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A CONVENIENT SYNTHESIS OF 2-CYANOPYRROLES FROM ISOCYANOACETONITRILE

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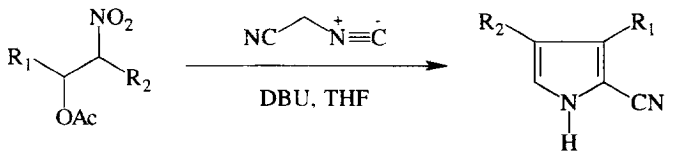
Summary: *2-Cyano-3,4-substituted pyrroles* ***2a-e****, important intermediates in the synthesis of porphyrins and related compounds, were prepared via base promoted condensation of α-acetoxynitro compound* ***1a-e*** *with isocyanoacetonitrile (**3**) in THF, in good yield.*

3,4-Substituted pyrrole derivatives with cyano or carboxylic acid in the 2-position are important intermediates in the synthesis of porphyrins and bile pigments, the tetrapyrrole products and also, porphobilinogen, the key building block in the biosynthesis of hemeproteins and other "pigments of life".[1,2] In addition, the tetrapyrrolic compounds have recently been used as therapeutic agents in photodynamic therapy (PDT) for the treatment of cancer.[3] Generally, the pyrroles and their 2-carboxylic acid derivatives with appropriate substitution patterns have been prepared by condensation of α-amino ketones with β-keto esters or β-diketo compounds (Paal-Knorr synthesis),[4] or reaction of nitro compounds with isocyano acetates.[5] However, there are only few syntheses reported for the preparation of 2-cyanopyrroles. Cohnen *et al.*[6] have 2-cyanopyrroles in 37-94% yield. Later, Breitmaier and Walizei[7] prepared 2-cyanopyrroles from aminoacetonitrile and Alberola *et al.*[8] from 3-alkoxyacroleins or β-enones in poor to moderate yields. These methods involve two steps and require rather harsh conditions.[9] Recently, we needed a suitable method for the preparation of 2-cyanopyrroles in connection with our program on the synthesis of variety of immunoreagents for the development of porphyrin assay. In this context, we describe here (scheme 1) an efficient and convenient method for the preparation of 2-cyano 3,4-disubstituted pyrroles **2a-e** from isocyanoacetonitrile (**3**) and α-acetoxynitro compounds **1a-e**.

Scheme 1



1a-e **2a-e**

a) R_1=Me; R_2=Et, b) R_1; R_2=Et, c) R_1=Ph; R_2=Et,

d) R1=Me; R_2=$CH_2CH_2CO_2Me$, e) R_1=Et; R_2=$CH_2CH_2CO_2Me$

The importance of isocyanoacetonitrile in the synthesis depends partly on its activating effect on the neighboring C-H bond and also more importantly on the ability of the "bivalent" isocyanide carbon which makes the subsequent heterocyclization possible.[10] Isocyanoacetonitrile (**3**),[11] the three carbon synthon, has been utilized in the synthesis of 2-oxazoline-4-carbonitriles[11b] and 4-cyano 1,3-thiazole.[11c] In the present study, typically the appropriate α-acetoxynitro compound **1a-e**[12] (1.0 mmol) and freshly prepared isocyanoacetonitrile[13] (3.0 equiv.) in THF (6 mL) were cooled to 0 °C and treated with DBU (3.2 equiv.). After 15 min, the mixture was allowed to warm to room temperature and stirred for 1.5-2.5 h and quenched with water (3 mL). The 2-cyanopyrroles **2a-e** were purified by silica gel column chromatography (20-25% EtOAc-*n*-hexane). The required α-acetoxynitro compounds were prepared by condensation of nitroalkanes with aldehydes (Henry reaction) followed by acetylation.[12]

Table: Synthesis of 2-cyano-3,4-substituted pyrroles **2a-e** from α-acetoxynitro compounds **1a-e**.

Entry	α-acetoxynitro compound **1**	R_1	R_2	Base[a,b]/Solvent/ Temp(°C)/ Time (h)	2-cyanopyrrole **2**	%Yield[c]	mp °C
1.	**1a**	Me	Et	DBU/THF/0-rt/2.0	**2a**	90	63-4
2.	**1a**	Me	Et	DBU/Ether/0-rt/2.5	**2a**	78	
3.	**1a**	Me	Et	TMG/THF/0-rt/2.0	**2a**	89	
4.	**1b**	Et	Et	DBU/THF/0-rt/2.5	**2b**	77	72-3
5.	**1c**	Ph	Et	DBU/THF/0-rt/2.0	**2c**	87	oil
6.	**1d**	Me	$CH_2CH_2CO_2Me$	DBU/THF/0-rt/2.0	**2d**	60	56-8
7.	**1d**	Me	$CH_2CH_2CO_2Me$	TMG/THF/0-rt/2.0	**2d**	83	
8.	**1e**	Et	$CH_2CH_2CO_2Me$	DBU/THF/0-rt/2.5	**2e**	70	oil

a) 3.0 eq. of freshly prepared isocyanoacetonitrile was used b). 3.2 equiv. of 1,8-diazabicyclo[5,4,0]undec 7-ene (DBU) or 1,1,3,3-Tetramethyl guanidine (TMG) were used. c) Isolated yield.

The method (table) generally afforded, good to excellent yields of 2-cyanopyrroles[14,15] (60-90%) using THF as solvent and DBU as a non-nucleophilic base. The synthesis was equally efficient when TMG was used to promote the reaction (see entries 1 and 3 or 6 and 7) which afforded comparable yields of the pyrrole product. Use of ether as solvent (entry 2) afforded pyrroles in somewhat lower yield [see entry 2 (78%) vs entry 1 (90%)] presumably due to the poor solubility of the reactants during the reaction. The reaction course might involve the addition of isocyanoacetonitrile conjugate base to the nitroalkene (generated *in situ* from α-acetoxynitro compound **1** in the presence of base) followed by intramolecular cyclization with the elimination of nitronate ion. The subsequent aromatization then lead to the formation of 2-cyanopyrroles, according to the similar mechanism proposed for synthesis of pyrrole 2-carboxylic acids by Barton and Zard.[5a]

In summary, a facile synthesis of 2-cyanopyrroles (**2**) is described in one step via base induced condensation of α-acetoxynitro compounds **1a-e** with isocyanoacetonitrile (**3**) in 60-90% yield. In the present synthesis, the 2-cyano group is incorporated into the pyrrole ring easily and also affords convergence and flexibility for the introduction of various substituents at 3 and 4-positions of the pyrrole system. Since the cyano group can be easily transformed into the other functionalities, the present strategy should be applicable for the preparation of variety of 2-functinalised 3,4-disubstituted pyrrole derivatives.

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12. α-acetoxynitro compounds **1a-e** were prepared in two steps from 1-nitropropane or from methyl 4-nitrobutyrate and appropriate aldehydes (acetaldehyde, propionaldehyde and benzaldehyde) and DMAP in CH_2Cl_2 followed by acetylation using Ac_2O and pyridine in CH_2Cl_2.

13. Isocyanoacetonitrile (**3**) was freshly prepared from N-formyl aminoacetonitrile[11b,d] prior to the condensation reaction with **1** and used immediately without purification due to its unstability.

14. All new compounds were fully characterized by ^1H and ^{13}C NMR, IR and Mass Spectrometry and the yields refer to the chromatographically and spectroscopically homogeneous materials.

15. **Typical procedure: 2-cyano-4-ethyl-3-methylpyrrole (2a):** In a dry 25 mL single-necked round bottom flask equipped with magnetic stir bar, nitrogen inlet was placed N-formylamino acetonitrile[11c,d] (0.21 g, 3.0 mmol) in dry CH_2Cl_2 (5 mL), added triethyl amine (0.75 mL, 5.4 mmol, 1.8 equiv.) and cooled to -25 °C (acetone-limited amount of dry ice and monitored by thermometer). Phosphorous oxychloride (0.28 mL, 3.0 mmol, 1.0 equiv.) was added via syringe slowly over 2 min. The mixture was stirred foradditional 10 min., the cooling bath was removed and slowly allowed the reaction mixture to warm to room temperature for 10 min. The mixture was diluted CH_2Cl_2 (20 mL) and poured in to 20% Na_2CO_3 soln (4 mL). The brown/dark red color organic layer was separated and washed with 20% Na_2CO_3 soln (4 mL), water (5 mL), dried ($MgSO_4$) and the solvent was removed using rotary evaporator at low temperature (between about 0-5 °C by placing the round bottom flask occasionally in the water bath). The crude isocyanoacetonitrile (0.24 g) was dissolved in THF (4 mL) and cooled to 0 °C and α-acetoxynitro compound **1a** (0.175 g, 1.0 mmol) in THF (3 mL) was added via double ended needle followed by DBU (0.53 mL, 3.2mmol) with syringe. After stirring the mixture for 30 min at 0 °C, the cooling bath was removed, the mixture was allowed to warm to room temperature and stirred for 2.0 h. The resulting orange-red color precipitate was quenched with water (3 mL) and extracted with ethyl acetate (3 X 25 mL). The combined organic layer was washed with brine (5 mL), dried ($MgSO_4$) and the solvent was removed via rotary evaporator. The crude compound was purified by silica gel column chromatography (20% ethyl acetate in *n*-hexane) to afford 0.12 g of **2a** in 90% yield as colorless solid. mp: 63-4 °C; ^1H NMR ($CDCl_3$): δ 1.17 (t, 3H, J=7.5 Hz), 2.17 (s, 3H), 2.41 (q, 2H, J=7.5 Hz), 6.66 (d, 1H, J=3.3 Hz), 8.49 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ9.78, 14.30, 18.23, 99.41, 115.03, 120.61, 126.49, 130.26; mass spectrum (m/z): 134 $(M)^+$, 152 $(M+NH_4)^+$, 169 $(M+NH_4+NH_3)^+$; exact mass calcd for $C_8H_{10}N_2$:134.0844; found: 134.0842.

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