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Mechanochemistry (grinding): An efficient route to synthesize of 6-amino-4 alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-carbonitrile

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ABSTRACT

Grinding was used as an effective instrument for the synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-carbonitriles by a four-component reaction of a mixture of ethyl acetoacetate, hydrazine hydrate, aldehyde and malononitrile without using any catalyst and solvent is reported.

KEYWORDS

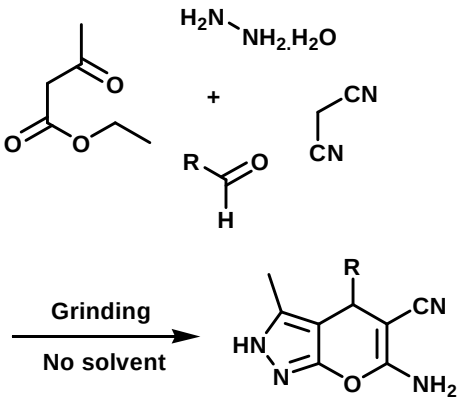
Grinding;
Dihydropyrano-[2,3-c]pyrazole;
Catalyst-free;
Solvent-free.

INTRODUCTION

Very often than not, mechanochemistry (grinding)[1] is used for organic synthesis under solvent and catalyst-free conditions, where the reactants are grinded either in a pestle and mortar or with the use of ball mills. Because of the high reactant concentrations and the efficient mixing, other solvent-free reactions, including those between solids with intermediate local melting and those with at least one liquid reactant, can benefit from the use of grinding. In chemical synthesis, grinding modifies the reaction conditions and enhances the reactivity of the reactants by mechanical activation. The increase of reactivity may be either due to mechanical-induced breaking of molecular bonds (mechanochemistry), or a result of the more efficient mixing and the large increase of reactant surfaces is close contact between the starting materials on a molecular scale[2].

In recent years, the synthesis of dihydropyrano[2,3-c]pyrazole derivatives is getting tremendous attention among the synthetic chemist for their diverse bioactivity profiles, which include anticancer[3a], anti-inflammatory[3b], insecticidal[3c], antimicrobial[3d], and analgesic properties[3e]. Nevertheless, the discovery of the inhibitory activity of the Chk1 kinase[4] by dihydropyrano[2,3-c]pyrazole derivatives from docking studies on a large electronic catalogue of compounds to its ATP-binding site, and by assaying a relatively small number of prioritised compounds having dihydropyrano[2,3-c]pyrazole moiety have prompted development of many efficient methods for their synthesis. Although most of the works along this line involved environmentally non-compatible base catalysis[5], recent reports suggest that such synthesis can be carried out in aqueous medium with highly environment-compatible catalysts, such as L-proline[6a], γ-alumina[6b], and per-6-amino-β-cyclodextrin[6c]. But the use of hazardous organic solvents either in the reaction process[7] or in the isolation and purification[5,6a-b] belies the claims of the development of green methodologies for the said synthesis. Traditional stirring of ethyl acetoacetate, hydrazine hydrate, aldehyde and malononitrile also led to formation of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano [2,3-c]pyrazolecarbonitrile[8], but yields

in most of the cases are not good. Here we wish to report the synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano [2,3-c]pyrazolecarbonitrile by grinding a mixture of ethyl acetoacetate, hydrazine hydrate, aldehyde and malononitrile in a mortar with a pestle without using any catalyst and solvent.



Scheme 1

EXPERIMENTAL

All reagents were commercially available and used without further purification. Most of the aldehydes are commercially available and purchased from Sigma Aldrich. Aldehydes in entry 14 was synthesized from their corresponding alcohols by PCC oxidation as per literature procedure[9]. All the products were characterized by IR, ^{1}HNMR, ^{13}CNMR, Mass spectroscopy and elemental analysis. The IR spectra were recorded on a Perkin Elmer spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a Bruker AC-400 using DMSO-d_6 as solvent and TMS as internal standard, unless otherwise stated.

General procedure

A mixture of ethyl acetoacetate (1 mmol) and hydrazine hydrate (1 equiv) was ground together to observe the instantaneous formation of a solid mass and then aldehyde (1 equiv) and malononitrile (1 equiv) was added into it. Upon grinding the mixture with a pestle in a mortar for the specified time, the starting materials got converted to the desired product quantitaively to give solid mass. Unless otherwise stated, the nearly pure crude products were purified by recrystallization from ethanol.

Spectral data of new compounds

6-Amino-4-(benzo[d][1,3]dioxol-5-yl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile, (1i)

IR (KBr): 1043, 1248, 1401, 1493, 1600, 1646, 2190, 3184, 3370 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.75 (s, 3H), 4.46 (s, 1H), 5.91 (s, 2H), 6.59 (m, 2H), 6.76 (s, 1H), 6.78 (s, 1H), 12.03 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): 9.7, 35.8, 57.3, 97.6, 100.9, 107.6, 107.9, 120.5, 120.7, 135.6, 138.5, 145.9, 147.3, 154.6, 160.7 ppm. MS (ES$^+$) *m/z* 297.0 (M + H)$^+$, 319.0 (M + Na)$^+$. Elemental analysis for $C_{15}H_{12}N_4O_3$: Calculated C 60.81, H 4.08, N 18.91; Observed C 60.76, H 4.04, N 18.95.

6-Amino-3-methyl-4-(pyridin-3-yl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile, (1m)

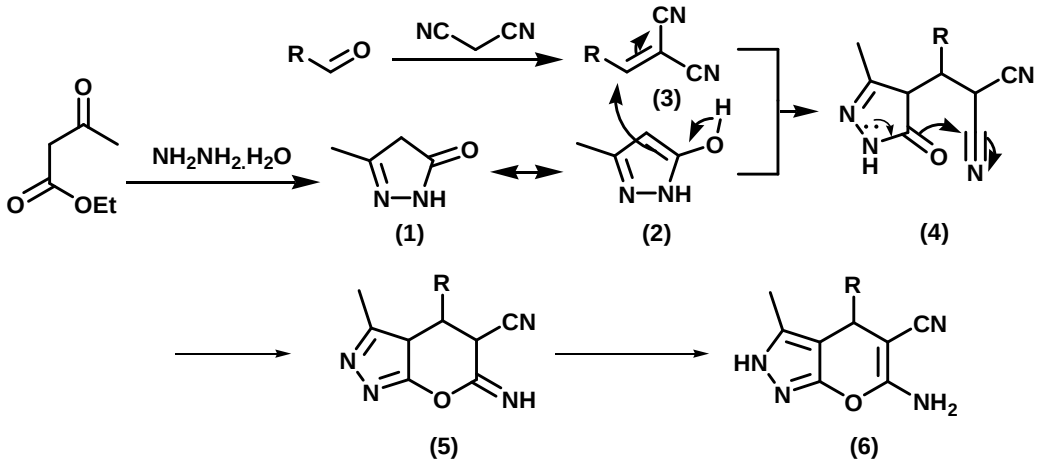
IR (KBr): 1049, 1414, 1493, 1606, 1646, 2203, 3177, 3350, 3396 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.72 (s, 3H), 4.63 (s, 1H), 6.93 (s, 1H), 7.28 (dd, *J* = 3.2, 12 Hz, 1H), 7.46 (d, *J* = 8 Hz, 1H), 8.38 (d, *J* = 2.4 Hz, 2H), 12.12 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): 9.7, 33.6, 56.2, 96.7, 120.6, 123.8, 135.1, 135.7, 139.7, 148.2, 148.7, 154.7, 161.0 ppm. MS (ES$^+$) *m/z* 254.0. Elemental analysis for $C_{13}H_{11}N_5O$: Calculated C 61.65, H 4.38, N 27.65; Observed C 61.68, H 4.34, N 27.59.

RESULTS AND DISCUSSION

To start with, we took a mixture of hydrazine hydrate (1 mmol) ethyl acetoacetate (1 equiv) in a mortar and ground to observe instantaneous liquification followed by formation of a solid mass. At the same time, we ground a mixture of *p*-nitrobenzaldehyde and malononitrile to get another set of solid mass. When both the fractions were ground together for 20 min, all the starting materials were found to be consumed to form a single product without any side product. After confirming the structure, we mixed the same set of reactants together and ground for 20 min to find that reaction gave many side products along with the desired product. This observation led us assume that the order of addition of aldehyde is very important factor because it may react with all the remaining reactants to generate the Schiff base, (4-nitrobenzylidene)hydrazine and Knovenagel condensation products. Therefore, we added the aldehyde (1 mmol) and malononitrile (1 equiv) to a premixed

hydrazine hydrate (1 equiv) and ethyl acetoacetate (1 equiv) mixture and ground for 20 min. To our pleasure, the reactants got converted to form only the desired product without any side product justifying our assumption regarding the order of addition of aldehyde. Instead of grinding, when we stirred the same mixture with a magnetic stirrer, we observed the formation of product within 10 min along with many by products, which is exactly may be the reason behind poor yields for the reaction, as reported by Reddy *et.al.*[8]

Having standerdize the process, we set out to generalize the application of this method to synthesize a series of dihydropyrano[2,3-c]pyrazoles from various aliphatic and aromatic aldehydes. In case of aromatic aldehydes, the nature of substituent on the phenyl rings did not have appreciable effect on overall yields of the product. The reaction gave excellent yields for the electron deficient aldehydes even at room temperature (entry 1-5, TABLE 1). The position (*o*-, *m*- and *p*-) of the substituent on the phenyl ring did not any noticable effect on either the reaction time or the yield. Less electrophilic aromatic aldehydes (entry 7-13, TABLE 1) having +M-effect have shown slower reactivity at room temperature and takes comparatively longer time to complete. This led to the conclusion that it is the inductive (I) effect which affect the reaction rate, not the mesomeric (M) effect. In the case of aliphatic aldehydes (entry 14-15), these effects were found very much negligible to make any huge



Scheme 2 : Plausible mechanism for catalyst-free synthesis of pyrano[2,3-c]pyrazoles

TABLE 1 : Synthesis of 6-amino-4 alkyl/aryl-3-methyl-2,4-dihydropyrano [2,3-c]pyrazole-carbonitriles *via* Scheme 1[a]

Entry	Aldehyde	Product[b]	Time (min)	% Yield[c]	m.p. (°C)	Ref
1	*p*-Nitrobenzaldehyde	a	20	98	191-194	[5d]
2	*m*-Nitrobenzaldehyde	b	25	95	190-192	[6c]
3	*o*-Nitrobenzaldehyde	c	20	95	189-191	[6b]
4	*p*-Chlorobenzaldehyde	d	35	88	171-173	[5e]
5	*m*-Bromobenzaldehyde	e	30	80	181-184	[5f]
6	Benzaldehyde	f	45	85	163-167	[5e]
7	*p*-Anisaldehyde	g	90	78	175-177	[5b]
8	*m*, *p*-Dimethoxybenzaldehyde	h	180	80	190-193	[5c]
9	*m*, *p*-Methylenedioxybenzaldehyde	i	180	82	200-203	
10	*p*-Hydroxybenzaldehyde	j	120	90	211-213	[5e]
11	*p*-Hydroxy-*m*-methoxybenzaldehyde	k	180	73	233-237	[5e]
12	*p*-*N*, *N*-Dimethylaminobenzaldehyde	l	180	75	162-165	[6c]
13	Pyridine-3-carbaldehyde	m	30	95	212-214	
14	n-Hexanal	n	300	72	147-150	[7a]
15	Butyraldehyde	O	270	74	143-145	[6c]

[a]**Reaction conditions: Stoichiometric ratio of ethyl acetoacetate, hydrazine hydrate, aldehyde, and malononitrile were ground with a pestle in mortar.** [b]**Unless otherwise stated, the products were purified by recrystallisation from ethanol.** [c]**Yield of the pure product.**

difference in reactivity. It has also been established that many sensitive functional groups, such as phenolic hydroxy, *N*,*N*-dimethylamino, methoxy, and methylenedioxy are very much compatible to our reaction conditions, as evident from their exceedingly good reaction yields.

As for the mechanism (Scheme 2), the 3-methyl-1*H*-pyrazol-5(4*H*)-one, **(1)** resulted from condensation of ethyl acetoacetate and hydrazine hydrate, undergoes tautomerisation to generate 5-methyl-4*H*-pyrazol-3-ol, **(2)** that undergoes Michael type addition with the Knovengel product, **(3)**. As reported in the earlier literature[6b], the intermediate **(4)** so generated, might have undergone Thorpe-Ziegler like intermolecular cyclization followed by tautomerization to give the dihydropyrano[2,3-c]pyrazole derivatives, **(6)**.

CONCLUSION

It has been reported that grinding of a mixture of ethyl acetoacetate, hydrazine hydrate, aldehyde and malononitrile at room temperature leads excellent synthesis of 6-amino-4 alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-carbonitrile almost quantitatively in pure form. The reaction works much better than conventional stirring by magnetic stirrer in a round-bottomed flask. The reaction takes very short time, requires no heating, conventional aqueous work-up and prification by column chromatography using hazardous solvent. Given the operational simplicity and environmental benign nature of this protocol, it can readily be applied to prepare large library of 6-amino-4- alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-carbonitrile for further biological studies.

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