Synthesis of 2-((1, 3-diphenyl-1*H*-pyrazol-4-yl) methylene) malononitriles

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ABSTRACT:

In the present investigation synthesis of 2-((1,3-diphenyl-1H-pyrazol-4-yl) methylene) malononitriles have been accomplished using substituted pyrazole aldehydes and malononitrile under grinding conditions. All the compounds were synthesized in good to excellent yield without any purification. The structures of these compounds were confirmed by their elemental analysis, IR, H^1 NMR and mass spectral data.

Keywords: *Synthesis, malononitrile, pyrazole moiety, mechanochemical grinding*

1. INTRODUCTION:

The condensation of aldehydes or ketones, usually possessing □-hydrogen, with compounds of the form Z-CH$_2$-Z' or Z-CH$_2$-Z where Z and Z' are electron withdrawing groups is called the Knoevenagel reaction [1]. Knoevenagel condensation is a classic reaction in organic synthesis [2], for its significant synthetic utility in C-C bond formation reactions, which is pivotal in organic chemistry [3]. Knoevenagel condensation has numerous applications in the elegant synthesis of the fine chemicals, speciality chemicals, drugs, dyes etc. [4].

Knoevenagel condensation is base catalyzed reaction and sometimes reported in acid catalysis also. In literature, the most of the synthetic protocols are being described in basic catalysts and organic/ aqueous medium. Various catalysts are known to effect the Knoevenagel condensation reactions using NaOH, KOH, $AlPO_4$-Al_2O_3 [5], $BiCl_3$ [6], $ZnCl_2$ [7] etc. Several other methods include P_2O_5-piperidine [8-9], modified hydrotalcite [10], KF-Al_2O_3 [11], graphite [12], IR irradiation [13] and solvent free reactions using mechanochemical grinding, ball milling, MWI and ultrasound sonication irradiation.

One of the important catalysts in Knoevenagel condensation is 1, 8 Diazabicyclo (5.4.0) undecene-7 or DBU. DBU is a bicyclic amine which is a clear light-yellow liquid of relatively low volatility. DBU has been widely used as a catalyst in many organic transformations such as Michael addition reaction of □-ketoesters to acrylates and enones [14], conjugate addition of acylsilanes to unsaturated esters and ketones [15], for intramolecular aldehyde-ketone benzoin reactions [16] and in combination with other catalysts for oxidation of aldehydes to methyl esters [17].

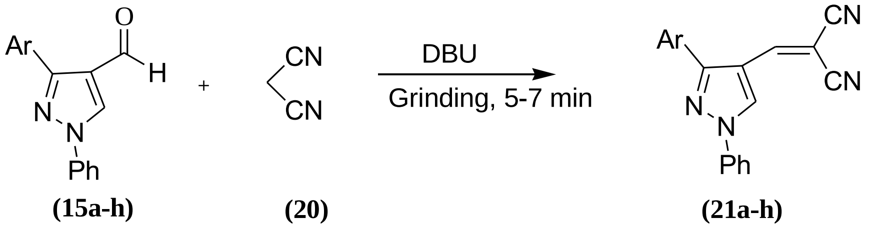
Mechanochemical grinding and ball milling are useful tools in organic synthesis that allows a highly efficient mixing of reagents under solvent free conditions [18, 19]. In organic chemistry it found numerous applications including C-C bond formations [20], amine condensations, in syntheses of heterocycles [21] and fullerene modifications [22]. In grinding, efficient mixing is particularly important in solid-solid reactions which continuously develop fresh contacts between the reacting components. Grinding and ball milling, in particular, milling generates new contact sites between the solids more efficiently. Due to high reagent concentrations and the efficient mixing, the reactions between solids with intermediate local melting and those with at least one liquid reagent gets benefited from such techniques.

In chemical synthesis, these tools modify the reaction conditions and enhance the reactivity of the reagents (mechanical activation). This is due to induced mechanical breaking of molecular bonds (mechanochemistry) and efficient mixing and the enormous increase of the reagent surfaces which both lead to a close contact between starting components on an almost molecular scale. Besides this, the factors like temperature and pressure have a significant role for such change in reactivities of the components. For example, during the milling, extreme conditions occur on the surfaces of two colliding bodies for times in the order of microseconds. According to a model developed by Urakaev and Boldyrev, local temperatures of 400-1500 K and pressures of thousand atmospheres can be part of typical conditions in the ball mill [23].

Condensation reactions of aldehydes with active methylene compounds in organic chemistry are well explored and thoroughly studied but in pyrazole chemistry the reaction is not exploited as such. In case of pyrazole, 4-formyl pyrazole was condensed with few active methylene compounds. Hangarge *et al.* [24] have carried out the reaction of 4-formyl pyrazoles with 3-methyl-1-phenyl pyrazolin-5-(4*H*)-one in Dioxane by using basic hydrotalcite at room temperature. Shindalkar and co-workers [25] reported the same reaction using heterogeneous borate-zirconia catalyst. Similarly, Shingare *et al.* [26] have reported the Knoevenagel condensation of 4-formyl pyrazoles with 1, 2-dihydro-3-methyl-1-phenylpyrazol-5-one.

DBU catalyzed Knoevenagel condensation has been described by Ware and co-workers [27] by reacting aromatic aldehydes and active methylene compounds like cyano ethylacetate, cyanoacetamide and malononitrile. Although in literature the reaction was studied in case of pyrazole aldehyde, the scope of the reaction is not explored and only two derivatives were synthesized by Knoevenagel condensation of 4-formyl pyrazole with malononitrile. Some reactions require expensive reagents, harsh reaction conditions and time-consuming purification techniques.

In present work, condensation of various 4-formyl pyrazoles with malononitrile is carried out by Knoevenagel condensation by DBU catalyst by mechanochemical grinding. (Scheme 1)



Scheme 1

2. EXPERIMENTAL SECTION:

2.1 Materials and methods

All the reagents and solvents were obtained from SD-Fine Chemicals ltd. and used without further purification. The melting points of all synthesized compounds were determined in open capillary tubes and are uncorrected. The purity of all compounds was checked by TLC on silica gel plates. IR spectra were recorded on Jasco FT-IR-4100 in KBr disc. H^1 NMR spectra were recorded on a Varian 400 MHz spectrometer in DMSO-d_6 and $CDCl_3$; chemical shifts (δ) were in ppm relative to TMS and coupling constant (J) were expressed in hertz (Hz) using tetramethylsilane as an internal standard. Mass spectra were recorded on a Macro mass spectrometer (Waters) by electro spray method (ESI). Elemental analysis was performed on Perkin-Elmer EAL-240 elemental analyzer.

2.2 Synthesis of the 2-((1, 3-diphenyl-1*H*-pyrazol-4-yl) methylene) malononitrile (21a)

To a mixture of 4-formyl pyrazole **15a** (0.5gm, 0.002mol) and malononitrile **20** (0.132gm 0.002mol) was added DBU (0.1gm) as catalyst in mortar. Following this, it was grounded by pestle till the completion of reaction (checked by TLC after 5 min.). The whole reaction mixture then transferred into water to separate out the product. The compound was filtered, dried and crystallized using alcohol.

Yield 86%, m.p. 190-192^{O}C H^1 NMR (DMSO-d_6) d: 7.48-7.68 (m, 8H); 7.92 (s, 2H); 8.2 (s, 1H); 9.2 (s, 1H) FT-IR(KBr) cm^{-1}: 3035, 2225 (C≡N), 2189 (C≡N), 1593 (C=N), 1528 (C=C). Mass: m/z 296 [M]+·, Anal. Calcd. for C19H12N4 (260.127), C, 77.03 H, 4.05, N, 18.91. Found: C, 76.98, H, 4.10, N, 18.87%.

Other derivatives of the series were synthesized by the above representative procedure and yield and physical constant of compounds were recorded as in Table X.

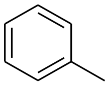
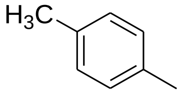
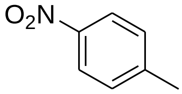
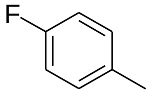
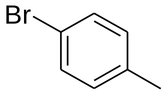
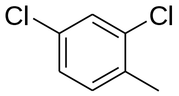
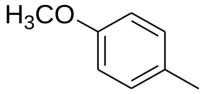
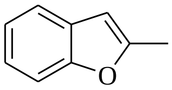
3. RESULT AND DISCUSSION

In the present investigation the reaction of formyl pyrazole **15a** with malononitrile **20** in presence of DBU catalyst under mechanochemical grinding afforded product **21a** in quantitative yield of 86%. The structure of **21a** was confirmed by its physical constant and IR spectral data. The formation of product **21a** was a neat reaction which does not require any solvent or temperature to complete the reaction. The catalyst DBU proved its efficacy and complete the reaction within 5 min. the formation of compound **21a** was established using analytical techniques viz. IR, NMR and Mass spectrometry. The IR spectrum of **21a** exhibited characteristic absorption bands in the region 2225cm^{-1} due to, another band at 2189 cm^{-1} due to C≡N stretching of two nitrile groups. Further, the presence of absorption band at 1528cm^{-1} due to C=N group indicated the existence of C-N bond in resulting compound.

The H^1 NMR spectrum of 21a displayed four signals. A multiplet at δ 7.48-7.68 due to 8 protons of aromatic ring, another singlet at δ 7.92 due to two aromatic protons and two singlets at δ 8.2 and 9.2 corresponding to pyrazolyl and ene protons respectively.

Mass spectrometry revealed the compound has molecular mass which agrees with the theoretical value.

Table X: Physical data of the compounds. 21(a-j)

Comp. No.	Ar	Yield (%)	M. P. (°C)
21a		86	190-192
21b		88	178-180
21c		70	202-204
21d		78	194-196
21e		82	172-174
21f		80	188-190
21g		75	198-200
21h		90	182-184

4. CONCLUSION

In the present investigation synthesis of 2-((1,3-diphenyl-1H-pyrazol-4-yl) methylene) malononitriles (21a-21h) have been achieved in good yield. The structures of these compounds were confirmed by their elemental analysis, IR, H^{1}NMR and mass spectral data.

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CONFLICT OF INTERESTS: The authors declare no conflict of interest.

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