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A Green and Facile Synthesis of Biopertinent Pyrazole-Decorated Nitriles and Acrylates under Catalyst-Free Conditions

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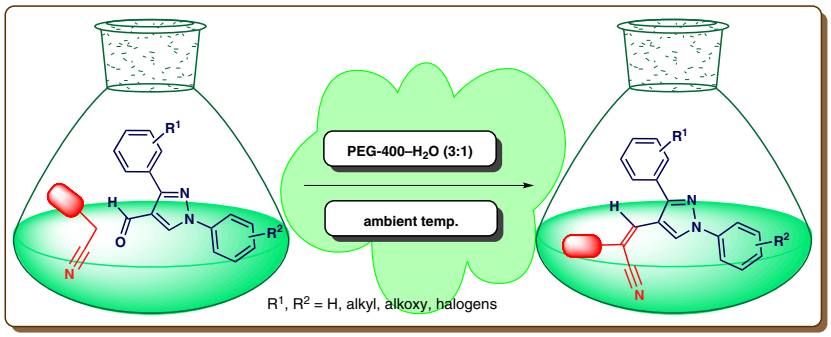

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Abstract A green and efficient methodology has been developed for the construction of 2-[(1,3-diaryl-4-pyrazolyl)methylene]malononitriles, potent antioxidant molecules, in good to excellent yields in five minutes from 1,3-diarylpyrazole-4-carbaldehydes and malononitrile using PEG-400 and water at ambient temperature under catalyst-free conditions. The PEG-400 could be reused without appreciable loss in the yield. The methodology has been extended to the synthesis of a diverse range of homo/heteroaryl-based nitriles and acrylates, reflecting its versatility.

Key words pyrazoles, green chemistry, condensation

Pyrazole-based chemical entities are one of the most important classes of nitrogen heterocycle possessing a diverse range of biological activities.[1] In continuation of our research on the synthesis of heterocycles and methodology development,[2] we initially synthesized 2-{[3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylene}malononitrile (**1a**) and 2-{[3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]methylene}malononitrile (**1b**) from their corresponding aldehyde precursors and malononitrile using sodium ethoxide and ethanol with a view to evaluate their antioxidant activities (Figure 1). Since **1a** and **1b** showed good antioxidant properties in their preliminary screening, we decided to synthesize an array of 2-[(1,3-diaryl-4-pyrazolyl)methylene]malononitriles for further exploration of antioxidant and anticancer activities.

Such an approach involving condensation between aldehydes and active methylene compounds, first reported in 1894,[3] can be effected using either a base or an acid. Various synthetic protocols include exploitation of zeolites, metal-based/encapsulated nanoparticles, ionic liquids, inorganic/organic bases, metal organic frameworks, ammonium salts, and mesoporous materials as catalysts.[4–6] We herein report a green and simple process for the construction of a diverse range of homo-/heteroaryl-based nitriles and acrylates.

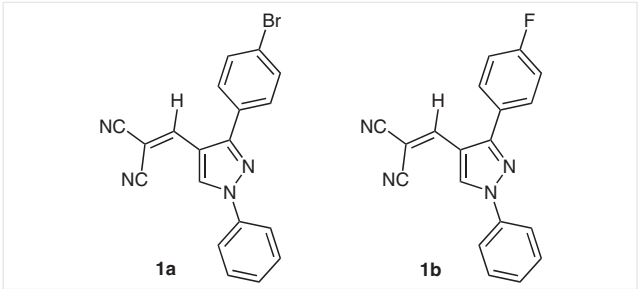
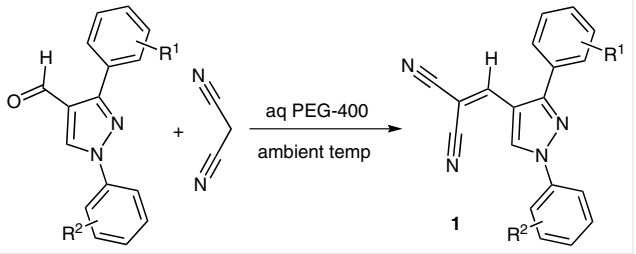


Figure 1 Pyrazole-based nitriles with antioxidant activity

Reaction between 3-(4-bromophenyl)-1-phenylpyrazolecarbaldehyde and malononitrile was chosen as a model one in this study (Scheme 1,Table 1).



Scheme 1 Synthesis of 2-[(1,3-diaryl-4-pyrazolyl)methylene]malononitriles **1**

Table 1 Optimization of the Model Reaction

Entry	Cat. (0.5 equiv)	Solvent	Yield **1a** (%)
1	–	H_2O	–
2	–	H_2O (50 °C)	trace
3	–	H_2O (100 °C)	trace
4	$(n\text{-}Bu)_4N^+Br^-$	H_2O	trace
5	$(n\text{-}Bu)_4N^+Br^-$	H_2O (100 °C)	<10
6	$Bn(Et)_3N^+Cl^-$	H_2O	trace
7	$Bn(Et)_3N^+Cl^-$	H_2O (100 °C)	<10
8	NH_4OAc	H_2O	trace
9	NH_4OAc	H_2O (100 °C)	<10
10	K_2CO_3	H_2O	trace
11	K_2CO_3	H_2O (100 °C)	<10
12	KOH	H_2O	trace
13	KOH	H_2O (100 °C)	<10
14	–	PEG-400	86
15	–	PEG-400[a]	97
16	–	PEG-400[b]	96

[a] Reactants were stirred in a PEG-400–H_2O (3:1) mixture at ambient temperature.
[b] Reactants were stirred in a PEG-400–H_2O (2:1) mixture at ambient temperature.

When equimolar amounts of model reactants were stirred under catalyst-free conditions in water at ambient temperature, the product **1a** was not formed even after 12 hours. Elevating the reaction temperatures (i.e., at 50 °C and 100 °C) also led to no reaction. Attempts utilizing phase-transfer catalysts such as tetrabutylammonium bromide and benzyltriethylammonium chloride as well as common bases such as ammonium acetate, potassium carbonate, and potassium hydroxide in water (at ambient temperature and 100 °C) were also ineffective. However, Fujita et al., Xie et al., and Zhang et al. have performed this type of reaction efficiently in water,[6b,7] but very specific catalysts are vital.

Polyethylene glycols (PEG) have a diversity of benign properties as they are nonvolatile and biocompatible, have low flammability, and show good stability towards bases, acids, elevated temperatures, and some of the oxidation/reduction systems.[8] When the model reaction was performed in PEG-400 under catalyst-free conditions at ambient temperature, to our satisfaction, the target **1a** was obtained in 86% yield in just a few minutes. The model reaction was also executed using some common protic solvents. When the reaction was performed either in ethanol or methanol at ambient temperature for two hours, no significant improvement in the yield was observed. In addition, use of branched alcohols, such as isopropanol and tertiary butanol, also resulted in poor yields though slightly higher than the former. Surprisingly, addition of water to PEG-400 (i.e., PEG–H_2O = 3:1) improved the yield significantly compared to the use of PEG-400 alone, and the reaction was also complete within two minutes (Table 1). Further increase in the proportion of water (PEG-400/H_2O ratio to 2:1) resulted in almost no appreciable change in the yield. Thus, stirring equimolar amounts of 3-(4-bromophenyl)-1-phenylpyrazolecarbaldehyde and malononitrile in aqueous PEG-400 (3:1 ratio) at ambient temperature was found to be the optimal conditions for the efficient synthesis of **1a**.[9] Luo et al.,[10] Ye et al.,[11] and Siddiqui et al.[12] reported the reaction of commercially available simple aldehydes with malononitrile to produce their corresponding olefins using PEG, however, modification of PEG (i.e., tertiary amine functionalized ionic liquid, diethylamine-functionalized PEG, and sulfuric acid modified PEG, respectively) was required prior to use.

The effect of variation in the substrate structure was then investigated. Although the model reaction was complete within a couple of minutes, all the reactions were carried out for five minutes as some unreacted starting aldehyde was observed in a few cases after two minutes. Akin to the model aldehyde, all the other pyrazole-based carbaldehydes also produced the corresponding (pyrazolylmethylene)malononitriles **1b–j** in good to excellent yields irrespective of the nature of the substituents (Table 2).[13] To investigate the reactivity on a larger scale, the model reaction was then performed with fivefold increase in the concentration of the substrates (i.e., 5.0 mmol). In this case, the corresponding product **1a** was formed in good yield (83%) within five minutes.

Table 2 Green and Facile Synthesis of Pyrazole-Decorated Nitriles in PEG400–H_2O (3:1) at Ambient Temperature

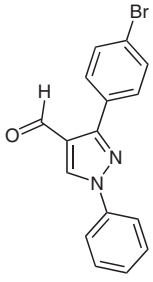
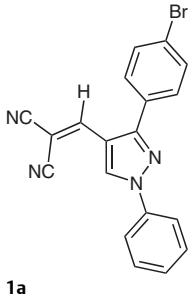
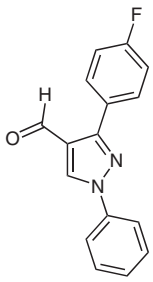
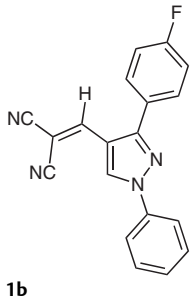
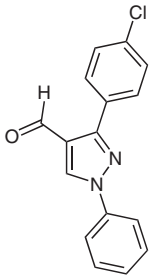
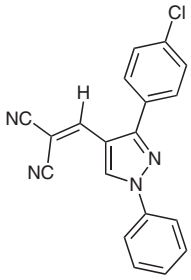
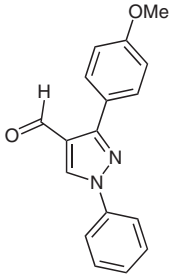
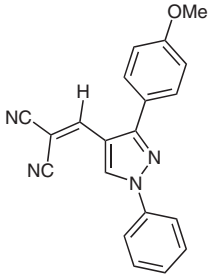
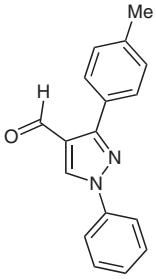
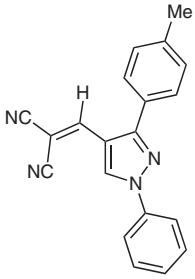
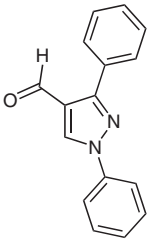
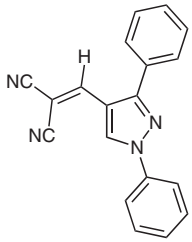
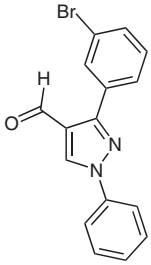
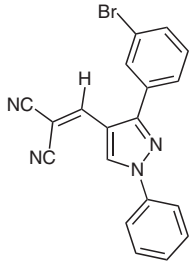
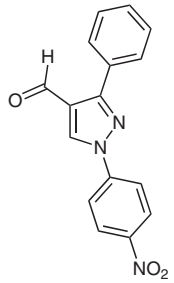
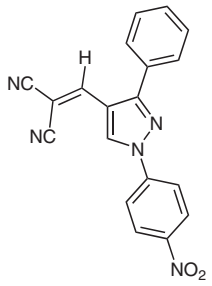
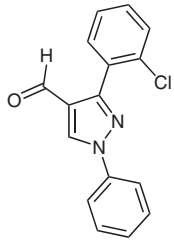
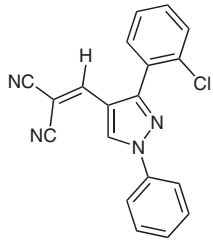
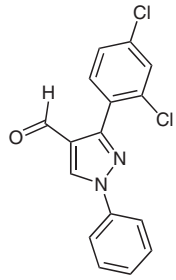
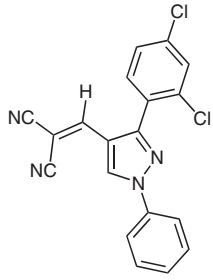
Entry	Reactant	Product	Yield (%)
1		 **1a**	97
2		 **1b**	95

Table 2 (continued)

Entry	Reactant	Product	Yield (%)
3		 **1c**	92
4		 **1d**	94
5		 **1e**	96
6		 **1f**	96
7		 **1g**	94
8		 **1h**	88
9		 **1i**	92
10		 **1j**	89

For further exploration of the reaction scope, substituted benzaldehydes were also utilized in place of the pyrazole-based carbaldehydes. Notably, all furnished the corresponding arylidenemalononitriles **2a**–**f** in good to excellent yields within five minutes irrespective of the nature of the substituents (Table 3).

To demonstrate the system's versatility, reactions of various pyrazole-based heteroaromatic aldehydes (1.0 mmol) with ethyl 2-cyanoacetate (1.0 mmol) were executed under the optimal conditions, and the results are summarized in Table 4.[16] In all the cases, the reactions proceeded smoothly at ambient temperature and culminated in the formation of the corresponding acrylates in good to excellent yields, albeit with longer reaction times (4 h). The longer reaction time is due to the lower reactivity of ethyl 2-cyanoacetate compared to malononitrile.

The recyclability of the PEG400 for the model reaction was subsequently explored. After separating the product by filtration, the filtrate was subjected to distillation under reduced pressure to separate the PEG400 and water. The PEG400 was then reused along with the required amount of water for further consecutive runs. The PEG400 could be re-

used for six consecutive runs with no appreciable loss in the yield of **1a**.

Table 3 Green and Facile Synthesis of 2-Arylidenemalononitriles in PEG400–H_2O (3:1) at Ambient Temperature

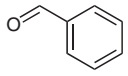
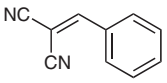
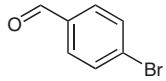
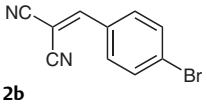
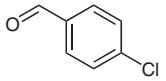
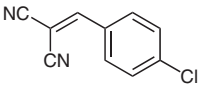
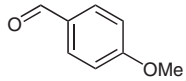
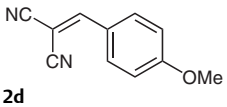
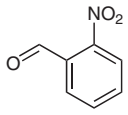
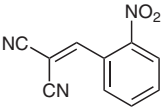
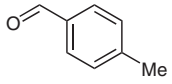
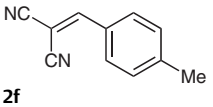
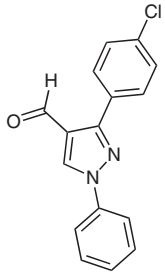
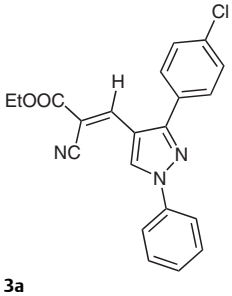
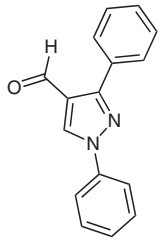
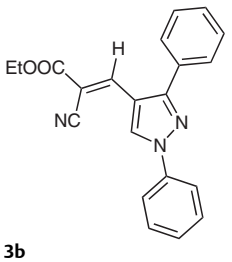
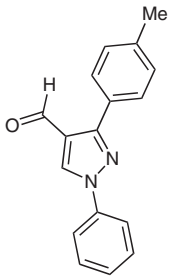
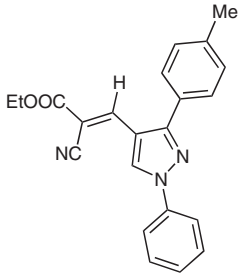
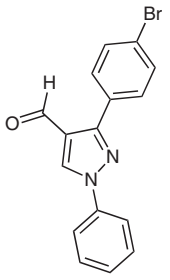
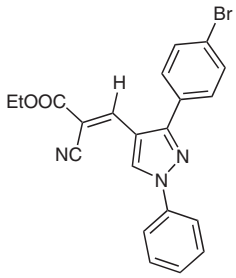
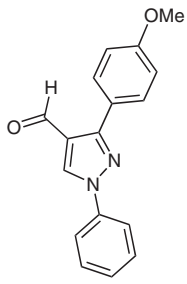
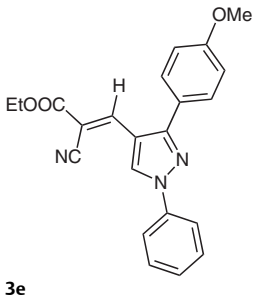
Entry	Reactant	Product	Yield (%)
1		 **2a**	94[8c]
2		 **2b**	97[6a]
3		 **2c**	95[14]
4		 **2d**	92[15]
5		 **2e**	88[6a]
6		 **2f**	93[8c]

Table 4 Green and Facile Synthesis of Pyrazole-Decorated Acrylates in PEG400–H_2O (3:1) at Ambient Temperature

Entry	Reactant	Product	Yield (%)[a]
1		 **3a**	97
2		 **3b**	95
3		 **3c**	92
4		 **3d**	96
5		 **3e**	94

[a] The reaction period was 4 h.

The expediency of this methodology lies in the fact that the reaction occurs in a rapid manner to furnish (pyrazolylmethylene)malononitriles in good to excellent yields using an aqueous PEG-400 solvent system under catalyst-free conditions. This method is applicable to the synthesis of a diverse range of aryl/heteroaryl-decorated malononitriles and acrylates from their corresponding aldehydes showing compatibility for various substituents such as halogen, alkyl, alkoxy, and nitro substituents in the substrates. PEG-400 is a cost effective, nonvolatile, biocompatible, and stable liquid with low flammability, and so this protocol is likely to have a broad scope for the synthesis of arylidene/heteroarylidenemalononitriles and acrylates.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380742.

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(9) **Typical Experimental Procedure**
An equimolar quantity of 3-(4-bromophenyl)-1-phenylpyrazolecarbaldehyde (1.0 mmol) and malononitrile (1.0 mmol) was stirred in polyethylene glycol (PEG-400)–H_2O (3:1) mixture at ambient temperature for 5 min when a solid was obtained. H_2O was then added, and the mixture was filtered and dried under reduced pressure to give 2-{[3-(4-bromophenyl)-1-phenylpyrazolyl]methylene}malononitrile (**1a**). Recrystallization from an EtOH–DMF mixture afforded analytically pure product as a pale yellow solid; mp 199–200 °C. IR (KBr): ν = 2362.8, 2223.9, 1570.1, 1518.0, 1436.9, 1402.2, 1338.6, 1240.2, 1076.3, 1008.8, 974.1, 954.8, 831.2, 812.0, 754.2, 729.1, 705.9, 682.8, 630.7, 609.5 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.01 (s, 1 H), 7.74–7.63 (m, 5 H), 7.50–7.41 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 151.3, 138.6, 132.5, 131.5, 130.2, 129.4, 128.9, 126.5, 123.9, 120.0, 115.0, 114.7, 114.0, 78.3. GC–MS: *m/z* = 374 [M^+]. Anal. Calcd for $C_{19}H_{11}BrN_4$: C, 60.82; H, 2.95; N, 14.93. Found: 60.85; H, 2.91; N, 14.91.

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(13) **Characterization Data of Representative Unsubstituted Nitrile 1f**
Pale yellow solid; mp 214–215 °C. IR (KBr): ν = 2357.0, 2223.9, 1581.6, 1521.8, 1502.6, 1469.8, 1448.5, 1344.4, 1238.3, 1184.3, 1018.4, 952.8, 821.7, 758.0, 715.6, 678.9, 611.4 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.06 (s, 1 H), 7.84–7.80 (m, 3 H), 7.58–7.52 (m, 7 H), 7.47–7.44 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 151.0, 138.5, 130.6, 129.6, 129.5, 129.3, 129.1, 128.9, 119.9, 114.9, 113.8, 78.5. GC–MS: *m/z* = 296 [M^+]. Anal. Calcd for $C_{19}H_{12}N_4$: C, 77.01; H, 4.08; N, 18.91. Found: 77.05; H, 4.11; N, 18.88.

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(16) **Characterization Data of Representative Acrylate 3a**
Off-white solid; mp 106–107 °C. IR (KBr): ν = 2987.7, 2218.1, 1726.3, 1643.4, 1593.2, 1519.9, 1429.3, 1373.3, 1267.2, 1236.4, 1190.1, 1093.6, 1020.3, 947.1, 887.3, 817.8, 721.2, 673.2, 578.6, 526.6 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.14 (s, 1 H), 8.24 (s, 1 H), 7.82 (d, *J* = 8.0 Hz, 2 H), 7.55–7.47 (m, 7 H), 7.41 (t, *J* = 6.9 Hz, 1 H), 4.37–4.32 (m, 2 H), 1.37 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.6, 155.1, 145.7, 138.8, 135.7, 130.4, 129.7, 129.4, 129.3, 128.3, 120.0, 116.6, 114.9, 100.2, 62.5, 14.2. MS: *m/z* = 377 [M^+]. Anal. Calcd for $C_{21}H_{16}ClN_3O_2$: C, 66.76; H, 4.27; N, 11.12. Found: C, 66.85; H, 4.33; N, 11.01.