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Reactions of ethyl cyanoformate with cycloimmonium salts: a direct pathway to fused or substituted azaheterocycles

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ABSTRACT

Aromatic cycloimmonium salts underwent different reaction pathways when treated with ethyl cyanoformate in triethyl amine medium, including selective γ-cyano substitutions (in case of phenanthrolinium and quinolinium salts) and 3+2 dipolar cycloadditions (for phthalazinium and isoquinolinium salts). When using phthalazinium salts, besides the 3+2 cycloaddition products (imidazo[2,1-*a*]phthalazines), we obtained 8,8*a*,16,16*a*-tetrahydropyrazino-[2,1-*a*;4,5-*a*′]-diphthalazines as secondary products via a 3+3 cycloaddition dimerization. The structures of the synthesized compounds have been proved by spectral data, and X-ray diffraction for three of the new derivatives.

1. Introduction

Methyl cyanoformate, known as Mander's reagent, is commonly used to perform the regioselective methoxycarbonylation of lithium enolates.[1] Ethyl and methyl cyanoformates are also known for formation of α-ketoesters from arylboronic acids in rhodium-catalysed reactions[2] and for use as selective cyanoethoxycarbonylation reagents,[3] cyanation reagents[4,5] or dipolarophiles in different cyclization reaction.[6–9]

Imidazole is a therapeutically active moiety exploited in recent years for the synthesis of diverse derivatives with various biological activities.[10] The fusion of two or more heterocycle rings results in different classes of compound, and fused heterocycles containing an imidazole ring are showing a broad range of properties including biological activity[11–13] optical[14] or electron-transport properties.[15]

Inspired by a recent report of using ethyl cyanoformate as a dipolarophile in the 3+2 cycloaddition of pyridinium ylides, with formation of a new fused imidazo[1,2-*a*]pyridine system,[7] and as a continuation of our work in the field of 3+2 cycloaddition reactions,[16,17] we decided to use ethyl cyanoformate in similar reactions of 1,10-, 1,7- and 4,7-phenanthrolinium ylides in order to obtain new imidazophenanthroline systems. Surprisingly, instead the expected cycloadducts, we prepared new γ-cyano-substituted phenanthrolines. This interesting behaviour prompted us to extend the study of the reactions of ethyl cyanoformate with different cycloimmonium salts (phthalazinium, quinolinium and isoquinolinium) in basic medium, and the results are presented herein.

2. Results and discussion

In our first attempt to synthesize a new imidazophenanthroline skeleton, we used 1,10-phenanthrolin-1-ium halides[18] **1** in basic medium (trimethylamine in dichloromethane) for the generation of the corresponding ylides in order to react with ethyl cyanoformate in 3+2 cycloaddition reaction. Instead the expected cycloadducts **2**, we obtained 4-cyano substituted 1,10-phenanthrolines **3** (Scheme 1). Interestingly, in case of the reaction of salt **1c**, the final product **3c** contained a methyl ester group instead the initial amide group, this replacement probably occurring during the column chromatography when we used $CHCl_3$/MeOH as eluent.

The structures of the compounds **3a**–**c** were established on the basis of spectral analyses (NMR, IR) and X-ray diffraction for compound **3a** (Fig. 1). Thus, the crystal structure of **3a** indicates that this compound has the following crystallographic characteristics: monoclinic, space group $P2_1/c$ (no. 14), a=4.973 Å, b=40.94 Å, c=8.604 Å, β=96.11°, V=1742.1 Å^3, Z=4. The analysis of data reveals that in the crystals of compound **3a** a series of C–H···O and C–H···N hydrogen bonds exists but no π–π interactions.

Regarding the mechanism, we suppose that ethyl cyanoformate reacts with triethylamine (TEA) used in excess and generates the

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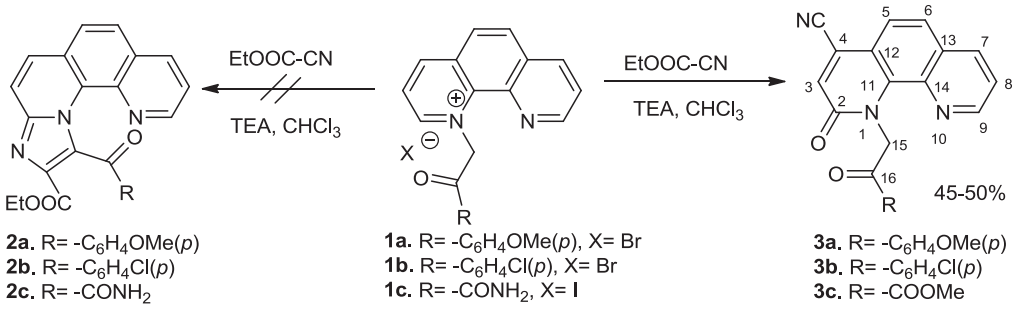


Scheme 1. Synthesis of 4-cyano-substituted 2-oxo-1,2-dihydro-1,10-phenanthrolines **3**.

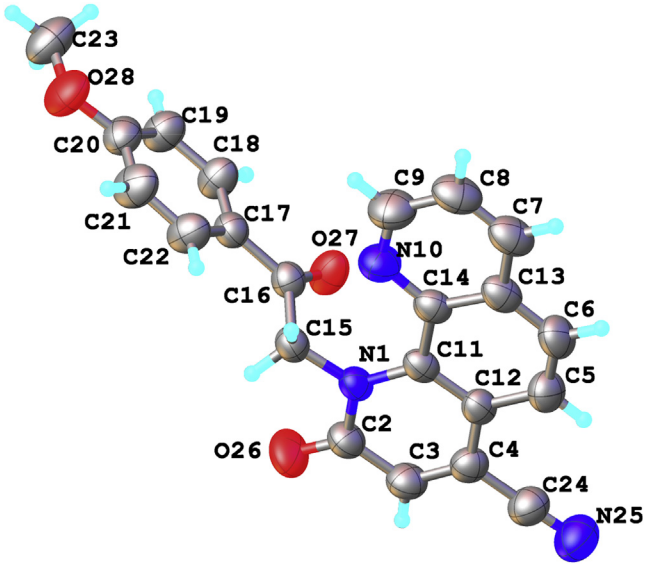
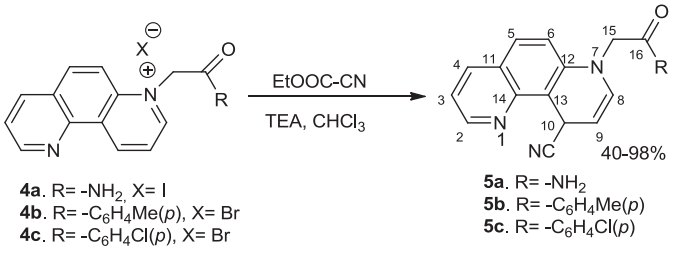


Fig. 1. X-ray crystal structure of compound **3a** with thermal ellipsoids at 50% probability level.

cyanide ion (CN^-). This ion acts as a nucleophile in reaction with the in situ generated phenanthrolinium ylides, leading selectively only to γ-cyano substituted 1,4-dihydro-1,10-phenanthrolines that are stabilised by α-oxidation in air during the work up, to lead to the final compounds **3**. As for the regioselectivity, the γ-substitution takes place in accordance with the existing theory stipulating that 'soft' nucleophiles (including cyanide ion) with high polarizability attack selectively at the 'softest' γ position of the heterocycle.[19–21]

We continued our study using 1,7-phenanthrolin-7-ium salts[22] **4** as substrates for the reaction with ethyl cyanoformate under similar conditions, and we obtained γ-substituted-7,10-dihydro-1,7-phenanthrolines **5**. In this case, derivatives **5** have not undergone the α-oxidation that was observed with the 1,10-phenathrolin-1-ium salts (Scheme 2).



Scheme 2. Synthesis of 10-cyano-substituted 1,7-phenanthrolines **5**.

Spectral data and X-ray diffraction of compound **5b** confirmed the proposed structure **5**. Interestingly, in the ^1H NMR of compounds **5**, the hydrogen atoms at C-15 showed two strongly coupled doublets induced by the asymmetry of carbon 10. The X-ray structure of compound **5b** (Fig. 2) indicates the following main crystal data: orthorhombic, space group $P2_12_12_1$ (no. 19), a=4.788 Å, b=14.184 Å, c=26.17 Å, V=1777 Å^3, Z=4. The crystallographic data shows that in the crystals of this compound a series of C–H···O and C–H···N hydrogen bonds exists but no π–π interactions are present.

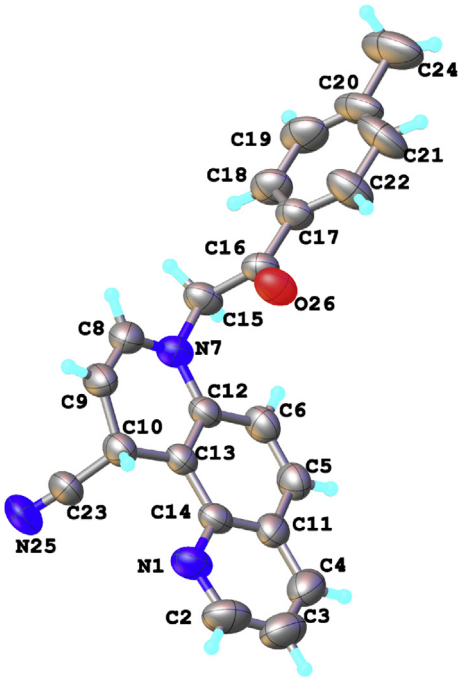


Fig. 2. X-ray crystal structure of compound **5b** with thermal ellipsoids at 50% probability level.

With 4,7-phenanthrolin-4-ium salts[23] **6** treated under similar conditions (Scheme 3), we isolated both γ-cyano-substituted 1,4-dihydro-4,7-phenanthrolines **7**, and 3-oxo-3,4-dihydro-4,7-phenanthrolines **8** (Scheme 3).

We then decided to extend the study to reactions of other cycloimmonium salts under similar conditions. Thus, quinolinium salts[24] **9** underwent similar γ-cyanation and α-oxidation yielding compounds **10a**–**c** and other byproducts (**11**, **12** and **13**) suggesting an instability of the in situ ylides generated from the salts **9** under the reaction conditions (Scheme 4).