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Convenient syntheses of dihydropyrrolo[2′,1′:3,4]pyrazino- and dihydropyrrolo[2′,1′:3,4][1,4]diazepino-[2,1-*a*]isoindolones

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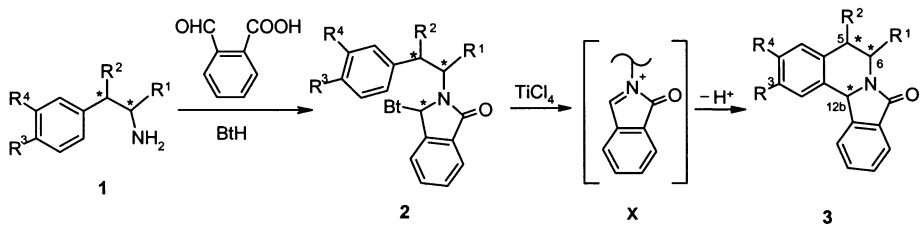
Abstract—Dihydropyrrolo[2′,1′:3,4]pyrazino[2,1-*a*]isoindolones **10a**–**10c** were obtained in 76–81% yields by the reaction of 2-(1*H*-pyrrol-1-yl)ethylamine **8** with 2-formylbenzoic acids **9a**, **9b** or 2-acetylbenzoic acid **9c** via *N*-acyliminium cation aromatic cyclizations. Similarly, dihydropyrrolo[2′,1′:3,4][1,4]diazepino[2,1-*a*]isoindolones **12a**, **12b** were prepared in one-pot reactions from 3-(1*H*-pyrrol-1-yl)propylamine **11** and 2-formylbenzoic acids **9a**, **9b**.

[1,4]Diazaheterocycles, such as quinoxalines and [1,4]benzodiazepines, are biologically active. For example, isoindoloquinoxalines are antihypertensive;[1] pyrrolo[1,4]benzodiazepines exhibit antitumor and antibiotic activities[2] and cytotoxicity.[3]

Syntheses of pyrroloisoquinolinones over recent years have included *N*-acyliminium cyclization as a key ring-forming step.[4] We recently reported the preparation of 5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-ones **3** in two steps from 2-aryl-1-ethanamines **1**, benzotriazole and 2-formylbenzoic acid via Lewis acid promoted *N*-acyliminium cation aromatic cyclization using benzotriazole methodology (Scheme 1).[5] Using 2-(1*H*-pyrrol-1-yl)ethylamine **8** or 3-(1*H*-pyrrol-1-yl)propylamine **11** in place of **1**, analogous methodology is now shown to give the dihydropyrrolo[2′,1′:3,4]pyrazino[2,1-*a*]isoindolones **10a**–**10c** and dihydropyrrolo[2′,1′:3,4][1,4]-diazepino[2,1-*a*]isoindolones **12a**, **12b** directly in one-pot reactions without need for the use of benzotriazole.

Ring systems **10** and **12** appear to be novel. Among their nearest analogues, dihydropyrrolo[2′,1′:3,4]pyrazino-[2,1-*a*]isoindolones (e.g. **4**) and dihydropyrrolo-[2′,1′:3,4][1,4]diazepino[2,1-*a*]isoindolones (e.g. **5**, **6**), were previously prepared in three steps from the substituted anilines or benzylamines via treatment of hydroxylactam intermediates with thionyl chloride in overall 28–90% yields (Fig. 1).[6] Similarly, indolodiazepinoisoindolone **7** was obtained in three steps from 1-(3-aminopropyl)-3-methylindole and phthalic anhydride.[7] Another paper reported a one-pot reaction of 2-(1*H*-pyrrol-1-yl)aniline and 2-formylbenzoic acid to give **4a**.[8]

2-(1*H*-Pyrrol-1-yl)ethylamine **8** and 3-(1*H*-pyrrol-1-yl)propylamine **11** were obtained by the reaction of pyrrole with 2-chloroethylamine hydrochloride or 3-chloropropylamine hydrochloride by reported procedures.[9] 3-Methylindole and 2-chloroethylamine hydrochloride similarly gave **14**. Compounds **8**, **11** and **14** were used as crude products for the subsequent cyclizations.



Scheme 1. (BtH = benzotriazole).

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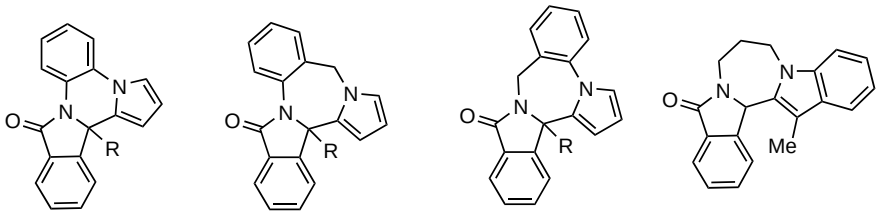


4a, R = H
4b, R = Et

5a, R = H
5b, R = Et

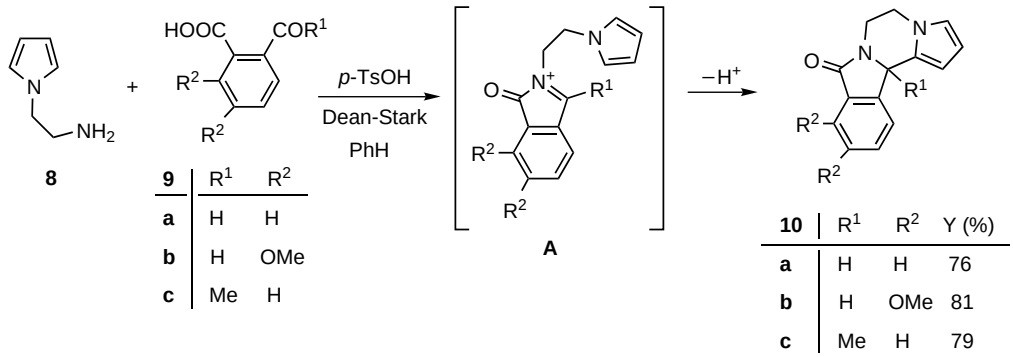
6a, R = H
6b, R = Et

7

Figure 1.

Dihydropyrrolo[2′,1′:3,4]pyrazino[2,1-*a*]isoindolones **10a**–**10c** were obtained in 76–81% yields by the reaction of 2-(1*H*-pyrrol-1-yl)ethylamine **8** with 2-formylbenzoic acids **9a**, **9b** or 2-acetylbenzoic acid **9c** in the presence of a catalytic amount of *p*-toluenesulfonic acid with a Dean–Stark apparatus to remove water formed (Scheme 2).[10] Compound **10a** was isolated as its hydrate, as determined by the ^{1}H NMR spectrum and microanalysis result. Structures of **10a**–**10c** are supported by their ^{1}H, ^{13}C NMR spectra and microanalysis. The ^{1}H NMR spectra show NC*H*-pyrrole singlet signals for **10a** and **10b** at 5.74 and 5.65 ppm, respectively. The reaction pathway is believed to involve the formation of transient hydroxylactam intermediates and subsequent generation of *N*-acyliminium cations **A**, which undergo intramolecular pyrrole cyclization to furnish **10a**–**10c**. Therefore, three new bonds are formed in one-step to generate the tetracyclic ring system.

Similarly, condensations of 2-formylbenzoic acids **9a** and **9b** with 3-(1*H*-pyrrol-1-yl)propylamine **11** afforded dihydropyrrolo[2′,1′:3,4][1,4]diazepino[2,1-*a*]isoindolones **12a** and **12b** in 76 and 66% yields, respectively. The NC*H*-pyrrole in **12a** and **12b** appear at 5.59 and 5.48 ppm, respectively, as a singlet. However, the reaction of **9c** with **11** did not give the desired tetracyclic ring system. The ^{1}H, ^{13}C NMR spectra show the disappearance of the methyl group and existence of two hydrogens attached to a carbon–carbon double bond. On consideration of GC–MS data [MS: 252 (M^+), 185, 159, 130, 107, 81 (base)], the structure was assigned to be 3-methylene-2-[3-(1*H*-pyrrol-1-yl)propyl]-1-isoindolinone **13** (MW: 252). Due to the positive NOE effect between H^a and H^c (7.68 ppm, doublet), H^a is believed to appear at the lower field (5.17 ppm, doublet); while H^b is at the higher field (4.69 ppm, doublet). The formation of **13** suggests a competitive reaction between deprotonation at the methyl group and deprotonation in the pyrrole ring in the transient intermediate (similar to **A**, R^1 = Me) and the first one is predominant (Scheme 3).

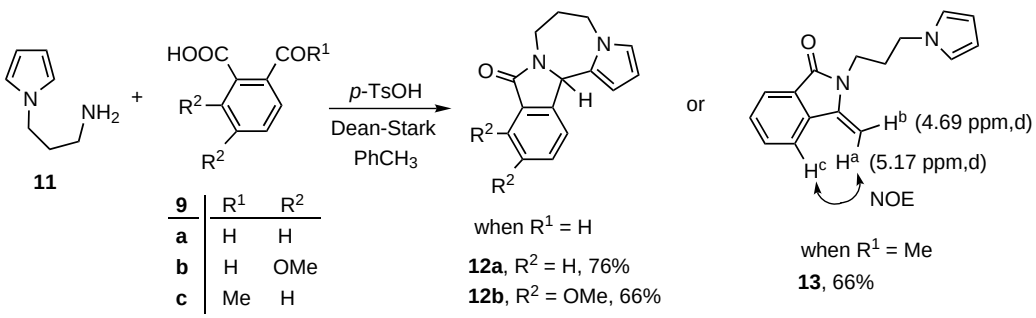


9	R^1	R^2
a	H	H
b	H	OMe
c	Me	H

A

10	R^1	R^2	Y (%)
a	H	H	76
b	H	OMe	81
c	Me	H	79

Scheme 2.



9	R^1	R^2
a	H	H
b	H	OMe
c	Me	H

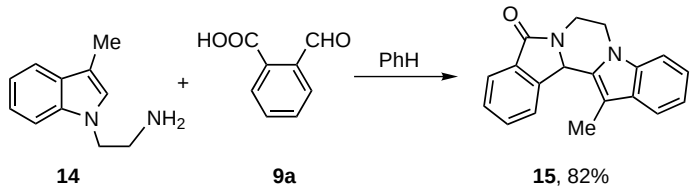
when R^1 = H
12a, R^2 = H, 76%
12b, R^2 = OMe, 66%

or

H^b (4.69 ppm,d)
H^c H^a (5.17 ppm,d)
NOE

when R^1 = Me
13, 66%

Scheme 3.



14 **9a** **15**, 82%

Scheme 4.

The reaction of 1-(3-aminoethyl)-3-methyl-indole **14** with 2-formylbenzoic acid **9a** afforded compound **15** in 82% yield (Scheme 4).

In summary, one-pot syntheses of dihydropyrrolo-[2′,1′:3,4]pyrazino[2,1-*a*]isoindolones **10a**–**10c** and dihydropyrrolo[2′,1′:3,4][1,4]diazepino[2,1-*a*]isoindolones **12a**, **12b** have been developed via *N*-acyliminium cation cyclizations.

References

1. Demerson, C. A.; Humber, L. G.; Ferland, J. M. US Patent 4,273,773, 1981; *Chem. Abstr*. **1981**, *95*, 115606f.
2. (a) Puvvada, M. S.; Forrow, S. A.; Hartley, J. A.; Stephenson, P.; Gibson, I.; Jenkins, T. C.; Thurston, D. E. *Biochemistry* **1997**, *36*, 2478–2484; (b) Barkley, M. D.; Cheatham, S.; Thurston, D. E.; Hurley, L. H. *Biochemistry* **1986**, *25*, 3021–3031; (c) Hurley, L. H.; Reck, T.; Thurston, D. E.; Langley, D. R.; Holden, K. G.; Hertzberg, R. P.; Hoover, J. R. E.; Gallagher, G., Jr.; Faucette, L. F.; Mong, S.-M.; Johnson, R. K. *Chem. Res. Toxicol*. **1988**, *1*, 258–268; (d) Baraldi, P. G.; Leoni, A.; Cacciari, B.; Manfredini, S.; Simoni, D.; Bergomi, M.; Menta, E.; Spinelli, S. *J. Med. Chem*. **1994**, *37*, 4329–4337.
3. Thurston, D. E.; Bose, D. S.; Howard, P. W.; Jenkins, T. C.; Leoni, A.; Baraldi, P. G.; Guiotto, A.; Cacciari, B.; Kelland, L. R.; Foloppe, M.-P.; Rault, S. *J. Med. Chem*. **1999**, *42*, 1951–1964.
4. (a) Garcia, E.; Arrasate, S.; Ardeo, A.; Lete, E.; Sotomayor, N. *Tetrahedron Lett*. **2001**, *42*, 1511–1513; (b) Padwa, A.; Hennig, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem*. **1998**, *63*, 1144–1155; (c) Allin, S. M.; James, S. L.; Martin, W. P.; Smith, T. A. D. *Tetrahedron Lett*. **2001**, *42*, 3943–3946; (d) Padwa, A.; Waterson, A. G. *J. Org. Chem*. **2000**, *65*, 235–244; (e) Lee, J. Y.; Lee, Y. S.; Chung, B. Y.; Park, H. *Tetrahedron* **1997**, *53*, 2449–2458.
5. Katritzky, A. R.; Mehta, S.; He, H.-Y. *J. Org. Chem*. **2001**, *66*, 148–152.
6. Othman, M.; Pigeon, P.; Netchitailo, P.; Daich, A.; Decroix, B. *Heterocycles* **2000**, *52*, 273–281.
7. von Harter, H. P.; Schindler, O. *Chimia* **1977**, *31*, 362–365.
8. Raines, S.; Chai, S. Y.; Palopoli, F. P. *J. Heterocycl. Chem*. **1976**, *13*, 711–716.
9. de Pablo, M. S.; Gandasegui, T.; Vaquero, J. J.; Navio, J. L. G.; Alvarez-Builla, J. *Tetrahedron* **1992**, *48*, 8793–8800.
10. General experimental part: ^{1}H (300 MHz), ^{13}C (75 MHz) NMR and NOE spectra were recorded on a Gemini 300 NMR spectrometer in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as the internal reference). Column chromatography was performed on silica gel (200–425 mesh). All of the reactions were carried out under N_2.
Typical procedure: A mixture of the primary amine **8**, **11** or **14** (1.2 mmol), 2-formylbenzoic acids **9a**, **9b** or 2-acetylbenzoic acid **9c** (1 mmol) and p-$MeC_6H_4SO_3H{\cdot}H_2O$ (0.02 g, 0.1 mmol) was refluxed in benzene (for **10a**–**10c** and **15**) or toluene (for **12a**, **12b** and **13**) for 8–16 h using a Dean–Stark apparatus. After being cooled, most of the solvent was evaporated in vacuo and the residue was diluted in EtOAc. The organic phase was washed with 1 M NaOH, brine and dried over anhydrous Na_2SO_4. After removal of solvents in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (4:1 to 2:1) to give the final product.
The melting points are: **10a**, 129.5–130°C; **10b**, 143–144°C; **10c**, 158.5–159°C; **12a**, 106–107°C; **12b**, 205°C (decomposition); **13**, colorless oil; **15**, 173°C (decomposition).
5,6-Dihydropyrrolo[2′,1′:3,4]pyrazino[2,1-*a*]isoindol-8(12b*H*)-one 10a. Obtained as hydrate; colorless needles; yield, 76%; ^{1}H NMR δ 2.01 (br s, for hydrate), 3.60 (ddd, J=13.5, 10.5, 5.1 Hz, 1H), 3.94–4.08 (m, 2H), 4.68 (ddd, J=13.2, 4.5, 2.1 Hz, 1H), 5.74 (s, 1H), 6.19 (t, J=3.0 Hz, 1H), 6.27 (br s, 1H), 6.61 (br s, 1H), 7.48 (t, J=7.4 Hz, 1H), 7.62 (t, J=7.4 Hz, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.85 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 37.6, 44.2, 56.2, 104.0, 108.6, 119.9, 122.9, 123.8, 125.4, 128.5, 131.6, 132.1, 144.3, 167.8. Anal. calcd for $C_{14}H_{12}N_2O{\cdot}H_2O$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.31; H, 5.69; N, 11.48.
6,7-Dihydro-5*H*-pyrrolo[2′,1′:3,4][1,4]diazepino[2,1-*a*]isoindol-9(13b*H*)-one 12a. Colorless flakes; yield, 76%; ^{1}H NMR δ 1.85–1.98 (m, 1H), 2.10–2.18 (m, 1H), 3.25 (td, J=13.2, 3.3 Hz, 1H), 4.25 (t, J=4.5 Hz, 2H), 4.76 (dt, J=14.1, 3.6 Hz, 1H), 5.59 (s, 1H), 5.87 (s, 1H), 5.96 (t, J=3.0 Hz, 1H), 6.65 (s, 1H), 7.52 (t, J=7.4 Hz, 1H), 7.62 (t, J=7.2 Hz, 1H), 7.68 (d, J=7.5 Hz, 1H), 7.87 (d, J=7.5 Hz, 1H); ^{13}C NMR δ 29.0, 43.2, 49.1, 58.8, 106.2, 108.5, 123.3, 124.0, 124.1, 128.7, 128.9, 131.3, 132.5, 142.4, 167.9. Anal. calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.53; H, 6.03; N, 11.68.