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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 CF_3 group in 2(1H) pyridones is described.

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, CF_3 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 CF_3 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 CF_3 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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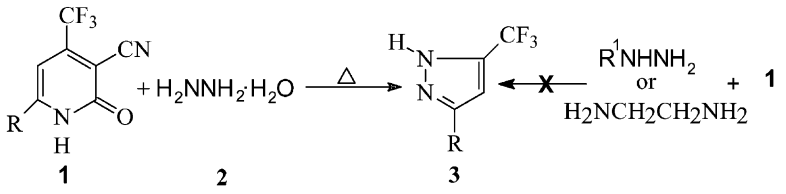
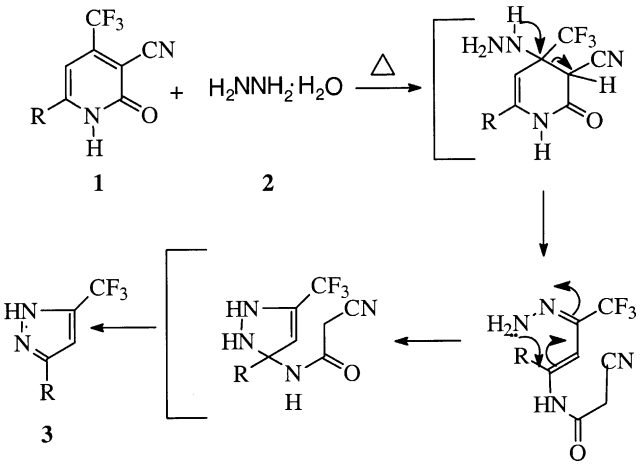


Scheme 1.

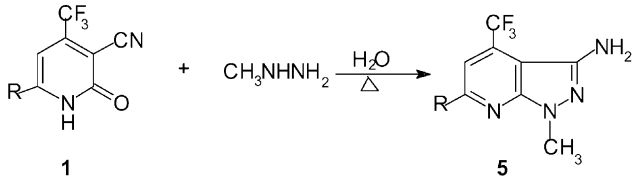
formation of product (**3**). As supporting evidence for the mechanism, it is reported [32] that when 2(1H) pyridones having electron withdrawing groups reacted with hydrazine hydrate ring transformation occurred to result in pyrazoles. The mechanistic pathway for the formation of product (**3**) is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

Mechanism



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 CF_3 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.



a) R = C_6H_5, b) R=p-ClC_6H_4.

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. ^{1}H NMR spectra were recorded on a Varian FT (200 MHz) spectrometer with TMS as the internal standard. ^{13}C 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}. ^{1}H NMR ($CDCl_3$, 200 MHz); 12.25 (s, 1H, NH); 7.55 (d, 2H); 7.45 (d, 2H); 6.75 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 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 $C_{10}H_6ClF_3N_2$; 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 ($CDCl_3$): δ 4.00 (s, 3H, CH_3); 4.25 (s, 2H, NH_2); 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 $C_{14}H_{11}F_3N_4$: 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 ($CDCl_3$): δ 4.00 (s, 3H, CH_3); 4.25 (s, br, 2H, $–NH_2$); 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 $C_{14}H_{10}ClF_3N_4$: C, 51.47; H, 3.08; N, 17.14%. Found: C, 51.32; H, 2.74; N, 17.02%.

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