Three-component One-pot Synthesis of Indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrazole Derivatives in Aqueous Media

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A series of indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrazoles was synthesized by the three-component reaction of aldehyde, 5-amino-3-methyl-1-phenylpyrazole and 1,3-indenedione in the presence of SDS in aqueous media. The structures were characterized by IR, ^{1}H NMR, high resolution mass spectra and were further confirmed by X-ray diffraction analysis.

Keywords: Indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrazole; Three-component reaction; Aqueous media.

INTRODUCTION

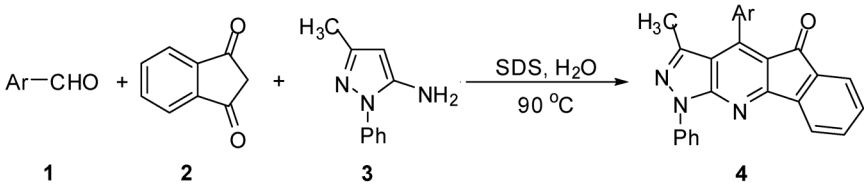
The need to reduce the amount of toxic waste and by-products arising from chemical processes requires increasing emphasis on the use of less toxic and more environmentally compatible materials in the design of new synthetic methods.[1] One of the most promising approaches uses water as the reaction medium.[2] Breslow,[3] who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic reactions in the 1980s. In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions.[4] The aqueous medium with respect to organic solvents is less expensive, less dangerous and more environmentally friendly. Generally, the low solubiblity[5] of most reagents in water is not an obstacle to the reactivity, which on the contrary, is reduced with the use of cosolvents.

Multi-component reactions (MCRs), in which multiple reactions are combined into one synthetic operation have been used extensively to form carbon-carbon bonds in synthetic chemistry.[6] Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. In the past decade there has been tremendous development in three- and four-component reactions and great efforts continue to be made to develop new MCRs.[7]

Sodium dodecyl sulfate (SDS) is an anionic surfactant and has been used in organic synthesis. Otto et al.[8] reported a Diels-Alder reaction using combined Lewis acid and SDS catalysis. Mori et al.[9] reported the method to greatly improve the enantioselectivity of lipase-catalyzed hydrolysis of racemic butyl propanoates in an aqueous buffer solution using SDS as an additive. Vashchenko et al.[10] reported palladium-catalyzed Suzuki cross-coupling reaction in the presence of SDS. Recently, Sharma et al.[11] reported an efficient synthesis of 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines by the reaction of 1,3-diaryl-2-propenones and 2-aminothiophenol in water catalyzed by SDS.

Pyrazolopyridines have received more and more attention in recent years. Pharmaceutical research into these kinds of compounds have been reported, such as a potent cyclin dependent kinase 1 (CDK1) inhibitor,[12] HIV reverse transcriptase inhibitorts,[13] CCR1 antagonists,[14] protein kinase inhibitors,[15] and inhibitors of cGMP degradation, together with several herbicidal and fungicidal activities.[16] On the other hand, indenopyridine compounds have shown a wide range of biological activities such as calcium antagonistic,[17] antioxidant,[18] antihistamine and antidepressant activities,[19] and have also acted as phosphodiesterase (PDE) inhibitors,[20] and NK-1 and dopamine receptor ligands.[21] Recently, several approaches have been developed for the synthesis of the indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrazole derivatives by three-component reaction of aldehyde, 1,3-indenedione and 5-amino-3-methyl-1-phenyl pyrazole in DMF[22] or in ethanol catalyzed by L-proline.[23] However, they were reacted in organic solvents[22,23] or had low yields.[22] Based on our previous studies on the use of water as solvent for carrying out carbon-carbon bond forming reactions un-

Scheme I



der heterogeneous catalysis,[24] we now report the synthesis of indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrazole derivatives (Scheme I) in aqueous media.

RESULTS AND DISCUSSION

When aromatic aldehyde **1**, 1,3-indenedione **2** and 5-amino-3-methyl-1-phenylpyrazole **3** were stirred for 4-13 h at 90 °C in aqueous medium in the presence of SDS, 3-methyl-1-phenyl-4-aryl-5-oxoindeno[2′,1′:5,6]pyrido[2,3-*d*]pyrazole **4** was obtained in good yields. The results are summarized in Table 1.

Table 1 shows the results using a series of substituted aromatic aldehydes that undergo the reaction to give high yields (90-98%) of the products. This procedure does not require the use of any organic solvent. In this reaction SDS is necessary. If SDS is not added the reaction takes a long time and the yield will be very low. The role of the SDS is to form micelles. This protocol could be applied to the aromatic aldehydes with either electron-withdrawing groups (such as nitro and halide groups) or electron-donating groups (such as alkyl, hydroxy and alkoxyl groups).

The structures of products **4** were identified by IR, ^{1}H NMR and HRMS. The structure of compound **4b** was further confirmed by crystal X-ray analysis. Fig. 1 shows an X-ray crystal structure of compound **4b**. The most important geometric features of this new compound **4b** are listed in Table 2.

Though the detailed mechanism of this reaction has not been clarified yet, the formation of **4** can be explained by the possible mechanism presented in Scheme II. The reaction occurs via an initial formation of the α,β-unsatu-

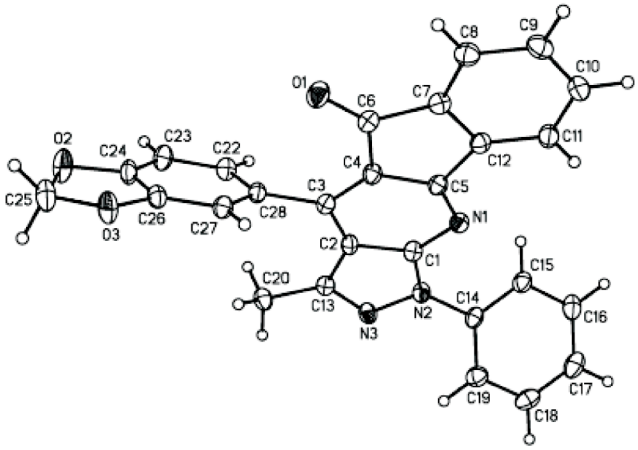


Fig. 1. Molecular structure of **4b**.

Table 1. Synthesis of indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrazoles in aqueous media

Entry	R	Reaction Time (h)	Yield (%)	m.p. (°C)	Lit. m.p. (°C)
4a	4-$CH_3OC_6H_4$	8	96	224-226	224-225[22]
4b	3,4-$OCH_2OC_6H_3$	6	97	223-225	223-224[22]
4c	4-HOC_6H_4	6	92	> 300	316-318[23]
4d	3,4-$(CH_3O)_2C_6H_3$	7	95	229-231	230-231[23]
4e	4-$(CH_3)_2NC_6H_4$	13	98	244-246	241-242[23]
4f	4-ClC_6H_4	4	98	273-275	269-270[23]
4g	4-BrC_6H_4	7	95	276-278	274-276[22]
4h	2,4-$Cl_2C_6H_3$	5	93	183-185	182-184[23]
4i	3,4-$Cl_2C_6H_3$	9	90	200-202	192-194[23]
4j	4-$NO_2C_6H_4$	12	98	> 300	318-319[23]
4k	Thiophen-2-yl	13	97	233-235	232-233[23]
4l	Pyridin-3-yl	2	98	212-214	216-217[23]
4m	CH_3CH_2	4	88	202-204	207-208[23]
4n	$CH_3CH_2CH_2$	4	86	142-144	146-148[23]

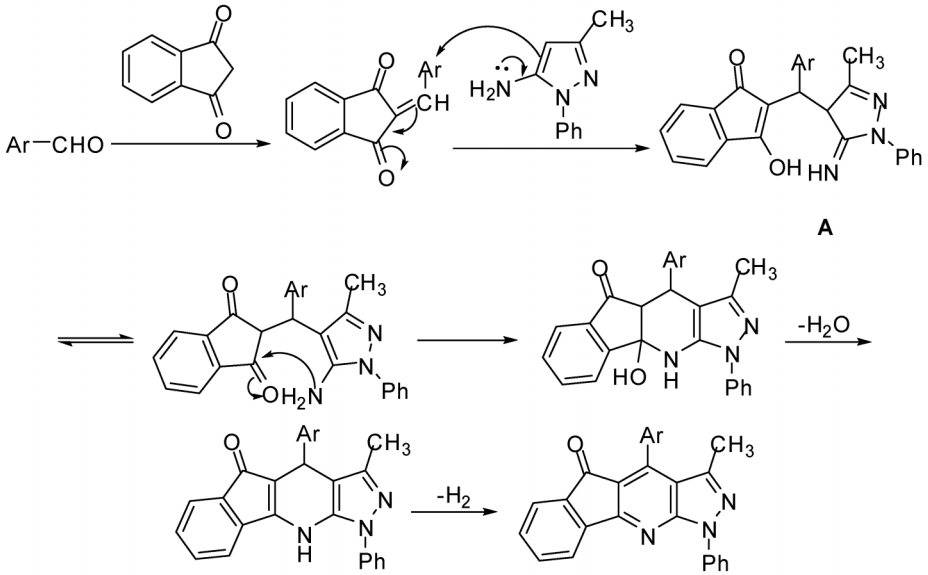
Table 2. Crystal data and structure refinement for compound **4b**

Empirical formula	$C_{27}H_{17}N_3O_3$	
Formula weight	431.44	
Temperature	193(2) K	
Wavelength	0.710730 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.8305(14) Å	α = 71.707(12)°
	b = 10.0706(16) Å	β = 72.455(13)°
	c = 12.6909(17) Å	γ = 81.468(15)°
Volume	1019.9(3) Å^3	
Z	2	
Density (calculated)	1.405 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F (000)	448	
Crystal size	0.30 mm × 0.25 mm × 0.18 mm	
Theta range for data collection	3.13° to 25.35°	
Index ranges	-10 ≤ h ≤ 10, -12 ≤ k = 12, -13 ≤ l ≤ 15	
Reflections collected	10081	
Independent reflections	3704 [$R_{(int)}$ = 0.0574]	
Refinement method	Full-matrix Least-squares on F^2	
Data/restraints/parameters	3704/0/300	
Goodness-of-fit on F^2	1.108	
Final Rindices [I > 2 signa (I)]	R_1 = 0.0660, wR_2 = 0.1340	
R indices (all data)	R_1 = 0.1049, wR_2 = 0.1518	
Largest diff. peak and hole	0.285 and -0.222 eÅ^{-3}	

rated ketone from the condensation of aldehyde and 1,3-indenedione as shown in Scheme II, which suffers nucleophilic attack to give the Michael adduct [A]. The intermediate [A] then isomerizates, cyclizes, dehydrates and subsequently loses a hydrogen molecule to afford the fully aromatized compound.

In summary, we developed an efficient three-component reaction of an aromatic aldehyde, 3-methyl-1-phenyl-5-aminopyrazole and 1,3-indenedione for the synthesis of indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrazole derivatives using

Scheme II



water as reaction medium. Compared with previous methods, this new protocol has the advantages of simple operation, higher yields, low cost and is an environmentally benign procedure.

EXPERIMENTAL SECTION

Melting points were determined with a TX-5 microscopic melting-point apparatus and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr. ^{1}H NMR spectra were measured on a Bruker DPX-400 MHz spectrometer using TMS standard and DMSO-d_6 as solvent. High resolution mass spectra were obtained using a TOF-MS instrument.

Typical procedure for preparation of indeno[2′,1′:5,6]-pyrido[2,3-*d*]pyrazole (4) derivatives

A mixture of aromatic aldehyde **1** (2 mmol), 1,3-indenedione **2** (2 mmol), 3-methyl-1-phenyl-5-aminopyrazole **3** (2 mmol) and SDS (0.2 g) in H_2O (10 mL) was stirred for 4-13 h at 90 °C, then cooled to room temperature. The crystalline powder formed was collected by filtration and washed with water. The crude products were purified by recrystallization from DMF to give **4**.

3-Methyl-1-phenyl-4-(4-methoxyphenyl)-5-oxoindeno -[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4a)

IR (KBr) ν (cm^{-1}): 2932, 1710, 1608, 1559, 1510, 1463, 1438, 1384, 1327, 1292, 1246, 1201, 1152, 1035, 834, 786, 757, 727; ^{1}H NMR (DMSO-d_6) δ: 8.28 (d, J = 8.0 Hz, 2H, ArH), 7.97 (d, J = 7.2 Hz, 1H, ArH), 7.75-7.71 (m, 1H, ArH), 7.64-7.57 (m, 4H, ArH), 7.51-7.41 (m, 3H, ArH), 7.10 (d, J = 8.4 Hz, 2H, ArH), 3.89 (s, 3H, CH_3O), 2.04 (s, 3H, CH_3); HRMS: Calcd for $C_{27}H_{19}N_3O_2$: 417.1477, found 417.1474.

3-Methyl-1-phenyl-4-(benzo[*d*][1,3]dioxol-5-yl)-5-oxo-indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4b)

IR (KBr) ν (cm^{-1}): 3075, 2879, 1715, 1594, 1560, 1504, 1483, 1382, 1239, 1196, 1160, 1138, 1106, 1045, 942, 820, 764, 730; ^{1}H NMR (DMSO-d_6) δ: 8.24 (d, J = 8.0 Hz, 2H, ArH), 7.85 (d, J = 7.2 Hz, 1H, ArH), 7.67-7.50 (m, 5H, ArH), 7.37-7.35 (m, 1H, ArH), 7.10-7.06 (m, 2H, ArH), 6.97 (d, J = 8.0 Hz, 1H, ArH), 6.97 (s, 2H, OCH_2O), 1.93 (s, 3H, CH_3); HRMS: Calcd for $C_{27}H_{17}N_3O_3$: 431.1270, found 431.1264.

3-Methyl-1-phenyl-4-(4-hydroxyphenyl)-5-oxoindeno-[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4c)

IR (KBr) ν (cm^{-1}): 3364, 3073, 1688, 1612, 1593, 1511, 1463, 1440, 1385, 1292, 1272, 1197, 1083, 836, 764, 731; ^{1}H NMR (DMSO-d_6) δ: 9.89 (s, 1H, OH), 8.26 (d, J = 8.4 Hz, 2H, ArH), 7.90 (d, J = 7.6 Hz, 1H, ArH), 7.70-7.67 (m, 1H, ArH), 7.61-7.51 (m, 4H, ArH), 7.41-7.34 (m, 3H, ArH), 6.88 (d, J = 8.0 Hz, 2H, ArH), 2.01 (s, 3H, CH_3); HRMS: Calcd for $C_{26}H_{17}N_3O_2$: 403.1321, found 403.1317.

3-Methyl-1-phenyl-4-(3,4-dimethoxyphenyl)-5-oxoin-deno[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4d)

IR (KBr) ν (cm^{-1}): 3053, 2938, 1703, 1606, 1549, 1510, 1463, 1381, 1287, 1261, 1195, 1122, 965, 815, 762, 750, 729; ^{1}H NMR (DMSO-d_6) δ: 8.29 (d, J = 8.0 Hz, 2H, ArH), 7.99 (d, J = 7.2 Hz, 1H, ArH), 7.77-7.74 (m, 1H, ArH), 7.63-7.61 (m, 4H, ArH), 7.65-7.57 (m, 1H, ArH), 7.21 (s, 1H, ArH), 7.11 (s, 2H, ArH), 3.88 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 2.09 (s, 3H, CH_3); HRMS: Calcd for $C_{28}H_{21}N_3O_3$: 447.1583, found 447.1599.

3-Methyl-1-phenyl-4-(4-dimethylaminophenyl)-5-oxo-indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4e)

IR (KBr) ν (cm^{-1}): 3017, 1705, 1616, 1561, 1531, 1510, 1441, 1370, 1292, 1232, 1194, 1020, 992, 815, 768, 729, 701; ^{1}H NMR (DMSO-d_6) δ: 8.28 (d, J = 8.0 Hz, 2H, ArH), 7.95 (d, J = 7.2 Hz, 1H, ArH), 7.74-7.70 (m, 1H, ArH), 7.63-7.56 (m, 4H, ArH), 7.40-7.39 (m, 3H, ArH), 6.83 (d, J = 8.4 Hz, 2H, ArH), 3.04 (s, 6H, $(CH_3)_2N$), 2.13 (s, 3H, CH_3); HRMS: Calcd for $C_{28}H_{22}N_4O$: 430.1794, found 430.1783.

3-Methyl-1-phenyl-4-(4-chlorophenyl)-5-oxoindeno-[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4f)

IR (KBr) ν (cm^{-1}): 3054, 1711, 1653, 1597, 1557, 1461, 1383, 1270, 1179, 1084, 952, 867, 835, 767, 728; ^{1}H NMR (DMSO-d_6) δ: 8.27 (d, J = 8.0 Hz, 2H, ArH), 7.98 (d, J = 7.6 Hz, 1H, ArH), 7.77-7.73 (m, 3H, ArH), 7.64-7.52 (m, 6H, ArH), 7.44-7.40 (m, 1H, ArH), 2.00 (s, 3H, CH_3); HRMS: Calcd for $C_{26}H_{16}{}^{35}ClN_3O$: 421.0982, found 421.0976.

3-Methyl-1-phenyl-4-(4-bromophenyl)-5-oxoindeno-[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4g)

IR (KBr) ν (cm^{-1}): 3053, 1711, 1594, 1569, 1503, 1460, 1435, 1383, 1269, 1200, 1178, 1082, 952, 866, 831, 766, 726; ^{1}H NMR (DMSO-d_6) δ: 8.27 (d, J = 8.0 Hz, 2H, ArH), 7.98 (d, J = 7.6 Hz, 1H, ArH), 7.77-7.73 (m, 3H, ArH), 7.64-7.56 (m, 4H, ArH), 7.53-7.42 (m, 3H, ArH), 2.00 (s, 3H, CH_3); HRMS: Calcd for $C_{26}H_{16}{}^{79}BrN_3O$: 465.0477, found 465.0493.

3-Methyl-1-phenyl-4-(2,4-dichlorophenyl)-5-oxoindeno-[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4h)

IR (KBr) ν (cm^{-1}): 2953, 1708, 1596, 1566, 1506, 1465, 1382, 1249, 1200, 1122, 996, 788, 767, 754, 727; ^{1}H NMR (DMSO-d_6) δ: 8.27 (d, J = 8.0 Hz, 2H, ArH), 8.01 (d,

J = 8.0 Hz, 1H, ArH), 7.92 (s, 1H, ArH), 7.79-7.75 (m, 1H, ArH), 7.66-7.60 (m, 6H, ArH), 7.44-7.40 (m, 1H, ArH), 1.98 (s, 3H, CH_3); HRMS: Calcd for $C_{26}H_{15}{}^{35}Cl_2N_3O$: 455.0592, found 455.0585.

3-Methyl-1-phenyl-4-(3,4-dichlorophenyl)-5-oxoindeno-[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4i)

IR (KBr) ν (cm^{-1}): 3064, 1710, 1673, 1593, 1565, 1545, 1498, 1465, 1386, 1326, 1310, 1243, 1197, 1084, 951, 895, 837, 768, 756, 726; ^{1}H NMR (DMSO-d_6) δ: 8.24 (d, *J* = 8.0 Hz, 2H, ArH), 7.91-7.81 (m, 3H, ArH), 7.71-7.69 (m, 1H, ArH), 7.61-7.54 (m, 5H, ArH), 7.41-7.39 (m, 1H, ArH), 1.93 (s, 3H, CH_3); HRMS: Calcd for $C_{26}H_{15}{}^{35}Cl_2N_3O$: 455.0592, found 455.0586.

3-Methyl-1-phenyl-4-(4-nitrophenyl)-5-oxoindeno-[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4j)

IR (KBr) ν (cm^{-1}): 3062, 1708, 1591, 1566, 1519, 1504, 1437, 1383, 1346, 1290, 1245, 1180, 1153, 1084, 996, 914, 865, 850, 767, 728, 718; ^{1}H NMR (DMSO-d_6) δ: 8.42 (d, *J* = 8.0 Hz, 2H, ArH), 8.29 (d, *J* = 8.0 Hz, 2H, ArH), 8.04 (d, *J* = 7.2 Hz, 1H, ArH), 7.90 (d, *J* = 8.4 Hz, 2H, ArH), 7.80-7.77 (m, 1H, ArH), 7.66-7.59 (m, 4H, ArH), 7.46-7.42 (m, 1H, ArH), 2.00 (s, 3H, CH_3); HRMS: Calcd for $C_{26}H_{16}N_4O_3$: 432.1222, found 432.1220.

3-Methyl-1-phenyl-4-(thiophen-2-yl)-5-oxoindeno-[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4k)

IR (KBr) ν (cm^{-1}): 3050, 1704, 1592, 1562, 1511, 1499, 1460, 1380, 1336, 1246, 1220, 1192, 1117, 1082, 991, 806, 770, 752, 720; ^{1}H NMR (DMSO-d_6) δ: 8.26 (d, *J* = 8.4 Hz, 2H, ArH), 7.96-7.91 (m, 2H, ArH), 7.75-7.71 (m, 1H, ArH), 7.63-7.57 (m, 4H, ArH), 7.43-7.38 (m, 2H, ArH), 7.30-7.28 (m, 1H, ArH), 2.08 (s, 3H, CH_3); HRMS: Calcd for $C_{24}H_{15}N_3OS$: 393.0936, found 393.0917.

3-Methyl-1-phenyl-4-(pyridin-3-yl)-5-oxoindeno-[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4l)

IR (KBr) ν (cm^{-1}): 3061, 1716, 1595, 1559, 1501, 1383, 1247, 1153, 1118, 1028, 764; ^{1}H NMR (DMSO-d_6) δ: 8.78-8.77 (m, 2H, ArH), 8.27 (d, *J* = 7.6 Hz, 2H, ArH), 8.04 (d, *J* = 8.0 Hz, 1H, ArH), 7.99 (d, *J* = 7.6 Hz, 1H, ArH), 7.75 (t, *J* = 8.0 Hz, 1H, ArH), 7.64-7.58 (m, 5H, ArH), 7.42 (t, *J* = 7.6 Hz, 1H, ArH), 2.01 (s, 3H, CH_3).

3-Methyl-1-phenyl-4-ethyl-5-oxoindeno[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4m)

IR (KBr) ν (cm^{-1}): 2968, 1704, 1585, 1500, 1384, 1193, 1129, 755; ^{1}H NMR (DMSO-d_6) δ: 8.25 (d, *J* = 7.6 Hz, 2H, ArH), 7.94 (d, *J* = 7.6 Hz, 1H, ArH), 7.76-7.71 (m, 2H, ArH), 7.60-7.58 (m, 3H, ArH), 7.41-7.34 (m, 1H, ArH), 2.71 (s, 3H, CH_3), 2.62-2.56 (m, 2H, CH_2), 1.33-1.27 (m, 3H, CH_3).

3-Methyl-1-phenyl-4-propyl-5-oxoindeno[2′,1′:5,6]pyrido[2,3-*d*]pyrazole (4n)

IR (KBr) ν (cm^{-1}): 2957, 1705, 1572, 1502, 1382, 1194, 1145, 1065, 753, 689; ^{1}H NMR (DMSO-d_6) δ: 8.25-8.23 (m, 2H, ArH), 7.86-7.85 (m, 1H, ArH), 7.69-7.58 (m, 5H, ArH), 7.40-7.39 (m, 1H, ArH), 2.65 (s, 3H, CH_3), 2.52-2.51 (m, 2H, CH_2), 1.68-1.66 (m, 2H, CH_2), 1.03-1.02 (m, 3H, CH_3).

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