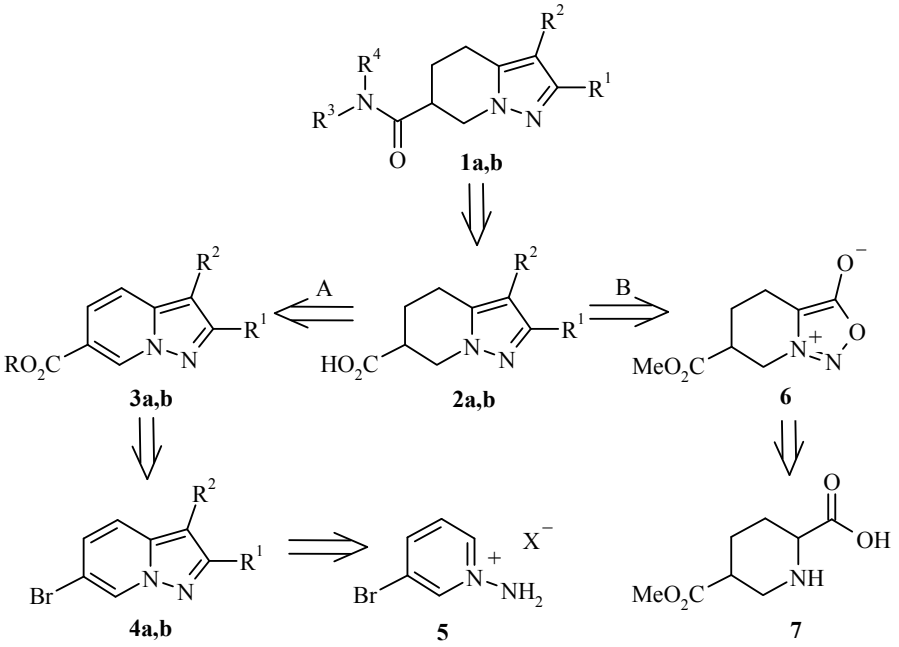
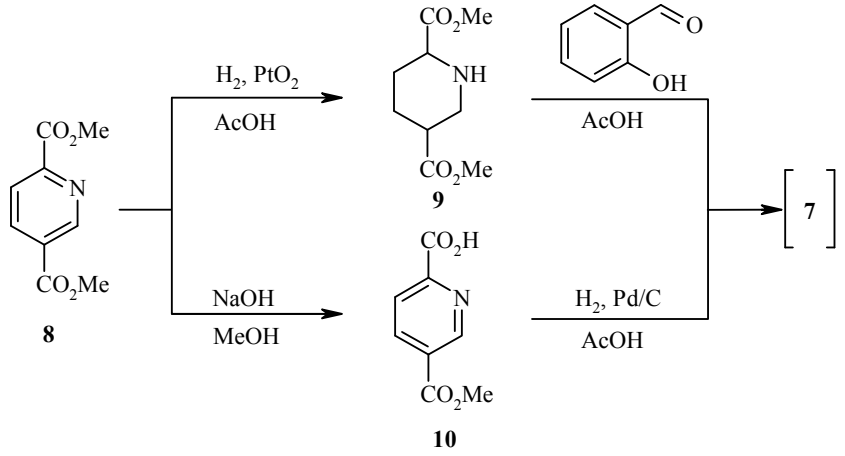
3-carboxylic acid derivatives **4b** are obtained in the reaction of compound **5** with propiolic acid derivatives [15, 16]. Therefore route A is not appropriate for parallel synthesis. This consideration, together with potential problems associated with differentiation of two carboxylic acids/ester/amide functionalities, prompted us to choose route B as synthetically more attractive.



1, **2 a** $R^1 = CONR^5R^6$, $R^2 = H$; **b** $R^1 = H$, $R^2 = CONR^5R^6$;
3, **4 a** $R^1 = CO_2R$, $R^2 = H$; **b** $R^1 = H$, $R^2 = CO_2R$; R = alkyl

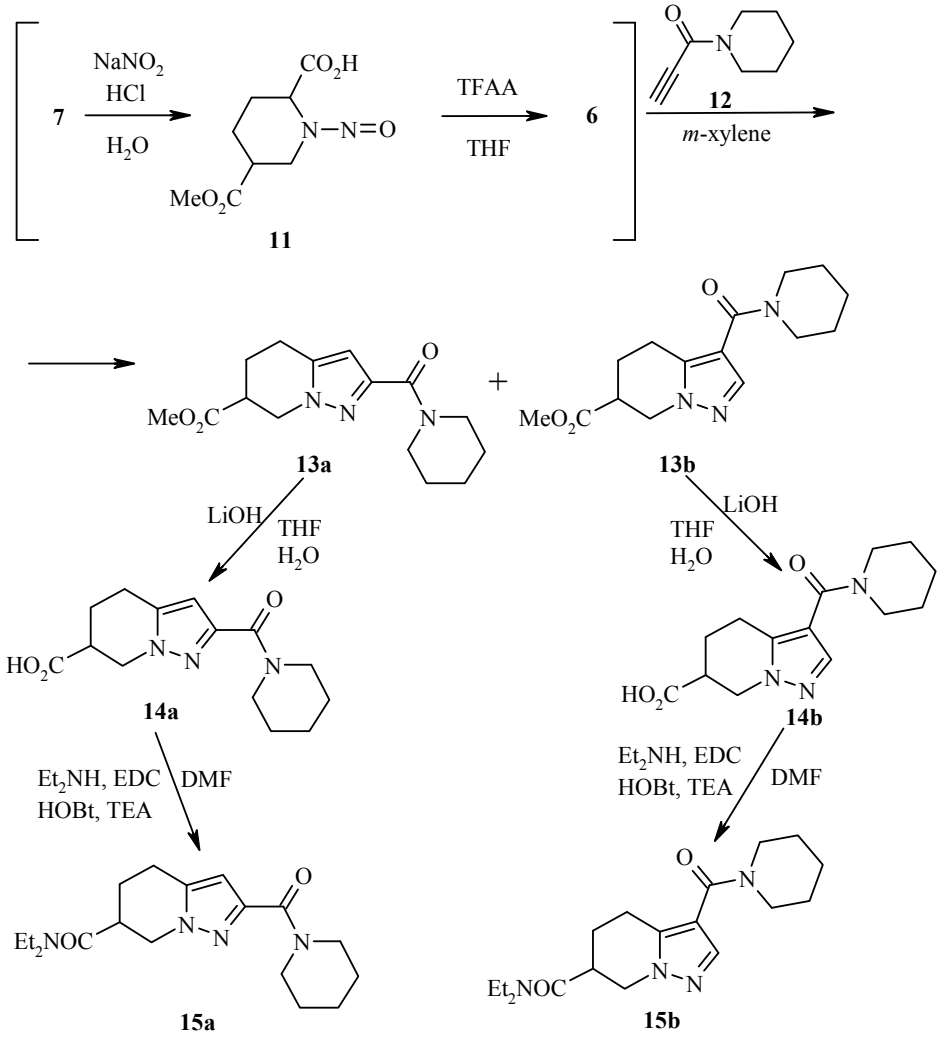
Route B is based on 1,3-dipolar cycloaddition of sydnones **6** to acetylenes. Although successful 1,3-dipolar cycloaddition of sydnone **6** to olefins [17], acetylenes [18], and propargylic acid esters [13, 19] is documented, there is no literature precedent of such reaction with propargylic acid amides. To enable the differentiation of the carboxylic amide at the 2- or 3-position from the ester at 6-position, we chose sydnone **6** 1,3-dipolar cycloaddition to propargylic amides as our approach.

The synthesis of key intermediate **2** began with the preparation of piperidine-2,5-dicarboxylic acid 5-methyl ester (**7**). According to the literature procedure [20], pyridine-2,5-dicarboxylic acid dimethyl ester (**8**) can be hydrogenated to piperidine **9** and then converted to compound **7**.



Although the described method is suitable for preparation of compound **7**, we found that saturation of the pyridine ring of compound **10** in the last step is more convenient. Dimethyl ester **8** was converted to monomethyl ester **10** [21] and then hydrogenated to provide the target piperidine **7**, which was used without purification.

Sydnone **6** was readily prepared in two steps. Piperidine-2-carboxylic acid **7** was converted to *N*-nitroso-piperidine **11**, treatment of which with trifluoroacetic anhydride (TFAA) according to the literature procedure [13, 17] led to sydnone **6**. 1,3-Dipolar cycloaddition of sydnone **6** to 1-piperidin-1-yl-propynone (**12**) led to the formation of two regioisomers **13a** and **13b,** which were easily separated by column chromatography on silica gel to give the desired compounds **13a** and **13b** in ~1:2 ratio in overall yield of 30% in four steps. The alkaline hydrolysis of esters **13a** and **13b** led to the key intermediates **14a** and **14b** in good yield.



The obtained acids **14a** and **14b** can be used in the parallel synthesis of different amides, which we exemplified by preparing diethylamides **15a** and **15b**.

In conclusion, a method for preparing differentiated diamides of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-2,6- and -3,6-dicarboxylic acids, suitable for parallel synthesis, has been elaborated.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury (200 MHz, compounds **13a**,**b**, **14a**,**b**) and Varian MR (400 MHz, compounds **15a**,**b**) spectrometers in $CDCl_3$. Chemical shifts are referenced to HMDS as the internal standard (δ = 0.05 ppm) or using the signal of the residual protonated solvent (δ = 7.26 ppm). High-resolution mass spectra analyses were performed using a Micromass Q-TOF Micro quadrupole time-of-flight high-resolution mass spectrometer with ESI ionization. Leucine enkephalin was used as internal lock mass for accurate mass calculation (*m/z* 566.2771). LC-mass spectra analyses were performed on a Shimadzu Prominence system connected to the Applied Biosystems API 2000 mass spectrometer (atmospheric pressure ionization).

Reagents and solvents were purchased from Aldrich, Acros and Alfa Aesar Chemical Industries. Pyridine-2,5-dicarboxylic acid 5-methyl ester hydrogen chloride (**10**) was prepared from pyridine-2,5-dicarboxylic acid dimethyl ester (**8**) according to the literature procedure [21].

2-(Piperidin-1-ylcarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-6-carboxylic Acid Methyl Ester (**13a**) **and 3-(Piperidin-1-ylcarbonyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyridine-6-carboxylic Acid Methyl Ester** (**13b**). Pyridine-2,5-dicarboxylic acid 5-methyl ester hydrogen chloride (**10**) (2.0 g, 9.2 mmol) was dissolved in a mixture of AcOH (40 ml) and MeOH (5 ml), and 10% Pd/C (0.53 g, 0.5 mmol) was added. Hydrogenation was carried out at room temperature at 10 atm for 24 h. The reaction mixture was filtered through Celite, washed with EtOAc, and evaporated to give 0.77 g of the **piperidine-2,5-dicarboxylic acid 5-methyl ester** (**7**) as a white solid which was used without purification in the next step. LC–MS, *m/z*: 188 $[M+H]^+$.

To a solution of methyl ester **7** in water (5 ml) at 0°C, concentrated hydrochloric acid (0.6 ml) was added, followed by $NaNO_2$ (0.885 g, 12.8 mmol) in small portions. The mixture was stirred at 0°C for 1 h, extracted with $CHCl_3$, dried over Na_2SO_4, filtered, and evaporated under reduced pressure at 30–35°C. The residue containing **1-nitroso-piperidine-2,5-dicarboxylic acid 5-methyl ester** (**11**) was immediately used in the next step.

To a stirred solution of compound **11** in dry THF (20 ml) at 0°C under argon atmosphere, a solution of trifluoroacetic anhydride (1 ml, 7 mmol) in THF (5 ml) was added dropwise. The mixture was stirred at 0°C for 5 h and then 16 h at room temperature. The solvent was evaporated and the crude material diluted with EtOAc and stirred with anhydrous K_2CO_3 (1 g). The mixture was filtered through a pad of silica gel, and the filtrate was evaporated. The obtained brownish oil containing **6-(methoxycarbonyl)-4,5,6,7-tetra-hydro[1,2,3]oxadiazolo-[3,4-*a*]pyridin-8-ium-3-olate** (**6**) was used in the next step without purification.

To a stirred solution of compound **6** in *m*-xylene (5 ml), propargylic acid amide **12** [22] (1.26 g, 9.2 mmol) was added, the reaction mixture was heated at 140°C for 8 h and evaporated; the residue was purified by flash chromatography on silica gel (eluent hexane–ethyl acetate, 1:1 to 1:4) to obtain 0.55 g of compound **13a** and 0.25 g of compound **13b** as oils. The overall yield of both products together was 30% (over 4 steps).

Compound 13a. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.65 (6H, m, 3',4',5'-CH_2 piperidine); 1.85-2.05 (1H, m) and 2.20–2.26 (1H, m, 5-CH_2); 2.74–3.06 (3H, m, 4-CH_2, 6-CH); 3.63–3.74 (4H, m, 2',6'-CH_2 piperidine); 3.71 (3H, s, OCH_3); 4.22 (1H, dd, *J* = 13.2, *J* = 8.8) and 4.37 (1H, dd, *J* = 13.2, *J* = 5.9, 7-CH_2); 6.25 (1H, s, H-3). Found: *m/z* 292.1659 $[M+H]^+$. $C_{15}H_{22}N_3O_3$. Calculated: M 292.1661.

Compound 13b. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.58–1.63 (6H, m, 3',4',5'-CH_2 piperidine); 1.87-2.06 (1H, m) and 2.25–2.34 (1H, m, 5-CH_2); 2.82–3.21 (3H, m, 4-CH_2, 6-CH); 3.56–3.62 (4H, m, 2',6'-CH_2 piperidine); 3.74 (3H, s, OCH_3); 4.24 (1H, dd, *J* = 13.2, *J* = 8.8) and 4.40 (1H, dd, *J* = 13.2, *J* = 5.9, 7-CH_2); 7.48 (1H, s, H-2). Found: *m/z* 292.1659 $[M+H]^+$. $C_{15}H_{22}N_3O_3$. Calculated: M 292.1661.

2-(Piperidin-1-ylcarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-6-carboxylic Acid (**14a**). To a solution of **13a** (58 mg, 0.20 mmol) in THF (1 ml), water (3 ml) was added followed by $LiOH \cdot H_2O$ (9 mg, 0.22 mmol), and the mixture was stirred at room temperature for 2 h. The THF was evaporated, and the water layer was acified with 10% HCl and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and evaporated to give 55 mg (99%) of the desired acid **14a** as a yellow oil. ^{1}H NMR spectrum, δ, (ppm)

(*J*, Hz): 1.50–1.74 (6H, m, 3',4',5'-CH_2 piperidine); 2.01–2.28 (2H, m, 5-CH_2); 2.70–3.07 (3H, m, 4-CH_2, 6-CH); 3.69–3.77 (4H, m, 2',6'-CH_2 piperidine); 4.24–4.38 (2H, m, 7-CH_2); 6.30 (1H, s, H-3); 7.78 (1H, br. s, OH). Mass spectrum, *m/z*: 278 $[M+H]^+$.

3-(Piperidin-1-ylcarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-6-carboxylic Acid (**14b**) was synthesized in the same manner as compound **14a** from ester **13b** (65 mg, 0.22 mmol) to give 48 mg (78%) of acid **14b** as a yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.75 (6H, m, 3',4',5'-CH_2 piperidine); 1.98-2.29 (2H, m, 5-CH_2); 2.81–3.18 (3H, m, 4-CH_2, 6-CH); 3.51–3.70 (4H, m, 2',6'-CH_2 piperidine); 4.26–4.44 (2H, m, 7-CH_2); 7.51 (1H, s, H-2); 7.78 (1H, br. s, OH). Mass spectrum, *m/z*: 278 $[M+H]^+$.

2-(Piperidin-1-ylcarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-6-carboxylic Acid Diethylamide (**15a**). To a solution of acid **14a** (55 mg, 0.20 mmol), HOBt·H_2O (41 mg, 0.24 mmol), EDC (46 mg, 0.24 mmol) in DMF (1.5 ml), diethylamine (25 μl, 0.24 mmol) and TEA (30 μl, 0.24 mmol) were added. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography on silica gel (eluent hexane–ethyl acetate, 1:1) to give 18 mg (27%) of the desired compound **15a** as an oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14 (3H, t, *J* = 7.4, $NCH_2C\underline{H}_3$); 1.23 (3H, t, *J* = 7.4, $NCH_2C\underline{H}_3$); 1.57–1.70 (6H, m, 3',4',5'-CH_2 piperidine); 2.03–2.09 (2H, m, 5-CH_2); 2.73–2.82 (1H, m, 6-CH); 3.02 (1H, dt, *J* = 16.8, *J* = 4.3, 4-CH); 3.07–3.15 (1H, m, 4-CH); 3.31–3.53 (4H, m, $2NC\underline{H}_2CH_3$); 3.64-3.72 (2H, m) and 3.78–3.85 (2H, m, 2',6'-CH_2 piperidine); 4.24–4.33 (2H, m, 7-CH_2); 6.32 (1H, s, H-3). Found: *m/z* 333.2281 $[M+H]^+$. $C_{18}H_{29}N_4O_2$. Calculated: M 333.2291.

3-(Piperidin-1-ylcarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-6-carboxylic Acid Diethylamide (**15b**) was synthesized in the same manner as compound **15a** from acid **14b** (48 mg, 0.17 mmol). Compound **15b** was obtained as a yellow oil, yield 21 mg (36%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 (3H, t, *J* = 7.4, $NCH_2C\underline{H}_3$); 1.22 (3H, t, *J* = 7.4, $NCH_2C\underline{H}_3$); 1.59–1.71 (6H, m, 3',4',5'-CH_2 piperidine); 1.97–2.11 (2H, m, 5-CH_2); 2.89–2.96 (1H, m, 6-CH); 3.06–3.14 (1H, m, 4-CH); 3.19 (1H, ddd, *J* = 18.0, *J* = 5.5, *J* = 2.4, 4-CH); 3.27–3.46 (4H, m, 2 $NC\underline{H}_2CH_3$); 3.60–3.62 (4H, m, 2',6'-CH_2 piperidine); 4.23–4.33 (2H, m, 7-CH_2); 7.48 (1H, s, H-2). Found: *m/z* 333.2281 $[M+H]^+$. $C_{18}H_{29}N_4O_2$. Calculated: M 333.2291.

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