

A novel approach to the synthesis of 5-trifluoromethyl-3-substituted pyrazoles[☆]

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Abstract

The 3-cyano-4-trifluoromethyl-6-phenyl or substituted phenyl 2(1H) pyridones (**1**) on reaction with hydrazine hydrate, gave exclusively in 5-trifluoromethyl-3-substituted pyrazoles (**3**) through a novel method. A possible mechanistic pathway for change in the site of nucleophilic attack due to the CF₃ group in 2(1H) pyridones is described. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: 2(1H) pyridones; Bis-nucleophiles; Pyrazoles

1. Introduction

A strategically positioned fluorine in heterocyclic compounds, especially those containing trifluoromethyl groups plays an important role in medicines and agrochemicals [1–6]. Specifically, the fluorinated pyrazoles have been shown to possess high biological activities [7–10] as herbicides, fungicides, insecticides, analgesics, antipyretics and anti-inflammatories. Recently, much attention was paid to the synthesis of trifluoromethyl substituted pyrazoles starting from perfluoro acetylacetylenes [11–13], phenylacetylenes [14–16], 1,3-diketones [17–20], β -ketoesters [21], alkoxy-trifluoro alkenones [22,23], β -aminovinyl ketones [24], bromofluoropropene [25], polyfluoro alkylenaminones [26] and fluoroalkylacetylenic imines [27].

Our continued interest in trifluoromethyl substituted 2(1H) pyridones [28,29] and their reactions with alkylating agents [30,31] has prompted us to investigate the reaction of 2(1H) pyridones with different nucleophiles. As the outcome of this study, we are reporting here a new synthetic methodology for the formation of trifluoromethyl substituted pyrazoles.

2. Results and discussion

The 3-cyano-4-trifluoromethyl-6-substituted 2(1H) pyridones **1(a–c)** [28] reacted with hydrazine hydrate with the

formation of 5-trifluoromethyl pyrazoles **3(a–c)** [23] in moderately good yield (Scheme 1). When compounds **1(a–c)**, reacted with methylhydrazine, phenylhydrazine and ethylenediamine, no reaction occurred and the starting 2(1H) pyridone was recovered.

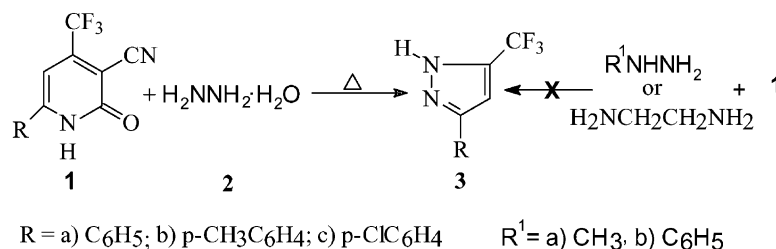
Initially we believed that, the 2(1H) pyridones decomposed into 1,3-diketones which reacted with hydrazine hydrate to give products (**3**). However, we observed that the 2(1H) pyridones did not decompose to 1,3-diketones when heated in water for 7 h. We also found that the presence of substituents such as nitrile (CN) groups on C-3, CF₃ group on C-4 and phenyl or substituted phenyl on C-6 position in 2(1H) pyridones plays a crucial role for the formation of products. In the absence of any of the three groups, no products are formed. This has been established after studying the reaction of 4-trifluoromethyl-6-phenyl-2(1H) pyridone (**4a**), 4-trifluoromethyl-6-*p*-fluorophenyl-2(1H) pyridone (**4b**), 3-cyano-4,6-dimethyl-2(1H) pyridone (**4c**) and 3-cyano-4-trifluoromethyl-6-methyl-2(1H) pyridone (**4d**) with hydrazine hydrate independently and observed no reaction.

In 2(1H) pyridones (**4a–d**) this lack of reactivity is attributed to the presence of the methyl group on the C-6 carbon which cancels the electron deficiency arising out of the CF₃ group on C-4 carbon and absence of nitrile (CN) group which is expected to generate carbonium ion character on C-3. Therefore, we formulate a possible mechanism where the CF₃ group directs the nucleophile to attack at the C-4 position, then bond dissociation between C-3 and C-4 carbon occurs followed by cyclization and elimination of cyanoacetamide (isolated from the filtrate) leads to the

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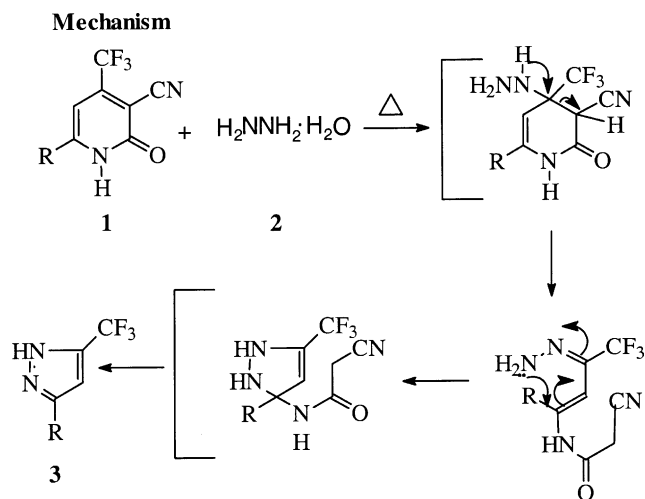
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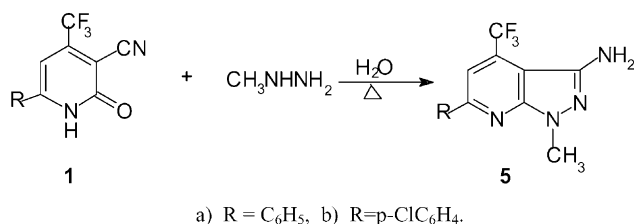
Scheme 1.

formation of product (3). As supporting evidence for the mechanism, it is reported [32] that when 2(1H) pyridones having electron withdrawing groups reacted with hydrazine hydrate ring transformation occurred to result in pyrazoles. The mechanistic pathway for the formation of product (3) is cited below.



Reaction of compound (1) with methylhydrazine in the presence of a small quantity of water resulted in *N*-methyl pyrazole pyridine (5) selectively (Scheme 2).

The increase in basicity of the nucleophile shifts the mode of attack onto nitrile carbon instead of C-4 carbon attached to CF₃ group and cyclization onto C-2 carbon to form product (5) selectively. Whereas for compound (1a) when reacted with phenylhydrazine and ethylenediamine in the presence of water, no reaction occurred. Therefore, it is concluded that the minimum basicity of a nucleophile in polar medium equal to that of hydrazine hydrate is necessary to drive the reaction towards products.



Scheme 2.

3. Experimental

3.1. General

Melting points were determined in open glass capillaries on a Mettler FP 51 melting point apparatus and are uncorrected. ¹H NMR spectra were recorded on a Varian FT (200 MHz) spectrometer with TMS as the internal standard. ¹³C NMR spectra were recorded on a INOVA (500 MHz) spectrometer. IR spectra were recorded on a Perkin-Elmer Model 283B and Nicolet 740 FT-IR instrument. Mass spectra were recorded on a VG micromass 7070H instrument. Elemental analyses were carried out on a Elementar Vario EL (Germany) apparatus.

3.2. General procedure for the preparation of 3-substituted-5-trifluoromethyl 1H pyrazoles (3a–c)

The 2(1H) pyridones (1) (1.28 g, 4.3 mmol) were suspended in excess hydrazine hydrate (10 ml) and heated to reflux while stirring for 4 h. Then the mass was brought to room temperature and poured on to crushed ice. The separated solid was filtered and dried to give (3). The product was purified by passing through a column of silica-gel (60–120 mesh) using chloroform and ethylacetate (9:1) as eluents and characterized by spectroscopy. The yields are in the range of 45–66%.

3.2.1. 5-Trifluoromethyl-3-phenyl 1H pyrazole (3a), 5-trifluoromethyl-3-*p*-tolyl 1H pyrazole (3b), 5-trifluoromethyl-3-*p*-chloro phenyl 1H pyrazole (3c)

Yield 66%, mp 155–156 °C, IR (KBr): 3250, 1500, 1275, 1150 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): 12.25 (s, 1H, NH); 7.55 (d, 2H); 7.45 (d, 2H); 6.75 (s, 1H) ppm. ¹³C NMR (CDCl₃, 500 MHz): δ 144.4, 135.5, 129.5, 126.8, 126.4 (q, *J* = 10.41 Hz), 121.9 (q, *J* = 267.2 Hz), 101.3 (q, *J* = 1.64 Hz). MS: *m/z* 246 (*M*)⁺, 177; analysis: calcd. for C₁₀H₆ClF₃N₂; C, 48.70, H, 2.45, N, 11.35%. Found: C, 48.86, H, 2.62, N, 11.41%.

3.3. 3-Amino-4-trifluoromethyl-6-arylsubstituted-*N*-methylpyrazole[3,4-*b*] pyridines (5a–b)

The compound (1) (1.0 mmol) was taken in excess monomethyl hydrazine (10 ml) and a small quantity of water

(2 ml) was added. The reaction mixture was heated at 140 °C bath temperature for 6 h. Then the mass was allowed to cool to room temperature and transferred onto crushed ice. The separated solid was collected on a Buchner funnel, dried and purified by column chromatography.

3.3.1. 3-Amino-4-trifluoromethyl-6-phenyl-N-methyl pyrazole[3,4-b] pyridine (**5a**)

Yield 44%, mp 196 °C, IR (KBr): 3460, 3300, 3200, 1375, 1275, 1125 cm⁻¹. ¹H NMR (CDCl₃): δ 4.00 (s, 3H, CH₃); 4.25 (s, 2H, NH₂); 7.5 (m, 3H, ArH); 7.65 (s, 1H, H-C(5)); 8.10 (m, 2H, ArH) ppm. MS: *m/z* 292 (*M*⁺, base peak); 263, 228, 77; analysis: calcd. for C₁₄H₁₁F₃N₄: C, 57.53; H, 3.79; N, 19.16%. Found: C, 57.38; H, 3.63; N, 19.05%.

3.3.2. 3-Amino-4-trifluoromethyl-6-p-chloro phenyl-N-methyl pyrazole[3,4-b] pyridine (**5b**)

Yield 49%, mp 202 °C, IR (KBr): 3310, 3250, 1240, 1150 cm⁻¹. ¹H NMR (CDCl₃): δ 4.00 (s, 3H, CH₃); 4.25 (s, br, 2H, -NH₂); 7.45 (d, 2H, ArH); 7.6 (s, 1H, H-C(5)); 8.1 (d, 2H, ArH) ppm. MS: *m/z* 326 (*M*⁺, base peak); 228, 163, 95, 77; analysis: calcd. for C₁₄H₁₀ClF₃N₄: C, 51.47; H, 3.08; N, 17.14%. Found: C, 51.32; H, 2.74; N, 17.02%.

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