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An effective synthesis of functionalized tetrahydro-4-oxoindeno[2,1-*b*]pyrroles

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Abstract: A one-pot synthesis of dialkyl 1,3a,4,8b-tetrahydro-3a,8b-dihydroxy-1-alkyl-4-oxoindeno[1,2-*b*]pyrrole-2,3-dicarboxylates *via* three-component reaction between indane-1,2,3-trione (ninhydrin), primary amines and dialkyl acetylenedicarboxylates is described.

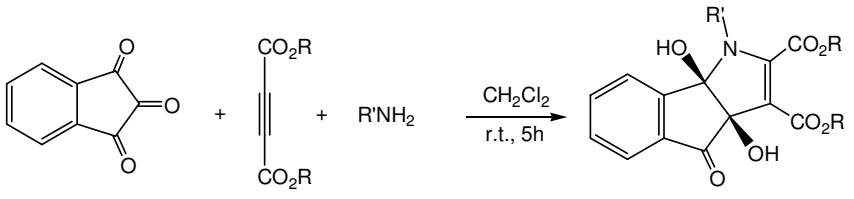
Keywords: Fused pyrroles; Three-component reaction; Benzylamine; Activated acetylenes.

Introduction

Five-membered, nitrogen-containing heterocycles are important building blocks in an extensive number of biologically active compounds [1]. Among them, pyrroles are heterocycles of great importance because of their presence in numerous natural products like heme, chlorophyll, vitamin B_{12}, and various cytochrome enzymes [2]. Some of the recently isolated pyrrole-containing marine natural products have been found to exhibit considerable cytotoxicity and function as multidrug resistant reversal agents [3]. Many of these biologically active compounds have emerged as chemotherapeutic agents. In addition, polysubstituted pyrroles are molecular frameworks having immense importance in material science [4]. They have been also employed as antioxidants, antibacterial, ionotropic, antitumor, anti-inflammatory, and antifungal agents [5-10]. Moreover, they are a highly versatile class of intermediates in the synthesis of natural products as well as in heterocyclic chemistry [11].

Results and Discussion

As part of our current studies on the development of new routes in heterocyclic synthesis,[12-14] we report an efficient procedure for direct synthesis of dihydroxy-tetrahydroindeno [2,1-*b*] pyrrole -2,3-dicarboxylates (**4**) from the reaction of ninhydrin (**1**), acetylenic esters **2** and primary amines (**3**) at room temperature (Scheme 1).



1 **2** **3**

4	R	R'	Yield/ %
a	Me	Bn	85
b	Me	4-Me-Bn	87
c	Me	4-MeO-Bn	90
d	Me	2-Cl-Bn	75
e	Et	Bn	84

Scheme 1

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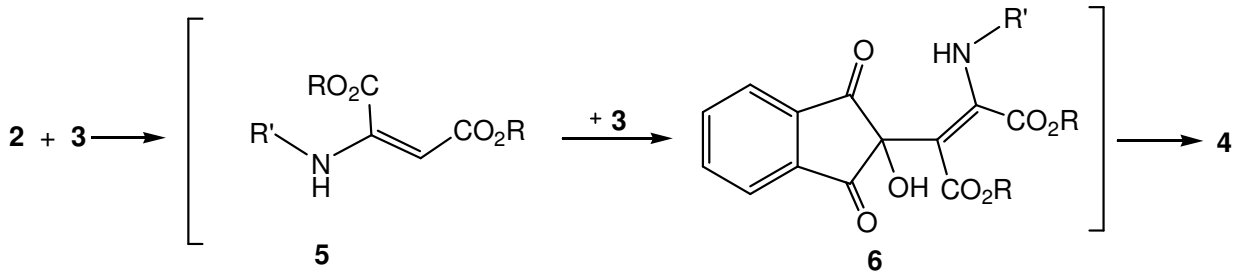
Structures of compounds **4a-e** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectrum of **4a** exhibited four singlets for methoxy (3.55 and 3.78 ppm) and hydroxy (4.99 and 5.41 ppm) protons. Due to the presence of stereogenic centers in these products, the protons of CH_2 group are diasterotopic, and exhibit AB systems. The carbonyl groups resonances in the ^{13}C NMR spectrum of **4a** appear at 162.1, 164.1 and 197.1 ppm. The mass spectrum of **4a** displayed the molecular ion peak at *m*/*z* = 409. Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation (Scheme 2). Presumably, the zwitterionic intermediate **5** formed from the reaction of **3** with activated acetylenes is attacked by ninhydrin to produce **6**. Intermediate **6** can undergo cyclization under the reaction conditions employed to produce **4**.



Scheme 2

In conclusion, we have described a convenient route to functionalized tetrahydroindeno[2,1-*b*]pyrroles from a three-component reactions of ninhydrin, acetylenic esters and primary alkylamines. The advantage of the present procedure is that the reaction is performed by simple mixing of the starting materials.

Experimental

General. Compounds **1**, **2** and **3** were obtained from *Merck* and used without further purification. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX-500 AVANCE* instrument, in $CDCl_3$ at 500.1 and 125.7MHz, resp.; δ in ppm, *J* in Hz. MS: *Finnigan-MAT-8430* mass spectrometer, at 70 eV; in *m/z*. Elemental analyses (C, H, N): *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the Preparation of Compounds **4**.

To a stirred solution of (**3a,** 2 mmol) and (**2a**, 2 mmol) in 5 mL of CH_2Cl_2, was added a solution of ninhydrin (0.32 g, 2 mmol) in 5 mL of CH_2Cl_2 at room temprature. After completion of the reaction (1-3 h) as indicated by TLC (hexane/AcOEt 8:1), the solvent was removed under reduced pressure to leave a residue that was purified by column chromatography (SiO_2; hexane/AcOEt 8:1) to afford pure desired products.

Dimethyl 1-benzyl-3a,8b-dihydroxy4-oxo-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrole-2,3-dicarboxylate (**4a**). Yield: 0.62g (85%). Colorless crystals. M.p. 126-128°C. IR (KBr): 3445 (br.), 1742, 1712, 1686, 1569, 1468, 1218, 1180. ^{1}H-NMR: 3.55 (3H, *s*, MeO); 3.78 (3H, *s*, MeO); 4.90 (1H, *d*, ^2J 15.7 Hz, CH); 4.99 (1H, *s*, OH); 5.07 (1H, *d*, ^2J 15.7 Hz, CH); 5.42 (1H, *s*, OH); 7.33 (2 H, *d*, ^3J 7.3 Hz, 2 CH); 7.38-7.42 (5 H, *m*, 5 CH); 7.76 (1H, *t*, ^3J 7.5 Hz, CH); 7.99 (1H, *d*, ^3J 8.1 Hz, CH). ^{13}C-NMR: 46.8 (CH_2-N); 51.2 (MeO); 52.7 (MeO); 83.7 (C); 95.4(C); 124.5 (CH); 124.7 (CH); 127.8 (CH); 128.1 (2 CH); 128.5 (2 CH); 130.6 (CH); 135.2 (C); 136.1 (CH); 136.5 (2 C); 147.4 (C); 151.1 (C); 162.2 (C=O); 164.2 (C=O); 197.1 (C=O). EI-MS: 409 (10), 346 (50), 300 (80), 105(100), 76 (30). Anal. Calcd (%) for $C_{22}H_{19}NO_7$ (409.39): C, 64.55; H, 4.68; N, 3.42. Found: C, 64.32; H, 4.51; N, 3.32.

Dimethyl 3a,8b-dihydroxy-1-(4-methylbenzyl)-4-oxo-1,3a, 4,8b-tetrahydroindeno [1,2-b]pyrrole-2,3-dicarboxylate (**4b**). Yield: 0.66 g (87%). White powder. M.P. 123-125°C. IR (KBr): 3450 (br.), 1742, 1713, 1665, 1573, 1466, 1205, 1179.^{1}H- NMR: 2.32 (3H, *s*, Me); 3.46 (3H, *s*, MeO); 3.67 (3H, *s*, MeO); 4.70 (1H, *d*, ^2J 15.0 Hz, CH); 4.90(1H, *s*, ^2J=15.0 Hz,

CH); 4.99 (1H, *s*, OH); 5.29 (1H, *s*, OH); 7.05 (2H, *d*, ^3J 7.8 Hz, 2 CH); 7.13 (2H, *d*, ^3J 7.8 Hz, 2 CH); 7.55 (1H, *t*, ^3J 7.5 Hz, CH); 7.67 (1H, *t*, ^3J 7.5 Hz, CH); 8.36 (2H, *d*, ^3J 8.0 Hz, 2 CH). ^{13}C-NMR: 21.1 (CH_3); 46.7 (CH_2-N); 51.2 (MeO); 52.7 (MeO); 83.7 (C);95.2 (C);124.4 (CH); 124.7 (CH); 128.0 (2 CH); 129.2 (2CH); 130.7 (CH); 131.8 (C); 133.4 (C); 135.2 (C); 136.1 (CH); 137.7 (C); 147.4 (C); 151.1 (C); 162.1 (C=O); 164.1 (C=O); 197.0 (C=O). EI-MS: 423 (15), 318 (65), 287 (54), 105 (100), 90 (84), 76 (42). Anal. Calcd (%) for $C_{23}H_{21}NO_7$ (423.42): C, 65.24; H, 5.00; N, 3.31. Found: C, 65.12; H, 4.87; N, 3.24.

Dimethyl 3a,8b-dihydroxy-1-(4-methoxybenzyl)-4-oxo-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrole-2,3-dicarboxylate (**4c**). Yield: 0.66g (78%). Yellow powder. M.p. 127-129°C. IR (KBr): 3445 (br.), 1742, 1712, 1662, 1569, 1468, 1240 ,1180.^{1}H-NMR: 3.47 (3 H, *s*, MeO); 3.66 (3H, *s*, MeO); 3.77 (3H, *s*, MeO); 4.67 (1H, *d*, ^2J 15.5 Hz, CH); 4.87(1H, *d*, ^2J 15.5 Hz CH); 4.92 (1H, *s*, OH); 5.41 (1H, *s*, OH); 7.05 (2H, *d*, ^3J 8.3 Hz, 2 CH); 7.12 (2H, *d*, ^3J 8.3 Hz, 2 CH); 7.55 (1H, *t*, ^3J 7.4 Hz, CH); 7.67 (1H, *t*, ^3J 7.7 Hz, CH); 8.36 (2H, *d*, ^3J 8.0 Hz, 2 CH). ^{13}C-NMR: 46.4 (CH_2-N); 51.2 (MeO); 52.7 (MeO); 55.3 (MeO); 83.7 (C); 95.3 (C); 114.0 (2CH); 124.5 (CH); 124.7 (CH); 128.4 (C); 129.5 (2CH); 130.6 (CH); 135.2 (2C); 136.2 (CH); 147.4 (C); 151.1 (C); 159.4 (C); 162.2(C=O); 164.2 (C=O); 197.1 (C=O).Anal. Calcd (%) for $C_{23}H_{21}NO_8$ (439.42): C, 62.87; H, 4.82; N, 3.19. Found: C, 62.74; H, 4.76; N, 3.08.

Dimethyl 1-(2-chlorobenzyl)-3a,8b-dihydroxy-4-oxo-1,3a,4,8b-tetrahydroindeno[1,2-b]pyrrole-2,3-dicarboxylate (**4d**). Yield: 0.66 g (82%).White powder. M.p. 130-132°C. IR (KBr): 3430 (br.); 1725; 1720; 1687; 1545; 1432; 1254;1100.^{1}H- NMR: 3.55 (3H, *s*, MeO); 3.71 (3H, *s*, MeO); 4.54 (1H, *s*, OH); 4.68 (1H, *s*, OH); 4.84 (1H, *d*, ^2J 15.6 Hz, CH); 4.97(1H, *d*, ^2J=15.6 Hz, CH); 7.07 (1H, *d*, ^3J 8.3 Hz, CH);7.18 (1H, *t*, ^3J 8.3 Hz, CH); 7.24 (1H, *t*, ^3J 7.5 Hz, CH); 7.36 (1H, *d*, ^3J 7.5 Hz, CH); 7.52-7.56 (2H, *m*, 2 CH); 7.62 (1H, *t*, ^3J 7.8 Hz, CH); 7.87 (1H, *d*, ^3J 7.5 Hz, CH). ^{13}C-NMR: 44.1 (CH_2-N); 51.4 (MeO); 52.9 (MeO); 83.6 (C); 95.4 (C); 124.4 (CH); 124.7 (CH); 126.8 (CH); 128.9 (CH); 129.0 (CH); 129.4 (CH); 129.7 (C); 130.7 (CH); 132.6 (C); 134.2 (C); 135.1 (C); 136.2 (CH); 147.3 (C); 151.1 (C); 161.8 (C=O); 164.1 (C=O); 196.9 (C=O). Anal. Calcd (%) for $C_{22}H_{18}ClNO_7$ (443.84): C, 59.54; H, 4.09; N, 3.16. Found: C, 59.45; H, 4.00; N, 3.10.

Diethyl 1-benzyl-3a,8b-dihydroxy4-oxo-1,3ª,4,8b-tetrahydroindeno[1,2-b]pyrrole-2,3-dicarboxylate (**4e**). Yield: 0.64 g (80%). White powder. M.p. 128-130°C. IR (KBr): 3435 (br.), 1749, 1714, 1666, 1559, 1474, 1195, 1159. ^{1}H-NMR: 0.98 (3H, *t*, ^3J 7.2 Hz, Me); 1.23 (3H, *t*, ^3J 7.3 Hz, Me); 3.85-3.89 (2H, *m*, (CH_2-O); 4.16-4.19 (2H, *m*, (CH_2-O); 4.32 (1H, *s*, OH); 4.59 (1H, *s*, OH); 4.76 (1H, *d*, ^2J 15.8 Hz, CH); 4.93 (1H, *d*, ^2J=15.8, CH); 7.19-7.28 (5H, *m*, 5 CH); 7.55 (2H, *t*, ^3J 7.8 Hz, 2 CH); 7.65 (1H, *t*, ^3J 7.5 Hz, CH); 7.89 (1H, *d*, ^3J 8.0 Hz, CH). ^{13}C-NMR: 13.4 (Me); 14.3 (Me); 46.7 (CH_2-N); 60.0 (CH_2-O); 62.4 (CH_2-O); 83.7 (C); 95.0 (C); 124.4 (CH); 124.8 (CH); 127.8 (CH); 127.9 (2CH); 128.5 (2CH); 130.6 (CH); 131.5 (C); 135.3 (C); 136.0 (CH); 136.7 (C); 147.5 (C); 150.8 (C); 161.7 (C=O); 163.7 (C=O); 196.9 (C=O). Anal. Calcd (%) for $C_{24}H_{23}NO_7$ (437.45): C, 65.90; H, 5.30; N, 3.20. Found: C, 65.78; H, 5.23; N, 3.14.

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