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ORIGINAL PAPER

Efficient synthesis of pyrano[3,2-*c*]pyridines via a green and catalyst-free method at ambient temperature, and related DFT calculations

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Abstract Twelve medicinally important pyrano[3,2-*c*]pyridine derivatives were precipitated, with high yields, from ethanol solutions of malononitrile and (*E*)-3,5-bis(benzylidene)-4-piperidones at ambient temperature, requiring almost no work-up. Natural bond order calculations at the B3LYP/6-31+G* level indicate that electron-withdrawing groups on the phenyl rings deplete electron density on β-atoms (with respect to the carbonyl groups) of the piperidones, leading to higher yields of the corresponding products with shorter reaction times. This green methodology appears in a clear contrast to all previous reports, where either a catalyst and/or microwave was employed. So, simplicity and short reaction time, non-toxicity of the solvent, as well as economic feasibility are major advantages of this chemically waste-free process.

Keywords Pyrano[3,2-*c*]pyridine · Catalyst free · Ambient temperature · (*E*)-3,5-Bis(benzylidene)-4-piperidones · Malononitrile · DFT calculations

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Introduction

Environmentally benign methods for syntheses of pharmaceutically and industrially important compounds are in great demand [1]. Elimination of solvents in chemical processes or performing reactions in eco-friendly solvents such as water and ethanol are procedures of choice for diminishing the environmental hazards of chemical reactions [2].

Pyrano[3,2-*c*]pyridine derivatives are important heterocyclic compounds with a broad range of biological, medicinal, and pharmacological properties. Some of them are constituents of antitumor, anti-inflammatory, and antifungal compounds [3, 4]. In view of these useful properties, a number of preparative methods have been reported for the synthesis of these molecules. El-Subbagh et al. [3, 5, 6] reported the preparation of pyrano[3,2-*c*]pyridine derivatives through two-component reactions between α,β-unsaturated ketones and malononitrile in refluxing BuOH. Microwave irradiation in the presence of DMF solvent was reported by Han et al. [7, 8]. Also, these compounds have been synthesized via sodium ethoxide catalysis under solvent-free conditions [9], or in methanol containing sodium [10], or by hexadecyltrimethylammonium bromide in aqueous media and 110 °C [11], or by KF-Al_2O_3 [12], as well as in sodium hydroxide or piperidine under microwave irradiation [13].

Most of these protocols are time-consuming and demand either classical thermal reaction conditions or microwave irradiation and require disposal of toxic solvents and/or catalysts. Hence, following our desire to adopt more economical and efficient reaction conditions [14–17], herein we report a green and catalyst-free synthesis of pyrano-[3,2-*c*]pyridine derivatives **1a–1m** through reactions between malononitrile (**2**) and (*E*)-3,5-bis(benzylidene)-4-piperidones **3** in ethanol at room temperature.

Table 1 Effect of the solvent on the synthesis of **1e**

Entry	Solvent	Reaction conditions	Time/min	Yield/%
1	EtOH	r.t.	20	98
2	CH_3OH	r.t.	45	83
3	CH_3CN	r.t.	60	No reaction
4	CH_3CN	Reflux	150	40
5	H_2O/DMF	Reflux	30	80
6	H_2O	Reflux	240	No reaction
7	BuOH	Reflux	300	65–97 [3, 5, 6]
8	DMF, NH_4OAc	Microwave	7	95 [7]

Results and discussion

Our main objective was to develop an efficient, catalyst-free, and simple method for the synthesis of pyrano[3,2-*c*]pyridine derivatives **1** in a non-toxic solvent at room temperature. Initially, we examined the reaction of **2** with **3e** in different solvents including H_2O/DMF, H_2O, CH_3CN, CH_3OH, and EtOH (Table 1; Scheme 1). At the first glance, running the reaction in DMF/NH_4OAc under microwave irradiation seemed appealing because it gave 95 % yield of **1e** in only 7 min (Table 1, entry 8) [7]. Yet, such a procedure suffers from using an extra reagent (NH_4OAc) along with a toxic solvent (DMF) [18] as well as employment of possibly harmful and/or rather expensive electromagnetic waves. Consequently, EtOH was adopted as the solvent of choice because it is green and gives **1e** with a high yield of 98 % in a reaction time of 20 min at ambient temperature (Table 1, entry 1).

Using similar conditions (Table 1, entry 1), we probed substituent effects on this reaction by dissolving **2** in EtOH and adding in turn 12 derivatives of **3** carrying either an electron-donating or -withdrawing group on the phenyl ring (Table 2). The latter groups afforded shorter reaction times with higher yields of **1a**, **1c**, **1d**, **1e**, **1i**, **1j**, **1k**, and **1l** (Table 2, entries 1, 3–5, 9–12). In contrast, longer reaction times and lower yields were encountered for derivatives with electron-donating groups: **1b**, **1f**, **1g** (Table 2, entries 2, 6, 7).

All reactions proceeded smoothly and required just a simple filtration to give pure **1a**–**1l**. Interestingly **3m** gave only a trace of **1m** (Table 2, entry 13), as a result of the relatively lower charge on the β-atom caused by the extended conjugation (Scheme 2).

Natural bond order (NBO) calculations at the B3LYP/6-31+G* level indicated that electron-withdrawing groups on the phenyl rings (Table 2, entries 1, 3–5, 9–12) deplete electron density on the corresponding β-atoms compared to electron-donating moieties (Table 2, entries 2, 6, 7). This results in higher yields and shorter reaction times for **1a**, **1c**, **1d**, **1e**, **1i**, **1j**, **1k**, and **1l** than **1b**, **1f**, and **1g** (Table 3).

In summary, an eco-friendly methodology was developed for the efficient synthesis of pyrano[3,2-*c*]pyridine derivatives in ethanol at ambient temperature. NBO calculations at the B3LYP/6-31+G* level indicate that electron-withdrawing groups on the phenyl rings induce greater charge on the β-atoms of **3**, leading to higher yields of the corresponding **1** with shorter reaction times.

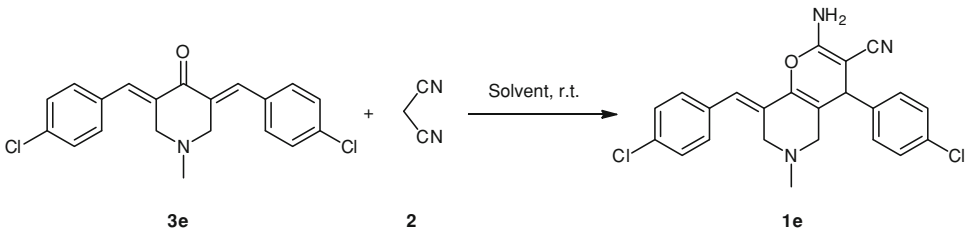
Experimental

Melting points were recorded on a Büchi B-540 apparatus. IR spectra were recorded on an ABB Bomem Model FTLA200-100 instrument. ^1H and ^{13}C NMR spectra were measured on a Bruker DRX-300 spectrometer, at 300 and 75 MHz, using TMS as an internal standard. Chemical shifts (δ) are reported relative to TMS, and coupling constants (J) are reported in Hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70-eV ionization potential. 3,5-Bis(benzylidene)-4-piperidones **3** were synthesized according to [3].

General procedure for the synthesis of pyrano[3,2-c]-pyridine derivatives

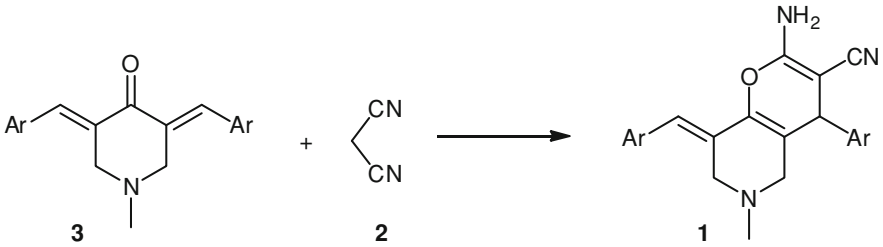
A mixture of 3,5-bis(benzylidene)-4-piperidone (0.33 mmol) and malononitrile (0.33 mmol) in 5 cm^3 ethanol was stirred at room temperature for an appropriate period of time (Table 2). After completion of the reaction (monitored by thin layer chromatography; petroleum ether/EtOAc 2:1), the product

Scheme 1



3e 2 1e

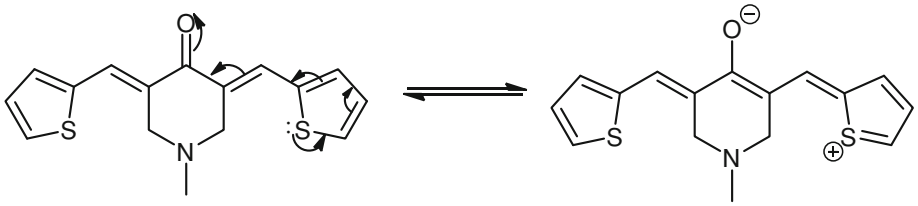
Table 2 Synthesis of pyrano[3,2-*c*]pyridines **3**



Entry	Product	Ar	Time/min	Yield[a]/%	M.p./°C	Lit. m.p./°C	References
1	**1a**	2,3-Cl_2-C_6H_3	25	98	213–215	–	–
2	**1b**	4-($C_6H_5CH_2O$)-C_6H_4	>60	89	193–195	–	–
3	**1c**	2-Cl-C_6H_4	20	92	213–216	208–210	[9]
4	**1d**	4-F-C_6H_4	10	98	204–205	197–198	[30]
5	**1e**	4-Cl-C_6H_4	20	98	238–239	238–240	[30]
6	**1f**	4-CH_3O-C_6H_4	60	80	203–204	203–204	[3]
7	**1g**	4-CH_3-C_6H_4	60	90	226–228	215–217	[8]
8	**1h**	C_6H_5	45	93	211–212	200–202	[8]
9	**1i**	4-NO_2-C_6H_4	15	96	238–240	238–240	[8]
10	**1j**	3-NO_2-C_6H_4	10	98	225–226	225–227	[8]
11	**1k**	4-Br-C_6H_4	30	95	245–246	245–246	[8]
12	**1l**	2,4-Cl_2-C_6H_3	25	95	198–200	199–200	[9]
13	**1m**	2-Thienyl	120	Trace	–	–	[3]

[a] Isolated yields

Scheme 2



was collected and recrystallized from 95 % EtOH to give the pure product.

(8E)-2-Amino-8-(2,3-dichlorobenzylidene)-4-(2,3-dichlorophenyl)-5,6,7,8-tetrahydro-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile
(**1a**, $C_{23}H_{17}Cl_4N_3O$)
M.p.: 213–215 °C; IR (KBr): $\bar{\nu}$ = 3,322, 3,260, 2,202, 1,678, 1,637, 1,601 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.09 (3H, s, N–CH_3), 2.51 (1H, d, J = 14.0 Hz), 3.02 (1H, d, J = 16.2 Hz), 3.15 (1H, d, J = 14.0 Hz), 3.31 (1H, d, J = 14.8 Hz), 4.7 (1H, s, CH), 6.94 (1H, s, C=CH), 7.05 (2H, s, NH_2), 7.24–7.44 (4H, m), 7.58 (2H, d, J = 8.0 Hz) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 44.2, 53.7, 54.2, 118.8, 119.9, 128.0, 128.9, 129.2, 129.4, 129.6, 130.3, 130.6, 132.0, 136.3, 139.5, 142.7, 160.1 ppm; MS (EI): *m/z* (%) = 42 (100), 81 (46), 113 (30), 149 (70), 181 (60), 216 (53), 250 (91), 293 (12), 346 (11), 390 (14), 449 (19), 492 (22).

(8E)-2-Amino-8-[4-(benzyloxy)benzylidene]-4-[4-(benzyloxy)phenyl]-5,6,7,8-tetrahydro-6-methyl-4H-pyrano[3,2-c]pyridine-3-carbonitrile (**1b**, $C_{37}H_{33}N_3O_3$)
M.p.: 193-195 °C; IR (KBr): $\bar{\nu}$ = 3,388, 3,301, 2,182, 1,683, 1,642, 1,606 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.13 (3H, s, N–CH_3), 2.54 (1H, d, J = 14.4 Hz), 2.94 (1H, d, J = 14.0 Hz), 3.25 (1H, d, J = 14.4 Hz), 3.45 (1H, d, J = 14.0 Hz), 3.97 (1H, s, CH), 5.06 (2H, s, OCH_2), 5.10 (2H, s, OCH_2), 6.75 (2H, s, NH_2), 6.83 (1H, s, C=CH), 7.00 (2H, d, J = 8.7 Hz), 7.03 (2H, d, J = 8.7 Hz), 7.12 (2H, d, J = 8.7 Hz), 7.18 (2H, d, J = 8.7 Hz), 7.29–7.46 (10H, m) ppm: ^{13}C NMR (75 MHz, DMSO-d_6): δ = 44.4, 53.9, 54.4,

Table 3 NBO charges for the β-atoms of **3a–3m** at B3LYP/6-31+G* level

Compound	Natural charge at β-atoms C-1′ and C-1″	Yield/%
3a	−0.1483	98
3b	−0.1526	89
3c	−0.1461	92
3d	−0.1404	98
3e	−0.1455	98
3f	−0.1629	80
3g	−0.1564	90
3h	−0.1473	93
3i	−0.1433	96
3j	−0.1435	98
3k	−0.1531	95
3l	−0.1496	95
3m	−0.1788	Trace

55.7, 113.0, 115.3, 115.5, 120.3, 120.4, 127.4, 129.4, 129.5, 130.9, 131.0, 132.3, 132.4, 139.1, 139.6, 139.7, 159.5, 159.6, 159.7, 162.8 ppm; MS (EI): *m*/*z* (%) = 42 (16), 65 (63), 91 (100), 131 (40), 174 (44), 198 (19), 222 (23), 250 (63), 382 (86), 410 (54), 473 (30), 501 (75), 567 (16).

Computational methods

Full geometry optimizations of **3a–3m** were accomplished without any symmetry constraints by means of hybrid functional B3LYP [19–21]. The applied basis set is comprised of Pople's well-known 6-31+G* basis set, using Gaussian 98 code [22–24] and an extra plus because of the importance of diffuse functions [25, 26]. The reliability of the optimized structures was confirmed through the development of the basis set B3LYP/6-31+G* [27, 28]. To obtain natural charge data of atoms NBO calculations were performed at the B3LYP/6-31+G* level [29].

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