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Easy One-Pot Synthesis of Fused Heterocycles from 1,2-Diaza-1,3-dienes

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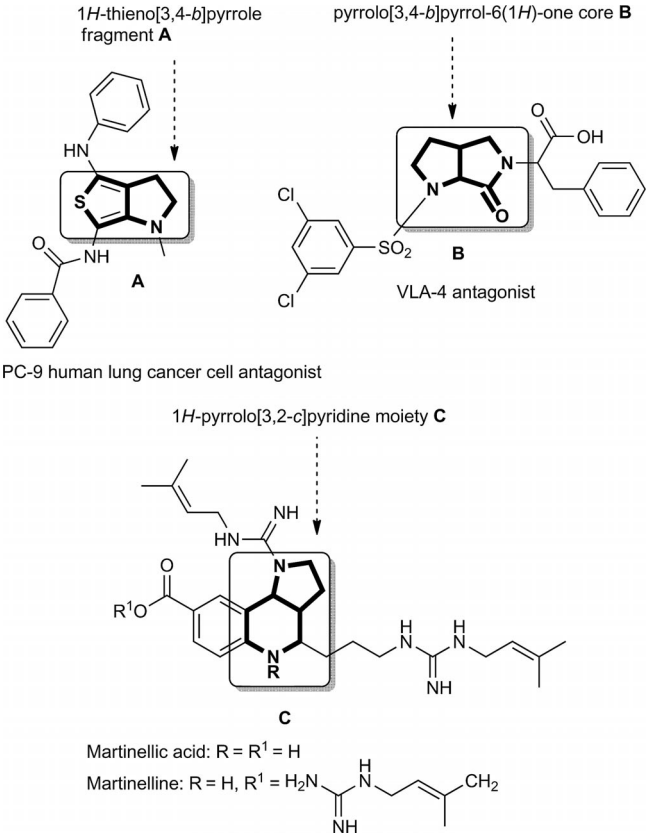
A base-promoted chemoselective synthesis of 6a-hydroxy-6,6a-dihydro-1*H*-thieno[3,4-*b*]pyrrole-3,3a(4*H*)-dicarboxylates, 5-(2-furylmethyl)-6a-hydroxy-6-oxo-4,5,6,6a-tetrahydropyrrolo[3,4-*b*]pyrrole-3,3a(1*H*)-dicarboxylates, and 5-benzyl-7a-hydroxy-1,4,5,6,7,7a-hexahydro-3a*H*-pyrrolo[3,2-*c*]pyridine-3,3a-dicarboxylates starting from diazadienes and heterocycles containing an activated methine group has been developed. This transformations proceeds by Michael addition/5-*exo* cyclization sequence.

Introduction

Because of the widespread application of structurally novel heterocycles in drug development, nitrogen-containing heterocyclic compounds have received considerable attention due to their applications ranging from medicinal chemistry[1] to materials science.[1a,2] Among them, the pyrroline/pyrrolidine fragment is a common structural motif present in several inhibitors and antagonists.[3] For example, the pyrroline/pyrrolidine core is contained in a series of HIV-1 reverse transcriptases that display the greatest degree of inhibition,[4] or in potent dopamine D_4 antagonists that are selective over D_2 and in α_1 receptors employed in the treatment of various disorders such as ADHD, Parkinson's disease and sexual dysfunction,[5] or in histamine H3 receptor antagonists.[6] Pyrrolines/pyrrolidines feature also in fused polycyclic structures of many bioactive molecules: the 1*H*-thieno[3,4-*b*]pyrrole fragment **A** is present in inhibitors of the biotin-dependent wheat acetyl-CoA carboxylase,[7] or in an antitumor agent;[8] the pyrrolo[3,4-*b*]pyrrol-6(1*H*)-one **B** is the core of a potent 5-HT_{2C} agonist,[9] of a peptidyl VLA-4 antagonist,[10] and of an inhibitor for glycosyltransferase enzymes (Scheme 1).[11] Particular attention is turned to the 1*H*-pyrrolo[3,2-*c*]pyridine moiety **C** that is a core structure in some biologically active natural products such as martinellic acid and martinelline (Scheme 1).[12] They are the first nonpeptide natural product bradykinin receptor antagonists. These compounds also exhibit potent antibiotic activities against both Gram-positive and Gram-negative bacteria, and they also have an affinity for several G-proteine coupled receptors.[13] Consequently, the 1*H*-pyrrolo[3,2-*c*]pyridine moiety **C** has been a significant subject of synthetic studies of biologically active compounds.[14] Based on our experience, we have planned a new simple methodology for the construction of pyrrolines containing



Scheme 1. Representative examples of fused polycyclic structures containing a pyrroline/pyrrolidine core with relevant biological activities.

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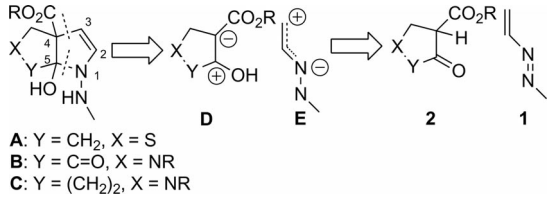
fused polycyclic structures that exploit the versatility of 1,2-diaza-1,3-dienes (DDs) in the syntheses of several five- and six-membered azaheterocycles.[15]

Our analysis of the fused polycyclic structures (Scheme 2) emphasizes two strategic disconnections of the pyrrolidine ring, along the carbon–carbon C(3)–C(4) and the carbon–nitrogen C(5)–N(1) bonds. This reveals two subunits that trace the left half back to the pertinent heterocyclic anion **D** and the right half to the zwitterionic hydrazone **E**. Fragment **D** can be correlated to the pertinent heterocycles **2** containing both an activated methine group and a carbonyl moiety, and fragment **E** to the azo-ene system of DD **1**. The high reactivity of these latter compounds, related to the electrophilicity of the terminal carbon atom of the heterodiene system,[16] permits the C(3)–C(4) junction by 1,4-addition (Michael-type) of the activated methine group of **2** to DD **1**. Subsequent regioselective intramolecular cyclization by nucleophilic attack of one of the nitrogen atoms deriving from the former azo group furnishes the second connection C(5)–N(1).



Scheme 2. Retrosynthetic analysis of fused polycyclic structures containing a pyrroline/pyrrolidine core.

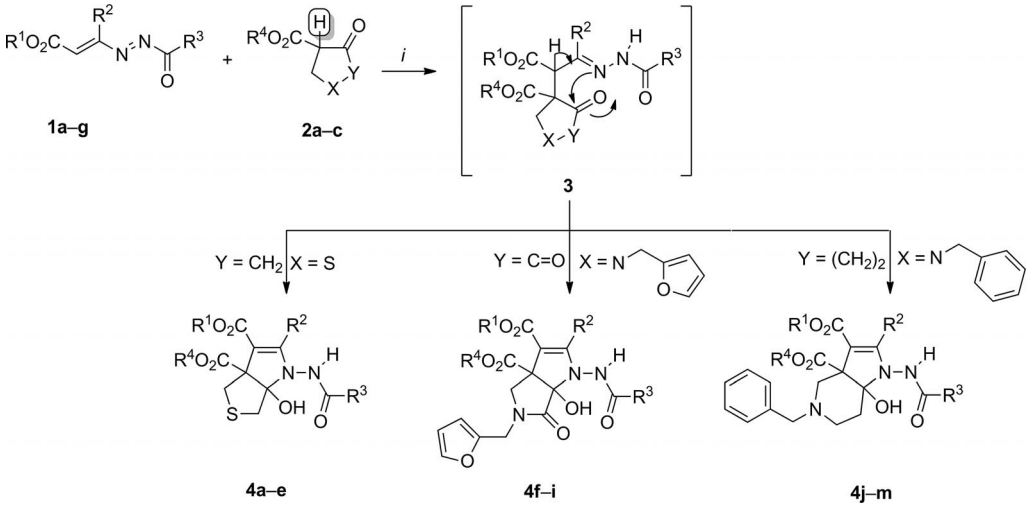
Here, we have verified that our hypothesis to construct the 1*H*-thieno[3,4-*b*]pyrrole fragment **A**, the pyrrolo[3,4-*b*]-pyrrol-6(1*H*)-one moiety **B**, or the 1*H*-pyrrolo[3,2-*c*]pyridine core **C** is confirmed by allowing DDs to react, under basic conditions, with the pertinent heterocycles containing an activated methine group through a domino process.

Results and Discussion

DDs **1a**–**g** easily reacted in tetrahydrofuran (THF) at room temperature with methyl 4-oxotetrahydrothiophene-3-carboxylate (**2a**) or ethyl 1-(2-furylmethyl)-4,5-dioxopyrrolidine-3-carboxylate (**2b**) in the presence of a catalytic amount of sodium hydride to give in a one-pot reaction 6a-hydroxy-6,6a-dihydro-1*H*-thieno[3,4-*b*]pyrrole-3,3a(4*H*)-dicarboxylates **4a**–**e**, or 5-(2-furylmethyl)-6a-hydroxy-6-oxo-4,5,6,6a-tetrahydropyrrolo[3,4-*b*]pyrrole-3,3a(1*H*)-dicarboxylates **4f**–**i**, respectively, in rather good yields (Scheme 3, Table 1). Under the same conditions, the reaction between DD **1a** and methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (**2c**) did not work, and, by increasing the amount of the sodium hydride until stoichiometric, a complicated mixture was obtained. This occurrence is probably due to the concomitant acid/base reaction of the hydrochloride of **2c** with the base.

Then, different bases were tested for this reaction (see Supporting Information). Sodium methoxide has shown the same behaviour of sodium hydride, sodium acetate (1.0 and 2.0 equiv.) has reacted with DDs giving the corresponding α-acetoxy-hydrazones, whereas potassium carbonate (2.0 and 5.0 equiv.) was ineffective. Only the strongly basic resin Merck 104767 ion exchanger III has furnished the desired 3-ethyl 3a-methyl 1-[(aminocarbonyl)amino]-5-benzyl-7a-hydroxy-2-methyl-1,4,5,6,7,7a-hexahydro-3a*H*-pyrrolo[3,2-*c*]-pyridine-3,3a-dicarboxylate (**4j**). The best result in term of yield (66%) and reaction time (2.0 h) was obtained by employing 1.5 equiv. of resin in THF, at room temperature. The use of these optimized conditions was then extended to the reaction of other DDs **1b**–**d** with **2c** to obtain the corresponding 3a*H*-pyrrolo[3,2-*c*]pyridines **4k**–**m** in 49, 52 and 55% yields, respectively (Scheme 3, Table 1).

The plausible mechanism of these reactions involves the preliminary nucleophilic attack (Michael-type) of the acti-



Scheme 3. Synthesis of 6a-hydroxy-6,6a-dihydro-1*H*-thieno[3,4-*b*]pyrrole-3,3a(4*H*)-dicarboxylates **4a**–**e**, 5-(2-furylmethyl)-6a-hydroxy-6-oxo-4,5,6,6a-tetrahydropyrrolo[3,4-*b*]pyrrole-3,3a(1*H*)-dicarboxylates **4f**–**i**, and 5-benzyl-7a-hydroxy-1,4,5,6,7,7a-hexahydro-3a*H*-pyrrolo[3,2-*c*]pyridine-3,3a-dicarboxylates **4j**–**m**. (i) NaH (0.1 equiv.), room temp., THF for the reaction between **1a**–**e** with **2a** and **1a**,**c**,**f**, **g** with **2b**. Resin Merck 104767 ion exchanger III (1.5 equiv.), room temp., THF for the reaction between **1a**–**d** with **2c**.

Table 1. Yields and reaction times for the synthesis of 6a-hydroxy-6,6a-dihydro-1*H*-thieno[3,4-*b*]pyrrole-3,3a(4*H*)-dicarboxylates **4a–e**, 5-(2-furylmethyl)-6a-hydroxy-6-oxo-4,5,6,6a-tetrahydropyrrolo-[3,4-*b*]pyrrole-3,3a(1*H*)-dicarboxylates **4f–i**, and 5-benzyl-7a-hydroxy-1,4,5,6,7,7a-hexahydro-3a*H*-pyrrolo[3,2-*c*]pyridine-3,3a-dicarboxylates **4j–m**.

1	R^1	R^2	R^3	2	R^4	X	Y	4	Yield [%][a]	Reaction time [h]
1a	Et	Me	NH_2	**2a**	Me	S	CH_2	**4a**	70	4.0
1b	*i*Pr	Me	NH_2	**2a**	Me	S	CH_2	**4b**	41	5.0
1c	allyl	Me	NH_2	**2a**	Me	S	CH_2	**4c**	59	4.0
1d	Et	Me	NHPh	**2a**	Me	S	CH_2	**4d**	81	5.5
1e	Me	Me	O*t*Bu	**2a**	Me	S	CH_2	**4e**	55	5.0
1a	Et	Me	NH_2	**2b**	Et		C=O	**4f**	59	6.0
1c	allyl	Me	NH_2	**2b**	Et		C=O	**4g**	70	6.0
1f	Me	Et	NH_2	**2b**	Et		C=O	**4h**	75	6.0
1g	Et	*n*Bu	NH_2	**2b**	Et		C=O	**4i**	83	6.0
1a	Et	Me	NH_2	**2c**	Me		$(CH_2)_2$	**4j**	66	2.0
1b	*i*Pr	Me	NH_2	**2c**	Me		$(CH_2)_2$	**4k**	49	2.0
1c	allyl	Me	NH_2	**2c**	Me		$(CH_2)_2$	**4l**	52	3.5
1d	Et	Me	NHPh	**2c**	Me		$(CH_2)_2$	**4m**	55	4.0

[a] Isolated yields based on starting DDs **1**.

vated methine group of compounds **2a–c** to the terminal carbon atom of the azo-ene system of **1** with formation of the non-isolable hydrazone intermediates **3** (Scheme 3). The subsequent regioselective 5-*exo* cyclization that converts **3** into the final products **4a–m** provides a further conjugate nucleophilic attack of the hydrazone sp^2-nitrogen atom to the oxo function derived from the starting heterocycles **2**. This process is due to the base-promoted loss of the hydrogen atom originally located in 4-position of the azo-ene system, activated by the presence of electron-withdrawing groups in α-position such as ester and hydrazone groups.

Conclusions

An efficient domino one-pot methodology toward chemoselective syntheses of 1*H*-thieno[3,4-*b*]pyrrolines **4a–e**, 6-oxo-pyrrolo[3,4-*b*]pyrrolines **4f–i**, and pyrrolo[3,2-*c*]-pyridines **4j–m** by starting from DDs **1** and heterocycles containing an activated methine group **2** has been developed. This transformation proceeds by a Michael addition/5-*exo* cyclization sequence. The obtained products represent interesting scaffolds deployed with a variety of functional groups as potential pharmacophores (ester, hydroxy, carbamate, urea etc.) that may exhibit enzyme or receptor-based activity. All these reactions proceed under mild conditions by using easily available starting materials without complicated workup procedures.

Experimental Section

General Procedure for the Synthesis of 6a-Hydroxy-6,6a-dihydro-1*H*-thieno[3,4-*b*]pyrrole-3,3a(4*H*)-dicarboxylates 4a–e, 5-(2-Furylmethyl)-6a-hydroxy-6-oxo-4,5,6,6a-tetrahydropyrrolo[3,4-*b*]pyrrole-3,3a(1*H*)-dicarboxylates 4f–i, and 5-Benzyl-7a-hydroxy-1,4,5,6,7,7a-hexahydro-3a*H*-pyrrolo[3,2-*c*]pyridine-3,3a-dicarboxylates 4j–m: To a magnetically stirred solution of DDs **1a–g** (1.0 mmol) as a mixture of (*E*)/(*Z*) isomers[17] and methyl 4-oxotetrahydrothiophene-3-carboxylate (**2a**) or ethyl 1-(2-furylmethyl)-4,5-dioxopyrrolidine-3-carboxylate (**2b**) in THF (20 mL) a catalytic amount of sodium hydride (0.1 mmol) was added. In the case of the reactions between DDs **1a–d** with methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (**2c**), DDs **1a–d** and **2c** were dissolved in THF (20 mL), and the strongly basic resin Merck 104767 ion exchanger III (1.5 equiv.) was added under gently magnetic stirring. The reaction mixture was allowed to stand at room temperature until the starting materials had disappeared (monitored by TLC). Then, the reaction solvent was evaporated under reduced pressure, and the residues were chromatographed (silica gel column; elution mixture: 0.8 ethyl acetate/0.2 cyclohexane) to obtain the corresponding pure 6a-hydroxy-6,6a-dihydro-1*H*-thieno[3,4-*b*]pyrrole-3,3a(4*H*)-dicarboxylates **4a–e**, 5-(2-furylmethyl)-6a-hydroxy-6-oxo-4,5,6,6a-tetrahydropyrrolo[3,4-*b*]pyrrole-3,3a(1*H*)-dicarboxylates **4f–i**, and 5-benzyl-7a-hydroxy-1,4,5,6,7,7a-hexahydro-3a*H*-pyrrolo[3,2-*c*]pyridine-3,3a-dicarboxylates **4j–m** that were crystallized from diethyl ether/light petroleum ether (40–60 °C).

Data for 3-Ethyl 3a-Methyl 1-[(Aminocarbonyl)amino]-6a-hydroxy-2-methyl-6,6a-dihydro-1*H*-thieno[3,4-*b*]pyrrole-3,3a(4*H*)-dicarboxylate (4a): Yield 242.0 mg (70%), obtained as white solid, m.p. 174–176 °C. IR (nujol): $\tilde{\nu}_{max}$ = 3426, 3351, 3304, 3230, 1733, 1725, 1703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, 3 H, J = 7.2 Hz, OCH_2CH_3), 2.21 (s, 3 H, CH_3), 2.95 (d, 1 H, J = 12.8 Hz, CHS), 3.00 (d, 1 H, J = 12.8 Hz, CHS), 3.12 (d, 1 H, J = 12.8 Hz, CHS), 3.70 (s, 3 H, OCH_3), 4.02–4.14 (m, 3 H, OCH_2CH_3 and CHS), 5.98 and 6.08 (2 br. s, 2 H, NH_2), 7.66 (br. s, 1 H, OH), 7.82 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7 (q), 14.3 (q), 39.4 (t), 40.1 (t), 52.9 (q), 59.6 (t), 65.3 (s), 102.8 (s), 108.0 (s), 160.8 (s), 161.1 (s), 165.0 (s), 171.7 (s) ppm. MS: *m*/*z* (%) = 345 (12) [M^+], 327 (15), 298 (7), 268 (100), 252 (12), 239 (14), 222 (27), 209 (21), 197 (24), 180 (22), 164 (26), 152 (25), 136 (35). $C_{13}H_{19}N_3O_6S$ (345.37): calcd. C 45.21, H 5.54, N 12.17; found C 45.32, H 5.49, N 12.24.

Data for Diethyl 1-[(Aminocarbonyl)amino]-5-(2-furylmethyl)-6a-hydroxy-2-methyl-6-oxo-4,5,6,6a-tetrahydropyrrolo[3,4-*b*]pyrrole-3,3a(1*H*)-dicarboxylate (4f): Yield 257.5 mg (59%), obtained as white solid, m.p. 142–144 °C. IR (nujol): $\tilde{\nu}_{max}$ = 3457, 3293, 3205, 1749, 1721, 1689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, 3 H, J = 7.2 Hz, OCH_2CH_3), 1.25 (t, 3 H, J = 7.2 Hz, OCH_2CH_3), 2.28 (s, 3 H, CH_3), 4.04–4.19 (m, 4 H, 2 OCH_2CH_3), 4.21–4.26 (m, 2 H, NCH_2), 4.33 (d, 1 H, J = 11.6 Hz, NCH_2furyl), 4.55 (d, 1 H, J = 11.2 Hz, NCH_2furyl), 5.64 (br. s, 1 H, NH_2), 6.24 (d, 1 H, J = 3.2 Hz, furyl), 6.30 (dd, 1 H, J = 3.2 Hz, J = 2.0 Hz, furyl), 7.25 (br. s, 1 H, NH_2), 7.35 (dd, 1 H, J = 1.6 Hz, J = 1.2 Hz, furyl), 8.39 (br. s, 1 H, OH), 9.68 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8 (q), 14.1 (q), 14.3 (q), 39.7 (t), 51.3 (t), 57.1 (s), 59.4 (t), 61.6 (t), 95.2 (s), 100.2 (s), 109.3 (s), 110.7 (d), 143.1 (d), 148.4 (d), 160.3 (s), 162.9 (s), 164.7 (s), 167.9 (s), 168.3 (s) ppm. MS: *m*/*z* (%) = 420 (4), 393 (10), 327 (12), 302 (17), 268 (100), 252 (18), 225 (45), 210 (43), 197 (44), 164 (57), 136 (67). $C_{19}H_{24}N_4O_8$ (436.41): calcd. C 52.29, H 5.54, N 12.84; found C 52.38, H 5.57, N 12.75.

Data for 3-Ethyl 3a-Methyl 1-[(Aminocarbonyl)amino]-5-benzyl-7a-hydroxy-2-methyl-1,4,5,6,7,7a-hexahydro-3a*H*-pyrrolo[3,2-*c*]pyridine-3,3a-dicarboxylate (4j): Yield 285.5 mg (66%), obtained as white solid, m.p. 142–144 °C. IR (nujol): $\tilde{\nu}_{max}$ = 3457, 3345, 3189, 1749, 1725, 1689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, 3 H, J = 7.2 Hz, OCH_2CH_3), 1.23–1.41 (m, 2 H, NCH_2CH_2), 1.88 (d, 1 H, J = 12.0 Hz, NCH_2C), 2.18 (s, 3 H, CH_3), 2.51–2.63 (m, 2 H, NCH_2CH_2), 2.79 (br. s, 1 H, OH), 3.46 (d, 1 H, J = 11.6 Hz, NCH_2C), 3.56 (s, 2 H, NCH_2Ph), 3.71 (s, 3 H, OCH_3), 4.11 (q, 2

H, J = 7.2 Hz, OCH_2CH$_3$), 5.66 (br. s, 2 H, NH_2), 7.21–7.36 (m, 6 H, Ph and NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3 (q), 13.7 (q), 29.5 (t), 52.1 (q), 57.1 (t), 58.2 (t), 59.4 (s), 60.2 (t), 61.9 (t), 93.7 (s), 106.0 (s), 126.9 (d), 127.9 (d), 128.7 (d), 127.9 (s), 128.7 (d), 137.9 (s), 158.7 (s), 160.2 (s), 164.8 (s), 172.1 (s) ppm. MS: *m*/*z* (%) = 432 (2) [M^+], 414 (30), 373 (20), 355 (100), 342 (73), 310 (12), 295 (18), 249 (25), 224 (78), 205 (41), 191 (78), 178 (50), 164 (42), 148 (36), 118 (90). $C_{21}H_{28}N_4O_6$ (432.27): calcd. C 58.32, H 6.53, N 12.96; found C 58.23, H 6.56, N 13.03.

Supporting Information (see footnote on the first page of this article): Experimental details, spectroscopic data, and screening of different reaction conditions for the synthesis of **4j**.

Acknowledgments

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