HETEROCYCLES, Vol. 85, No. 2, 2012, pp. 431 - 439. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 24th November, 2011, Accepted, 26th December, 2011, Published online, 10th January, 2012
DOI: 10.3987/COM-11-12399

SYNTHESIS OF 3-CYANOPYRAZOLES FROM 3-TRIFLUORO-METHYLPYRAZOLES *VIA* DIRECT AMMONOLYSIS REACTION

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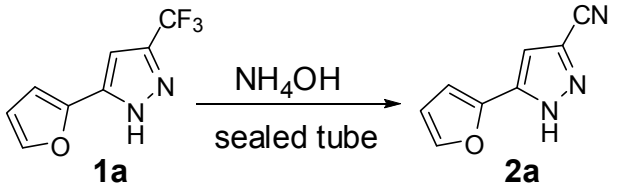
Abstract – A simple and green method to prepare 3-cyanopyrazoles in aqueous ammonia from easy-obtained 3-trifluoromethyl-pyrazoles was explored. Most substrates got acceptable yields. The hydrogen position of N1-H on cyanopyrazoles was assigned by X-ray crystal structure analysis.

3-Trifluoromethylpyrazoles play an important role in medicinal chemistry and agrochemicals and have been well studied.[1-12] However, 3-cyanopyrazoles have not been studied adequately. Cyano group is very important in medicinal chemistry as a functional group[13] and could be converted to amino methyl, amide, thioamide, and many other functional groups. Although 3-Cyanopyrazoles also serve as useful building blocks[14] and important insecticides such as Fipronil, only few reports described the synthesis of N1-unsubstituted 3-cyanopyrazoles.[15, 16] These methods have many disadvantages: starting materials are not easy obtained such as (Z)-3-p-tolylsulfinylacrylonitriles, N-phenylsydnone, and toxic agents as chlorosulphonyl isocyanate, $POCl_3$ are inevitable, and the procedure is tedious. As the facile synthesis and bioevaluation of cyanopyrazoles are still limited, the development of novel useful methods for their construction remains an urgent task. As far as we know some papers/patents disclosed the formation of cyano products through ammonolysis of trifluoromethyl derivatives, including 2-trifluoromethy1imidazoles,[17-19] 4-trifluoromethy1imidazoles,[20] 3-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]-pyridine,[21] and trifluoromethy1benzene.[22, 23] The ammonolysis of 3-trifluoromethylpyrazoles has not been explored. Herein we report the synthesis of 3-cyanopyrazoles from 3-trifluoromethylpyrazoles in aqueous ammonia without using any toxic reagent.

A series of 3-trifluoromethylpyrazoles were easily prepared by reported procedures.[24-29] At first, we chose the ammonolysis of 5-(furan-2-yl)-3-(trifluoromethyl)-1*H*-pyrazole **1a** as a model experiment (Table 1) to optimize the reaction.

Table 1. Optimization of the ammonolysis of 5-(furan-2-yl)-3-(trifluoromethyl)-1*H*-pyrazole[a]



1a **2a**

Entry	Concentration of ammonia (%)	T(°C)	Time(h)	additions	Yield of 1b[d]	Conv.(%)[c]
1	6	40	24		32	41
2	6	60	24		55	94
3	6	100	24		0	100
4	6	60	24	buffer 1[b]	trace	60
5	6	60	24	buffer 2[b]	trace	77
6	25	60	24		49	100
7	20	60	24		53	98
8	18	60	24		61	98
9	16	60	24		53	98
10	12	60	24		50	98
11	8	60	24		70	99
12	5	60	24		6	83
13	8	60	12		69	98
14	8	60	36		39	85
15	8	60	12	0.5 mL THF	55	98
16	8	60	12	0.5 mL Et_2O	66	95
17	8	60	12	0.5 mL EtOH	62	81

[a]All the experiments were carried out with 15 mL aqueous ammonia and 0.49 mmol **1a** in a sealed tube.
[b]Buffer 1 : the molar ratio (NH_4Cl : NH_3) = 1 : 1 ; Buffer 2 : the molar ratio (NH_4Cl : NH_3) = 1 : 2 .
[c]HPLC detected.
[d]Isolated yield. By products are corresponding amide and acid.

Initially, the effect of temperature was examined. Ammonolysis of **1a** gave the product only in the conversion of 41% at 40 ^oC (entry 1). Elevating the temperature to 60 ^oC could improve the yield and the conversion to 55% and 94% respectively (entry 2). But further boosting the temperature to 100 ^oC, no cyanopyrazole was detected because the desired product was hydrolyzed to corresponding amide or acid (entry 3). Secondly, pH value of the reaction solution was considered. Ammonium chloride and ammonia were used as buffer, but it turned to be useless (entries 4 and 5).

Then, the concentrations of aqueous ammonia were taken into consideration. The yields and the conversions were similar when the volume concentration of ammonia ranged from 20 to 12% (entries 7-10). To our pleasure, the yield increased to 70% when the volume ratio of ammonia to water was 1: 2 (entry 11). Surprisingly the yield decreased dramatically to 6% at the more diluted solution (entry 12).

Next, reaction time was investigated. Reducing the reaction time from 24 h (entry 11) to 12 h (entry 13), the same yield was obtained , while prolonging the time to 36 h the yield decreased to 39% (entry 14).

Finally, the effect of organic solvent was explored. We expected that yield and the conversion could be increased due to the improved solubility of **1a** in organic solvent. However, adding 0.5 mL of THF, Et_2O or EtOH into the reaction system decreased the yield slightly (entries 15-17).

Thus, the optimized procedure was as follows: 3-trifluoromethylpyrazoles in 8% aqueous ammonia was heated for 12 h at 60 °C in a sealed tube. Under the optimized condition, we investigated the scope and the limitations of the reaction employing a variety of easily prepared 3-trifluoromethylpyrazoles, the results were summarized in Table 2.

Considering the diversity of substrates, we chose 4- or 5-substituted 3-trifluoromethylpyrazoles and saturated cyclic alkyl fused 3-trifluoromethylpyrazole to explore the reaction. Functional groups at position 5 included heterocycles such as 2-furyl and 2-thienyl, phenyl, substituted phenyl with electron-donating group or electron-withdrawing group. Most substrates got moderate yields (20% to 69%) except for **2i** and **2n**. To our surprise **2i** could be obtained almost quantitatively (entry 9). As described above, **1a** could be converted to **2a** with good yield and conversion (entry 1). However, when 2-furyl group was replaced by 2-thienyl group, the yield and conversion decreased dramatically. To our surprise, the yield of **2b** could be increased greatly to 80% when the volume ratio of ammonia to water was adjusted to 1:4 (entry 2), under this condition, the yield of **2m** was also improved obviously from 48 to 60%. Although the yield of **2n** is very low, this approach could provide estrogenic derivative rapidly for drug screening. From Table 2, no obvious rules for ammonolysis could be drawn out and the electrical properties of functional groups had little effect on the yield (entry 5 *vs* entry 11, entry 6 *vs* entry 12). The concentration of the ammonia has great effect on the yield for different compounds.

It was well known that two tautomers existed for pyrazoles. For our substrates, the tautomer was was demonstrated by X-ray crystal structure of **2c** (Figure 1). This result was similar to the tautomerism of 3-trifluoromethylpyrazoles.[30] Kimoto and Cohen proposed the corresponding mechanism in their preparation of 2-cyanoimidazoles[17, 19]. So, we reasonably proposed the mechanism of this reaction as Scheme 1.

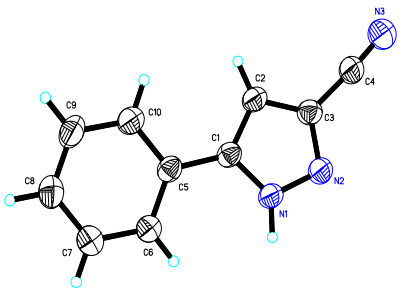
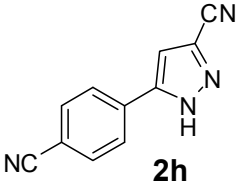
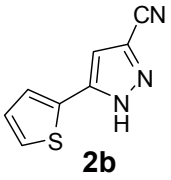
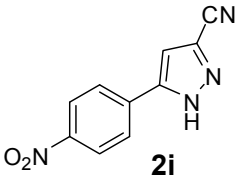
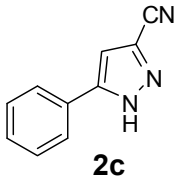
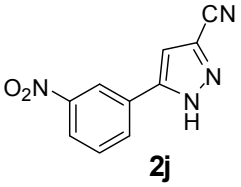
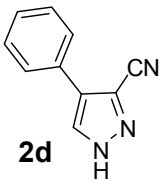
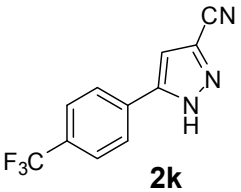
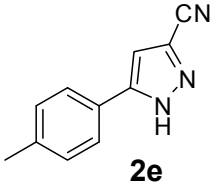
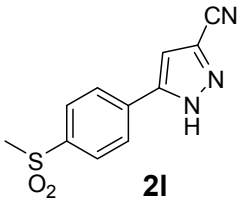
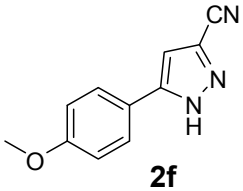
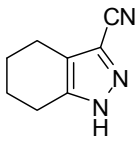
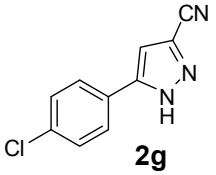
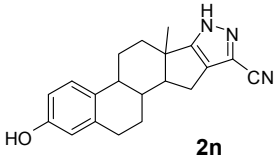


Figure 1. ORTEP diagram of **2c** with the atomic labeling scheme

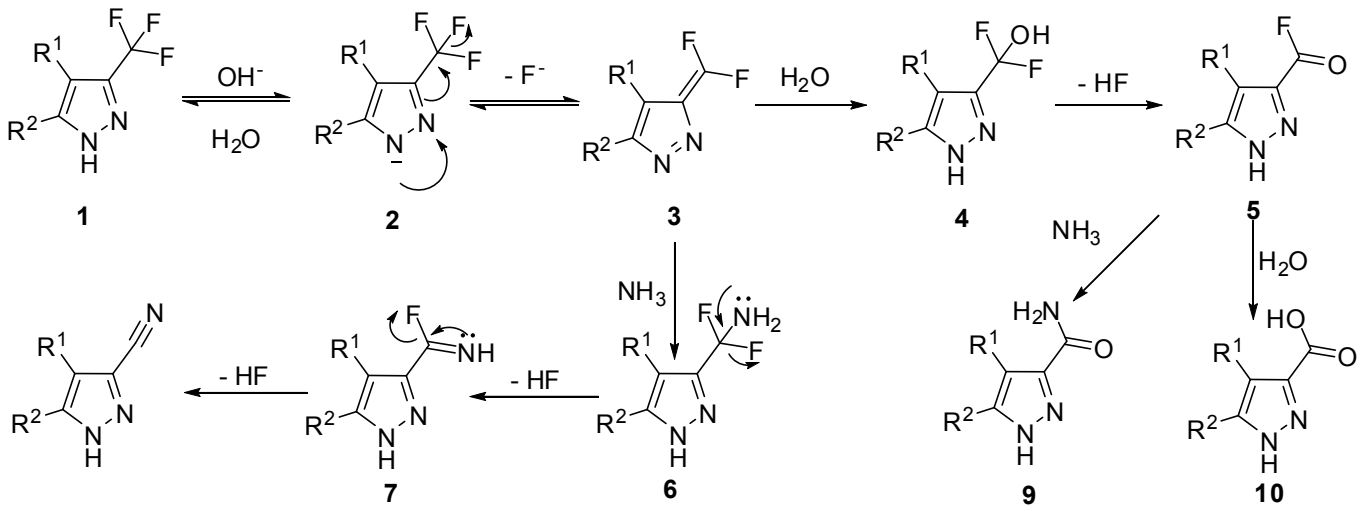
Table 2. Synthesis of 3-cyanopyrazoles **2 a - 2 n** via ammonolysis

Entry	Product (**b**)	Yield[b]	Conv. (%)	Entry	Product (**b**)	Yield[b]	Conv. (%)
1	 **2a**	69	98	8	 **2h**	54	69
2	 **2b**	30(80)[c]	69	9	 **2i**	99	100
3	 **2c**	46	74	10	 **2j**	42	41
4	 **2d**	27	51	11	 **2k**	20	27
5	 **2e**	49	89	12	 **2l**	41	45
6	 **2f**	26	50	13	 **2m**	48(60)[c]	96
7	 **2g**	31	33	14	 **2n**	6	60

[a] All the reactions were carried out in a sealed tube, 60 ºC, 12 h, 8% aqueous ammonia.

[b]Isolated yield.

[c]Yield under the condition of 60 ºC, 24 h, 5% aqueous ammonia.



Scheme 1

An eco-friendly route to prepare 3-cyanopyrazoles through ammonolysis of 3-trifluoromethylpyrazoles was explored. Most of functional 3-trifluoromethylpyrazoles afforded 3-cyanopyrazoles in acceptable yields. Electrical properties seem no effect on this reaction, while the concentration of ammonia makes great sense. Although the yields of some substrates are moderate, this method provides a rapid and simple approach to 3-cyanopyrazoles as building blocks or bioactive compounds for drug screening. The hydrogen on N1 was assigned by X-ray single crystal diffraction.

EXPERIMENTAL

All solvents and others reagents were used without further purification as acquired from commercial sources, the concenteation of commercial ammonia solution is 25%. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury-300 and Varian Mercury-500 spectrometers. IR spectra were recorded on FT-IR NICOLET 6700 spectrometer. HRMS spectra were performed on a Finnigan MAT 95 spectrometer. Melting points were measured by Büchi 510 melting point apparatus and were uncorrected. HPLC detections were done on an Agilent 1100 instrument equipped with a DAD detector, using a C18 reverse phase column. Conditions were as follows: flow rate, 1.0 mL/min; mobile phase, H_2O : MeCN=65 : 35; column temperature, 25 °C, wavelength, 260 nm.

A typical experimental procedure for 3-cyanopyrazoles (2a–2n): In a sealed tube, 3-trifluoromethylpyrazole (100 mg) and prepared aqueous ammonia (15 mL) was stirred at 60 °C for 12 h, then the mixture was cooled to rt and extracted with 10 mL AcOEt each for three times. The combined organic phase was dried with anhydrous Na_2SO_4, and concentrated in vacuum. The crude product was purified through column chromatography on silica gel to give white powder. HPLC detection was performed with reaction solution.

5-(Furan-2-yl)-1*H*-pyrazole-3-carbonitrile (2a)

White powder, mp 108–110 °C. ^{1}H NMR ($CDCl_3$, 300 Hz): δ 6.50– 6.57 (m, 1H), 6.72 (d, 1H, *J* = 3.4 Hz), 6.84 (s, 1H), 7.51–7.60 (m, 1H), 11.93 (brs, 1H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 143.95, 142.79, 135.36, 124.63, 114.57, 112.05, 108.76, 106.803. IR (KBr) 3426, 2919, 2254, 1014, 565 cm^{-1}. MS (EI) *m/z* (%): 159 (M^+, 100). HRMS (EI) calcd. for $C_8H_5N_3O$, 159.0433; found 159.0436.

5-(Thien-2-yl)-1*H*-pyrazole-3-carbonitrile (2b).

White powder, mp 182–184 °C. ^{1}H NMR ($CDCl_3$, 300 Hz): δ 6.85 (s, 1H), 7.12–7.15 (m, 1H), 7.34 (dd, 1H, *J* = 0.8, 3.3 Hz), 7.42 (dd, 1H, *J* = 0.7, 5.2 Hz), 11.15 (brs, 1H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 138.80, 131.98, 132.16, 128.74, 126.69, 125.18, 115.05, 108.29. IR (KBr) 3434, 2919, 2250, 1629, 1037, 559 cm^{-1}. MS (EI) *m/z* (%): 175 (M^+, 100). HRMS (EI) calcd. for $C_8H_5N_3S$, 175.0204; found 175.0203.

5-Phenyl-1*H*-pyrazole-3-carbonitrile (2c).

White powder, mp 108–110 °C. ^{1}H NMR ($CDCl_3$, 300Hz): δ 6.73 (s, 1H), 7.45–7.50 (m, 3H), 7.57 (dd, 2H, *J* = 1.8, 7.3 Hz), 11.10 (brs, 1H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 144.34, 129.67, 129.65, 127.96, 126.05, 125.21, 115.32, 108.39. IR (KBr) 3434, 3143, 3004, 2246, 1567, 1465, 1014, 761, 688, 516 cm^{-1}. MS (EI) *m/z* (%): 169 (M^+, 100). HRMS (EI) calcd. for $C_{10}H_7N_3$, 169.0640; found 169.0644.

4-Phenyl-1*H*-pyrazole-3-carbonitrile (2d).

White powder, mp 162–163 °C. ^{1}H NMR ($CDCl_3$, 300Hz): δ 7.88 (s, 1H), 7.65 (dd, 2H, *J* = 8.8, 1.5), 7.38-7.49 (m, 3H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 130.23, 129.60, 128.97, 128.32, 126.78, 126.17, 121.20, 115.71. IR (KBr) 3430, 3261, 2923, 2246, 1629, 1444, 1164, 1087, 574, 480 cm^{-1}. MS (EI) *m/z* (%): 169 (M^+, 100). HRMS (EI) calcd. for $C_{10}H_7N_3$,169.0640; found 169.0637.

5-(*p*-Tolyl)-1*H*-pyrazole-3-carbonitrile (2e).

White powder, mp 210–212 °C. ^{1}H NMR ($CDCl_3$, 300Hz): δ 2.40 (s, 3H), 6.87 (s, 1H), 7.29 (d, 2H, *J* = 8.1 Hz), 7.46 (d, 2H, *J* = 7.7Hz). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 144.54, 139.32, 130.20, 126.39, 125.87, 125.02, 115.33, 107.98, 20.99. IR (KBr) 3428, 2954, 2852, 2242, 1631, 1461, 1186, 1079, 518 cm^{-1}. MS (EI) *m/z* (%): 183 (M^+, 100). HRMS (EI) calcd. for $C_{20}H_{21}N_3O$, 183.0796; found 183.0791

5-(4-Methoxyphenyl)-1*H*-pyrazole-3-carbonitrile (2f).

White powder, mp 93–95 °C. ^{1}H NMR (DMSO-d_6, 300Hz): δ 3.78 (s, 3H), 7.00 (d, 1H, *J* = 8.6 Hz), 7.01 (d, 1H, *J* = 8.4 Hz), 7.69 (d, 1H, *J* = 8.8 Hz), 7.75 (d, 1H, *J* = 8.8 Hz), 13.36 (brs, 1H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 160.38, 144.32, 127.54, 125.08, 120.52, 115.43, 115.05, 107.39, 55.75. IR (KBr) 3400, 3145, 2948, 2864, 2242, 1619, 1515, 1465, 1255, 1180, 1018, 833, 526 cm^{-1}. MS (EI) *m/z* (%): 199 (M^+, 100). HRMS calcd. for $C_{11}H_9N_3O$, 199.0746; found 199.0745.

5-(4-Chlorophenyl)-1*H*-pyrazole-3-carbonitrile (2g).

White powder, mp 160–162 °C. ^{1}H NMR (DMSO-d_6, 300Hz): δ 7.17 (s, 1H), 7.52 (d, 2H, *J* = 6.7 Hz),

7.79 (2H, d, *J* = 6.7 Hz), 13.67 (brs, 1H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 142.96, 133.75, 129.24, 129.06, 127.31, 126.19, 114.58, 108.32. IR (KBr) 3432, 3141, 2927, 2848, 2244, 1608, 1490, 1187, 1059, 1012, 819, 516 cm^{-1}. MS (EI) m/z (%): 205 (31), 203 (M^+, 100). HRMS (EI) calcd. for $C_{10}H_6N_3Cl$. 203.0256; found 203.0246.

5-(4-Cyanophenyl)-1*H*-pyrazole-3-carbonitrile (2h).

White powder, mp 270–272 °C. ^{1}H NMR (DMSO-d_6, 300Hz): δ 7.64 (s, 1H), 7.98 (d, 2H, *J* = 8.0 Hz), 8.09 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 143.11, 133.67, 133.65, 130.12, 126.73, 125.21, 118.49, 111.27, 109.68. IR (KBr) 3430, 2917, 2242, 2227, 1614, 1502, 997, 842, 551 cm^{-1}. MS (EI) *m/z* (%): 194 (M^+, 100). HRMS (EI) calcd. for $C_{11}H_6N_4$, 194.0592; found 194.0604.

5-(4-Nitrophenyl)-1*H*-pyrazole-3-carbonitrile (2i).

White powder, mp 231-233 °C. ^{1}H NMR (DMSO-d_6, 300Hz): δ 7.67 (s, 1H), 8.33 (dd, 2H, *J* = 7.1, 2.0 Hz), 8.36 (dd, 2H, *J* = 8.9, 1.2 Hz). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 147.31, 141.83, 133.48, 126.58, 125.13, 124.52, 114.48, 107.59. IR (KBr) 3428, 3143, 2919, 2850, 2244, 1606, 1513, 1349, 1113, 995, 856, 568 cm^{-1}. MS (EI) *m/z* (%): 214 (M^+, 100). HRMS (EI) calcd. for $C_{10}H_6N_4O_2$, 214.0491; found 214.0491.

5-(3-Nitrophenyl)-1*H*-pyrazole-3-carbonitrile (2j).

White powder, mp 190–192 °C. ^{1}H NMR (DMSO-d_6, 300Hz): δ 7.67 (s, 1H), 7.80 (t, 1H, *J* = 8.0 Hz), 8.25 (t, 2H, *J* = 8.5 Hz), 8.70 (s, 1H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 148.89, 142.90, 132.37, 131.33, 129.9, 124.10, 124.09, 120.49, 114.66, 109.95. IR (KBr) 3517, 3421, 2252, 1629, 1517, 1361, 1012, 800, 740, 572 cm^{-1}. MS (EI) *m/z* (%): 214(M^+, 100). HRMS (EI) calcd. for $C_{10}H_6N_4O_2$, 214.0491; found 214.0488.

5-(4-(Trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbonitrile (2k).

White powder, mp 170–172 °C. ^{1}H NMR (DMSO-d_6, 300Hz): δ 7.60 (s, 1H), 7.86 (d, 2H, *J* = 8.2 Hz), 8.10 (d, 2H, *J* = 8.2 Hz). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 143.58, 132.27, 126.75, 129.13, 126.75, 126.61, 125.56, 114.86, 109.81. IR (KBr) 3430, 2919, 2250, 1627, 1326, 1062, 557, 472 cm^{-1}. MS (EI) *m/z* (%): 237(M^+, 100). HRMS (EI) calcd. for $C_{11}H_6N_3F_3$, 237.0514; found 237.0514.

5-(4-(Methylsulfonyl)phenyl)-1*H*-pyrazole-3-carbonitrile (2l).

White powder, mp: 205–207 °C.^{1}H NMR (DMSO-d_6, 300Hz): δ 3.27 (s, 3H), 7.63 (s, 1H), 8.05 (d, 2H, *J* = 8.1 Hz), 8.11 (d, 2H, *J* = 8.3 Hz). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 143.41, 141.15, 133.05, 128.29, 126.91, 125.39, 114.84, 110.09, 43.83. IR (KBr) 3430, 3143, 2921, 2240, 1633, 1298, 1153, 779, 536 cm^{-1}. MS (EI) *m/z* (%): 247 (M^+, 100). HRMS (EI) calcd. for $C_{11}H_6N_3O_2S$, 247.0514; found 247.0416.

4,5,6,7-Tetrahydro-1*H*-indazole-3-carbonitrile (2m).

White powder, mp 145–147 °C. ^{1}H NMR ($CDCl_3$, 300Hz): δ 2.60–2.64 (m, 4H), 2.71–2.75 (m, 4H), 7.26 (s, 1H), 11.77 (brs, 1H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 140.56, 121.94, 120.58, 115.32, 22.52, 22.17,

20.62, 19.58. IR (KBr) 3432, 2919, 2237, 1633, 1068, 468 cm^{-1}. MS (EI) m/z (%): 147 (M^+, 100). HRMS (EI) calcd. for $C_8H_9N_3$, 147.0796; found 147.0797.

3-Hydroxy-estra-1,3,5(10)-triene[17,16-*c*]pyrazole-5'-carbonitrile (2n).

White powder, mp 221–222 °C. ^1H NMR ($CDCl_3$, 300Hz): δ 7.14 (d, 1H, J = 9.2 Hz), 6.60 - 6.72 (m, 2H), 1.00–3.00 (m, 13H), 0.93 (s, 3H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 167.43, 159.88, 155.51, 137.45, 132.15, 132.00, 129.13, 127.92, 118.36, 115.46, 44.07, 41.84, 37.43, 31.62, 30.43, 27.23, 23.97, 22.57, 19.12, 14.03. IR (KBr) 3426, 2923, 2242, 1616, 1079, 561 cm^{-1}. MS (EI) *m/z* (%): 319 (M^+, 80), 159(M^+, 100). HRMS (EI) calcd. for $C_{20}H_{21}N_3O$, 319.1685; found 319.1678.

Crystallography. Colorless crystals of **2c** were obtained by recrystallization in MeOH, The crystal data was collected on a Bruker SMART CCD detector employing graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) at 293 K and operating in the φ-ω scan mode. The structure was solved by direct methods and refined with full-matrix least-squares calculations on F2 using SHELX-97. All non-hydrogen atoms were refined anisotropically. The hydrogen atom positions were geometrically idealized and allowed to ride on their parent atoms. Crystal data for 5-Phenyl-1*H*-pyrazole-3-carbonitrile (**2c**): $C_{10}H_7N_3$, M = 169.19, white needle, 0.285 x 0.127 x 0.115 mm^3, Rhombohedral, space group R3, a = 32.877 (5) Å, b = 32.877 (5) Å, c = 4.4202 (8) Å, α = 90 °, β = 90 °, γ = 120 °, V = 4137.6 (11) $Å^3$, Z = 18, D_{calc} = 1.275 mg/m^3, 1816 unique reflections, R1 = 0.0573, wR2 = 0.1296, GOF = 0.937. CCDC-848480 contains the supplementary crystallographic data for this compound. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK. [fax: (+44) 1223-336-033; or email: deposit@ccdc.cam.ac.uk).

ACKNOWLEDGEMENTS

The authors are grateful to the National Natural Science Foundation of China (20772138, 90713034), and Shanghai Municipality Science and Technology Development Fund (09JC1416600) for financial support.

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