A Novel Synthesis of 5-Aryl-3-Phenylpyrazole from 2-Aryl-3-Benzoyl-1,1-cyclopropanedicarbonitrile and Hydrazine

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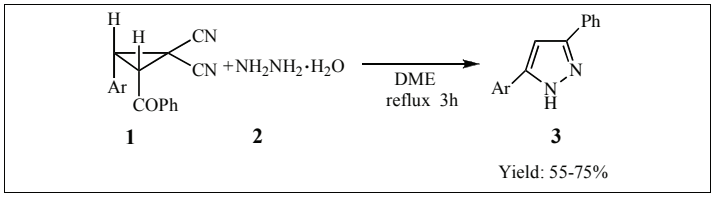

A new process for synthesis of 5-aryl-3-phenylpyrazole is achieved. The regioselective ring-opening reaction of 2-aryl-3-benzoyl-1,1-cyclopropanedicarbonitrile with hydrazine plays a crucial role in the described process.

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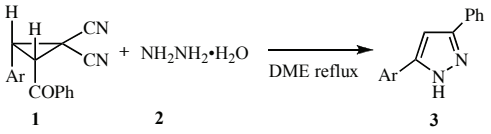
Pyrazoles have found wide uses in pharmaceuticals and agrochemistry [1]. The importance of this class of compounds led to extensive effort towards the development of methods for preparation of pyrazole [2]. Pyrazoles are usually prepared by the reaction between hydrazine with β-difunctional compounds and 1,3-dipolar cycloadditions of diazo compounds [3]. Although these methods are very frequently used, a mixture of regio-isomeric pyrazoles is produced when the unsymmetrically substituted compounds are used as substrates [4]. In general, the regioselectivity in the synthesis of the substituted pyrazole is still a problem. Much effort has been devoted to the development of regioselective synthesis of pyrazole [5].

A survey of the literature reveals that the methods for regioselective synthesis of the 5-aryl-3-phenylpyrazole were seldom reported in the past, such as the preparation of 5-aryl-3-phenylpyrazole by β-tosylhydrazone phosphonates [5d] or dilithiophenyl hydrazones [5e]. These processes suffered from harsh conditions, poor availability of starting material and lack of generality. The facts mentioned above prompted us to develop a general regioselective process for preparation of 5-aryl-3-phenylpyrazole.

For some years, our group has engaged in the nucleophilic addition reaction of cyclopropanes because these compounds can undergo regio- and stereoselective ring-opening reactions with various nucleophiles to yield a broad range of valuable products [6]. We have reported some reactions of electron deficient cyclopropane with oxygen [7] and nitrogen nucleophiles [8]. These processes are regio-and stereoselective.

It was reported that the reaction of α,β-unsaturated carbonyl compound with hydrazine afforded pyrazole derivates [5b,9]. It is well known that the chemistry of the cyclopropane C-C single bond resembles that of carbon-carbon double bond [6]. We think that the reactivity of the cyclopropane with carbonyl group is similar to that of a,b-unsaturated carbonyl compound. A natural extension of our work was to examine the reaction of cyclopropyl ketone with hydrazine. Here we reported a successful process for synthesis of 5-aryl-3-phenylpyrazoles from 2-aryl-3-benzoyl-1,1-cyclopropanedicarbonitriles with hydrazine (Scheme 1).

Scheme 1



In a typical general experimental procedure, the mixture of 2-aryl-3-benzoyl-1,1-cyclopropanedicarbonitrile (1 mmol) and hydrazine hydrate (85%) (120 mg, 2 mmol) in

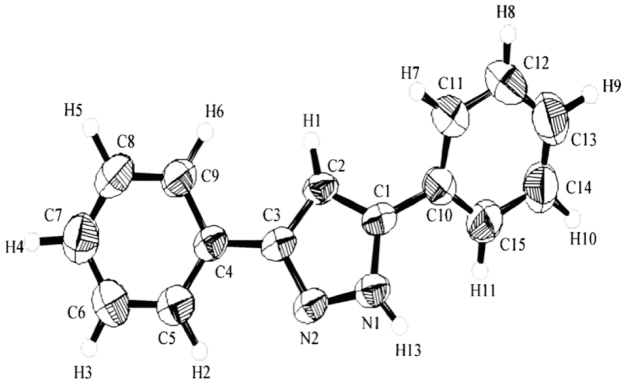
Table 1

Synthesis of Pyrazole from Cyclopropane and Hydrazine

Entry	Product	Ar	Yield %	Entry	Product	Ar	Yield %
1	**3a**	C_6H_5	58	5	**3e**	2-ClC_6H_4	75
2	**3b**	4-FC_6H_4	74	6	**3f**	2,4-$(Cl)_2C_6H_3$	70
3	**3c**	4-BrC_6H_4	69	7	**3g**	4-$CH_3C_6H_4$	69
4	**3d**	4-ClC_6H_4	70	8	**3h**	4-$CH_3OC_6H_4$	55

dimethoxyethane (DME) (4 ml) was refluxed for 3 h to afford 5-aryl-3-phenylpyrazoles in 55%-75%. The results were shown in Table 1.

The structures of pyrazoles **3a-h** were confirmed by ^{1}H NMR, MS, IR, elementary analysis and X-ray (**3a**).

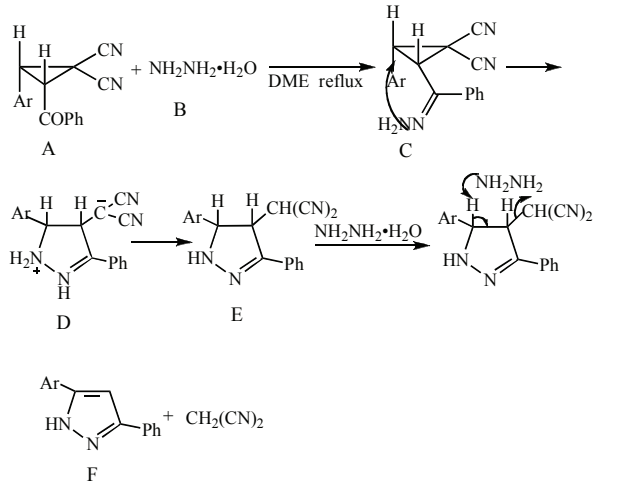


3a

We proposed a reasonable mechanism to account for this reaction as illustrated in Scheme 2.

In this reaction, the first step, the hydrazone C is formed by the condensation of carbonyl group on the cyclopropane **A** with hydrazine **B**. The second step, the intramolecular nucleophilic addition between the cyclopropane ring and the free amino group of hydrazone **C** generates the pyrazoline **D**, followed by the easy transformation of pyrazoline **D** into pyrazoline **E**. In the step forming pyrazoline **D**, the reason for the regioselective ring-opening reaction is that the carbanion formed in pyrazoline **D** is stabilized by two cyano groups. The last step, the aromatization of pyrazoline **E** converted to pyrazole **F** is achieved by the elimination of malononitrile in the presence of hydrazine as base.

Scheme 2



EXPERIMENTAL

All reagents and solvents were obtained from commercial source and used without purification. The 2-aryl-3-benzoyl-1,1-cyclopropanedicarbonitriles were prepared by methods reported in the literature [10]. All melting points are uncorrected. Melting points were determined on WRS-1 digital melting point apparatus made by Shanghai physical instrument factory (SPOIF), China. IR spectra were measured in KBr on a PE-580B spectrometer. ^{1}H NMR spectra were recorded using a Bruker AM-300, with $CDCl_3$ as solvent and TMS as internal reference. Mass spectra were obtained on the Agilent 5973N spectrometer. Elemental analyses were measured on the elementar vario EL III.

General procedure for 5-Aryl-3-Phenylpyrazole**.**

A mixture of *cis*-2-aryl-3-benzoyl-1,1-cyclopropanedicarbonitrile (1 mmol) and hydrazine hydrate (85%) (120 mg, 2 mmol) in DME (4 ml) was refluxed for 3 h. The DME was removed under reduce pressure and the residue was purified on a silica gel chromatographic column (petroleum ether/ethyl acetate, 5:1) to afford 5-aryl-3-phenylpyrazole.

5-Phenyl -3-Phenylpyrazole (**3a**).

This compound was obtained as a colorless solid, mp 199-200 °C (Lit. mp 198-199 °C) [11]; ^{1}H nmr (300 MHz, $CDCl_3$): δ 6.81 (1H, s, =CH), 7.25-7.36 (6H, m, Ph-H), 7.66-7.70 (4H, m, Ph-H), 10.21 (1H, s, NH); ir (potassium bromide): 3098, 3003, 1572, 1403 cm^{-1}; ms (m/z): 221 (M^+ +1, 17), 200 (M^+, 100), 191 (23), 189 (13), 165 (7), 89 (6), 77 (10), 51 (7).

Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.90, H, 5.41, N, 12.78.

5-(4-Fluorophenyl)-3-Phenylpyrazole (**3b**).

This compound was obtained as a colorless solid, mp 181-182 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 6.68 (1H, s, =CH), 6.92-6.98 (2H, t, Ph-H), 7.25-7.31 (3H, q, Ph-H), 7.58-7.62 (4H, q, Ar-H), 10.38 (1H, s, NH); ir (potassium bromide): 3118, 3015, 1606, 1400 cm^{-1}; ms (m/z) : 239 (M^+ +1, 17), 238 (M^+, 100), 209 (30), 207 (13), 104 (12), 95 (11), 77 (16), 51 (12).

Anal. Calcd. for $C_{15}H_{11}FN_2$: C, 75.62; H, 4.65; N, 11.76. Found: C, 75.62, H, 4.55, N, 11.75.

5-(4-Bromophenyl)-3-Phenylpyrazole (**3c**).

This compound was obtained as a colorless solid, mp 219-220 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 6.87 (1H, s, =CH), 7.25-7.44 (5H, m, Ph-H), 7.51-7.79 (4H, m, Ar-H), 13.78 (1H, s, NH). ir (potassium bromide): 3142, 3013, 1588, 1400 cm^{-1}; ms (m/z): 301 (M^+ +3, 16), 300 (M^+ +2, 90), 299 (M^+ +1, 19), 298 (M^+, 100), 269 (8), 191 (12), 190 (11), 189 (22).

Anal. Calcd. for $C_{15}H_{11}BrN_2$: C, 60.22; H, 3.71; N, 9.36. Found: C, 60.34, H, 3.70, N, 9.36.

5-(4-Chlorophenyl)-3-Phenylpyrazole (**3d**).

This compound was obtained as a colorless solid, mp 216-217 °C (Lit. mp 216-217 °C) [12]; ^{1}H nmr (300 MHz, $CDCl_3$): δ 6.81 (1H, s, =CH), 7.35-7.44(5H, m, Ph-H), 7.66-7.69 (4H, m, Ar-H). ir (potassium bromide): 3143, 3099, 1589, 1400 cm^{-1}; ms (m/z): 257 (M^+ +3, 6), 256 (M^+ +2, 35), 255 (M^+ +1, 19), 254 (M^+, 100), 225 (10), 191 (6), 189 (13), 89 (5).

Anal. Calcd. for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35; N, 11.00. Found: C, 70.74, H, 4.34, N, 10.95.

5-(2-Chlorophenyl)-3-Phenylpyrazole (**3e**).

This compound was obtained as a colorless solid, mp 127-128 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 6.99 (1H, s, =CH), 7.26-7.48 (6H, m, Ph-H, Ar-H), 7.68-7.77 (3H, d, Ar-H), 9.81 (1H, s, NH). ir (potassium bromide): 3205, 3007, 1585, 1398 cm^{-1}; ms (m/z): 257 (M^+ +3, 6), 256 (M^+ +2, 35), 255 (M^{+1} +1, 19), 254 (M^+, 100), 225 (10), 191 (7), 190 (7), 189 (18).

Anal. Calcd. for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35; N, 11.00. Found: C, 70.68, H, 4.28, N, 10.97.

5-(2,4-Dichlorophenyl)-3-Phenylpyrazole (**3f**).

This compound was obtained as a colorless solid, mp 181-182 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 6.95 (1H, s, =CH), 7.20-7.25 (1H, m, Ph-H), 7.33-7.46 (4H, m, Ph-H), 7.58-7.60 (1H, d, Ar-H), 7.67-7.70 (2H, d, d, Ar-H), 9.51 (1H, s, NH). ir (potassium bromide): 3148, 3026, 1592 1400 cm^{-1}; MS (m/z) (%): 290 (M^+ +1, 64), 289 (M^+, 6), 288 (M^+-1, 100), 190 (15), 189 (36), 187 (18), 94 (27), 77 (26).

Anal. Calcd. for $C_{15}H_{10}Cl_2N_2$: C, 62.31; H, 3.49; N, 9.69. Found: C, 62.52, H, 3.49; N, 9.71.

5-(4-Methylphenyl)-3-Phenylpyrazole (**3g**).

This compound was obtained as a colorless solid, mp 179-180 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 2.38 (3H, s, CH_3), 6.80 (1H, s, =CH), 7.19-7.25 (2H, t, Ph-H), 7.33-7.42 (3H, m, Ph-H), 7.60 (2H, d, J=8.0Hz, Ar-H), 7.74 (2H, d, J=8.2Hz, Ar-H). ir (potassium bromide): 3129, 3018, 1570, 1400 cm^{-1}; ms (m/z): 235 (M^+ +1,19), 234 (M^+, 100), 233 (M^+-1, 22), 205 (7), 202 (6), 189 (5), 130 (6), 117 (5).

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.15, H, 6.08, N, 11.93.

5-(4-methoxyphenyl)-3-Phenylpyrazole (**3h**).

This compound was obtained as a colorless solid, mp 160-161 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 3.74 (3H, s, CH_3O), 6.64 (1H, s, =CH), 6.76-6.77 (2H, d, Ph-H), 7.22-7.28 (3H, m, Ph-H), 7.55 (2H, d, J=8.3Hz, Ar-H), 7.64 (2H, d, J=8.0Hz, Ar-H), 11.36 (1H, s, NH). ir (potassium bromide): 3132, 3009, 1618, 1400 cm^{-1}; ms (m/z): 251 (M^+ +1, 20), 250 (M^+, 100), 236 (7), 235 (37), 207 (17), 178 (16), 125 (5), 77 (5).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.96, H, 5.56, N, 11.19.

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