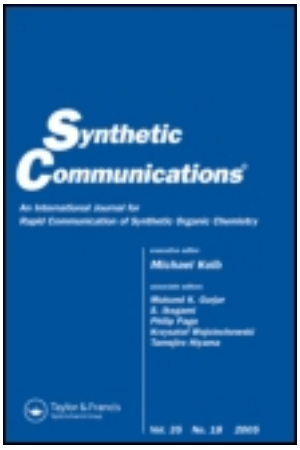

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Simple Procedure for the Synthesis of Arylmethylenemalononitrile Without Catalyst

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Abstract: Knoevenagel condensation of malononitrile with aromatic aldehydes can be achieved at room temperature in the absence of catalysts in short time, and the products of arylmethylenemalononitriles were isolated in a practically pure form without further purification.

Keywords: Arylmethylenemalononitrile, malononitrile, Knoevenagel condensation

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Arylmethylenemalononitriles are an important precursor of potentially bioactive pyrimidine derivatives,[1] and also are versatile tools for the construction of a variety of novel complex heterocycles.[2] They can be prepared via Knoevenagel condensation,[3–14] which is one of the most common synthetic methods of effecting carbon–carbon bond formation between malononitrile and various aromatic aldehydes. The reaction is usually catalyzed by various amines or their corresponding ammonium salts.[3] Subsequently, the use of Al_2O_3,[4] silica gel functionalized with amino groups,[5] $BiCl_3$,[6] CdI_2,[7] $TiCl_4$ base,[8] K_3PO_4,[9] KF/Al_2O_3,[10] zeolite,[11] xonntlite,[12] anion-exchange resin,[13] and many other methods[14] have been reported. More recently, Knoevenagel reactions under solvent-free conditions carried out by microwave irradiation,[15] by PEG400 and anhydrous K_2CO_3,[16] and by grinding methods[17] has rapidly increased.

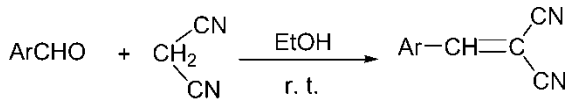
To our surprise, we found by chance that when aromatic aldehydes and malononitrile are added together in ethanol (Scheme 1), this reaction can be easily achieved at room temperature without catalysts in a few minutes or within a few hours. We have examined the reaction by various aromatic aldehydes containing electron-withdrawing or electron-donating groups as reactants; they all gave the expected result with good to excellent yield for almost all the tested substrates. The results are summarized in Table 1.

From Table 1, we can see that the electronic effect of substituents is the key element for the rates of the reaction and the product yield. The derivatives of benzaldehyde bearing electron-withdrawing substituents such as $-Cl$ and $-NO_2$ gave higher reaction rates and yields than those with electron-releasing groups such as $-N(CH_3)_2$ and $-OCH_3$. We cannot exactly explain the reason why a longer reaction time was necessary and gave lower yield for the reactants with 4-hydroxybenzaldehyde and 3-methoxy-4-hydroxybenzaldehyde. All the melting points of the known compounds conform to the references; the structures of the new compounds are characterized by IR and ^1H NMR.

In conclusion, we found a simple method for the synthesis of arylmethylenemalononitrile. This method has the advantages of an easy workup and milder reaction conditions.

EXPERIMENTAL

Melting points were determined on XT-5 microscopic melting-point spectrometer and are uncorrected. IR spectra were recorded on a Tensor 27



Scheme 1.

Table 1. Reaction time, yields, and melting points of the products **3**

Entry	Ar	Time (h)	Yields (%)	Mp (°C) Found	Mp (°C) Reported
3a	C_6H_5	3	63.6	82–84	82–83[17]
3b	4-$CH_3C_6H_4$	2	96.0	131–133	133–135[13]
3c	4-$CH_3OC_6H_4$	6	75.4	112–114	111–112[13]
3d	3,4-$OCH_2OC_6H_3$	6	88.4	200–201	199–201[13]
3e	4-ClC_6H_4	0.2	98.0	159–161	161–16[13]
3f	2-ClC_6H_4	0.2	92.0	97–98	95–96[13]
3g	3-$NO_2C_6H_4$	1.5	92.0	103–105	102–104[13]
3h	2,4-$Cl_2C_6H_3$	0.2	91.5	152–153	154–155[13]
3i	4-$(CH_3)_2NC_6H_4$	8	75.0	181–183	180–182[13]
3j	4-OHC_6H_4	24	48.5	190–191	186–187[13]
3k	3-CH_3O-4-OHC_6H_3	36	47.5	135–136	137–138[17]
3l	3-ClC_6H_4	0.2	91.0	119–120	120–121[13]
3m	4-BrC_6H_4	0.2	97.3	153–155	—
3n	2-$CH_3OC_6H_4$	4	94.6	84–86	—
3o	2,3-$(CH_3O)_2C_6H_3$	3	92.1	101–103	—
3p	3,4-$Cl_2C_6H_3$	0.2	94.6	145–147	—
3q	2,4-$(CH_3O)_2C_6H_3$	4	66.4	140–142	—
3r	2-NO_2-4-ClC_6H_3	1	89.3	138–140	—
3s	2-NO_2-3,4-$(CH_3O)_2C_6H_2$	4	86.9	148–150	—
3t	2-NO_2-3,4-$OCH_2OC_6H_2$	4	85.3	111–113	—
3u	2-$NO_2C_6H_4$	0.2	94.7	137–138	—
3v	3,4-$(CH_3)_2C_6H_3$	4	56.0	119–121	—
3w	3,4-$(CH_3O)_2C_6H_3$	4	86.0	141–142	—

spectrometer in KBr. ^{1}H NMR spectra were obtained from solution in $CDCl_3$ with Me_4Si as internal standard using a Bruker-400 spectrometer.

A 50-mL flask was charged with malononiteile 3.3 g (50 mmol), aromatic aldehydes (50 mmol), and ethyl alcohol (25 mL); the mixture was stirred at room temperature for times listed in Table 1. Without any further purification, the precipitate was filtered off to give **3**.

The IR and ^{1}H NMR of the new compounds are as follows.

3m: IR (KBr, ν, cm^{-1}): 3092, 3032, 2226, 1578, 1553, 1488, 1407, 1366, 1289, 1214, 1070, 1007, 938, 823 cm^{-1}. ^{1}H NMR: 7.69 (d, $J = 8.4$ Hz, 2H, ArH), 7.72 (s, 1H, CH═), 7.77 (d, $J = 8.4$ Hz, 2H, ArH).

3n: IR (KBr, ν, cm^{-1}): 3046, 2977, 2944, 2223, 1579, 1483, 1465, 1433, 1369, 1295, 1254, 1167, 1111, 1021, 755, 616 cm^{-1}. ^{1}H NMR: 3.93 (s, 3H, CH_3O), 6.99 (d, $J = 8.4$ Hz, 1H, ArH), 7.08 (dd, $J = 8.0$ Hz, $J' = 1.6$ Hz, 1H, ArH), 7.58 (dd, $J = 8.0$ Hz, $J' = 1.6$ Hz, 1H, ArH), 8.19 (d, $J = 8.4$ Hz, 2H, ArH), 8.31 (s, 1H, CH═).

3o: IR (KBr, ν, cm^{-1}): 3049, 2970, 2940, 2840, 2226, 1589, 1570, 1481, 1428, 1310, 1281, 1223, 1074, 990, 792, 751 cm^{-1}. ^{1}H NMR: 3.91 (s, 3H,

CH_3O), 3.95 (s, 3H, CH_3O), 7.15–7.21 (m, 2H, ArH), 7.85 (dd, $J = 7.6$ Hz, $J' = 2.8$ Hz, 1H, ArH), 8.26 (s, 1H, CH═).

3p: IR (KBr, ν, cm^{-1}): 3087, 3036, 2230, 1594, 1546, 1471, 1360, 1285, 1218, 1134, 1032, 952, 910, 883, 821, 699, 665 cm^{-1}. ^1H NMR: 7.63 (d, $J = 8.4$ Hz, 1H, ArH), 7.68 (s, 1H, CH═), 7.81 (dd, $J = 8.4$ Hz, $J' = 2.0$ Hz, 1H, ArH), 7.94 (d, $J = 2.0$ Hz, 1H, ArH).

3q: IR (KBr, ν, cm^{-1}): 3090, 3037, 2976, 2945, 2844, 2222, 1609, 1562, 1492, 1471, 1430, 1356, 1305, 1281, 1212, 1164, 1121, 1038, 1021, 852, 807 cm^{-1}. ^1H NMR: 3.90 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O), 6.44 (d, $J = 2.0$ Hz, 1H, ArH), 6.61 (dd, $J = 8.8$ Hz, $J' = 2.0$ Hz, 1H, ArH), 8.18 (s, 1H, CH═), 8.27 (d, $J = 8.8$ Hz, 2H, ArH).

3r: IR (KBr, ν, cm^{-1}): 3100, 3051, 2237, 1590, 1561, 1510, 1467, 1342, 1303, 1207, 1109, 1076, 922, 848, 754, 721, 674 cm^{-1}. ^1H NMR: 7.74 (s, 1H, ArH), 7.75 (d, $J = 8.4$ Hz, 1H, ArH), 8.32 (d, $J = 8.4$ Hz, 1H, ArH), 8.38 (s, 1H, CH═).

3s: IR (KBr, ν, cm^{-1}): 3052, 2942, 2856, 2235, 1608, 1567, 1523, 1464, 1440, 1365, 1323, 1290, 1227, 1180, 1070, 989, 872, 790, 738 cm^{-1}. ^1H NMR: 4.04 (s, 3H, CH_3O), 4.05 (s, 3H, CH_3O), 7.31 (s, 1H, ArH), 7.80 (s, 1H, ArH), 8.46 (s, 1H, CH═).

3t: IR (KBr, ν, cm^{-1}): 3049, 2938, 2234, 1610, 1575, 1526, 1505, 1505, 1479, 1434, 1385, 1329, 1153, 1029, 917, 877, 814, 752, 725, 694 cm^{-1}. ^1H NMR: 6.28 (s, 2H, OCH_2O), 7.19 (s, 1H, ArH), 7.76 (s, 1H, ArH), 8.33 (s, 1H, CH═).

3u: IR (KBr, ν, cm^{-1}): 3049, 3090, 2240, 1592, 1567, 1522, 1441, 1347, 1210, 1145, 1074, 916, 870, 835, 796, 731, 694, 670 cm^{-1}. ^1H NMR: 7.79–7.90 (m, 3H, ArH), 8.36 (d, $J = 8.0$ Hz, 1H, ArH), 8.45(s, 1H, ArH).

3v: IR (KBr, ν, cm^{-1}): 3023, 2978, 2945, 2921, 2225, 1588, 1561, 1053, 1447, 1407, 1385, 1311, 1246, 1223, 1128, 1019, 946, 816, 790, 772, 707 cm^{-1}. ^1H NMR: 2.33 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.29 (d, $J = 8.0$ Hz, 1H, ArH), 7.66–7.69 (m, 3H, ArH + CH═).

3w: IR (KBr, ν, cm^{-1}): 3008, 2964, 2935, 2831, 2222, 1601, 1567, 1508, 1441, 1423, 1341, 1272, 1206, 1168, 1143, 1016, 959, 933, 850, 822, 779, 733 cm^{-1}. ^1H NMR: 3.95 (s, 3H, CH_3O), 3.98 (s, 3H, CH_3O), 6.96 (d, $J = 8.4$ Hz, 1H, ArH), 7.39 (dd, $J = 8.4$ Hz, $J' = 2.0$ Hz, 1H, ArH), 7.64 (s, 1H, CH═), 7.69 (d, $J = 2.0$ Hz, 2H, ArH).

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REFERENCES

1. Quiroga, J.; Alvarado, M.; Insuatry, B.; Moreno, R. Reaction of 5-aminopyrazoles with β-dimethylaminopropiophenones synthesis of new pyrazole[3,4-*b*]pyridimes. *J. Heterocyclic Chem.* **1999**, *36*, 1311.
2. (a) Freeman, F. Properties and reactions of ylidenemalononitriles. *Chem. Rev.* **1980**, *80*, 329; (b) Freeman, F. Reactions of malononitrile derivatives. *Synthesis* **1981**, 925; (c) Sasaki, T.; Minamato, K.; Suzuki, T.; Yamashita, S. Search for a simple synthetic model system for intramolecular 1,3-dipolar cycloaddition to the 5,6-double bond of a pyrimidine nucleoside. *Tetrahedron* **1980**, *36*, 865.
3. Jones, G. *Organic Reactions*; John Wiley & Sons: New York, 1967; Vol. 15, p. 204.
4. Texiey-Boullet, F.; Foucaud, A. Knoevenagel reaction catalyzed by aluminium oxide. *Tetrahedron Lett.* **1982**, *23*, 4927.
5. Angeletti, E.; Canepa, C.; Martinetti, G.; Venturello, P. Silica gel functionalized with amino groups as a new catalyst for Knoevenagel condensation under heterogeneous catalysis conditions. *Tetrahedron Lett.* **1988**, *29*, 2261.
6. Prajapati, D.; Sandhu, J. S. Bismuth(III) chloride as a new catalyst for Knoevenagel condensation in the absence of solvent. *Chem. Lett.* **1992**, 1945.
7. Prajapati, D.; Sandhu, J. S. Cadmium iodide as a new catalyst for Knoevenagel condensations. *J. Chem. Soc., Perkin. Trans. 1* **1993**, 739.
8. Lehnert, W. Knoevenagel condensation with titanium(IV) chloride-base catalyst V. 3-alkylidene and 3-aralkylidene-2,4-pentanedione from aldehydes and acetylacetones. *Synthesis* **1974**, 667.
9. Li, Y. Q. Potassium phosphate as a catalyst for the Knoevenagel condensation. *J. Chem. Res., Synop.* **2000**, 524.
10. Zhou, L. H.; Gao, Y.; Shi, D. Q.; Dai, G. Y. Condensation reaction of *o*-nitroaromatic aldehyde with active methylene compound catalyzed by potassium fluoride on alumina. *Chin. Chem. Reagents* **1998**, *20*, 135.
11. Wang, Q. L.; Ma, Y. D.; Zuo, B. J. Knoevenagel condensation catalyzed by usy zeolite. *Synth. Commun.* **1997**, *27*, 4107.
12. Chalais, S.; Laszle, P.; Mathy, A. Catalysis of the Knoevenagel condensations. *Tetrahedron Lett.* **1985**, *26*, 4453.
13. Jin, T. S.; Zhang, J. S.; Wang, A. Q.; Li, T. S. An efficient and environment friendly procedure for the synthesis of arylmethylenemalononitrile catalyzed by strong base anion-exchange resin in water. *Synth. Commun.* **2004**, *34*, 2611.
14. (a) Rao, P. S.; Venkataratnanm, R. V. Zinc chloride as a new catalyst for Knoevenagel condensation. *Tetrahedron Lett.* **1991**, *32*, 5821; (b) Cabello, J. A.; Campelo, J. M.; Garcia, A.; Luna, D.; Marinas, J. M. Knoevenagel condensation in the heterogeneous phase using $AlPO_4$-Al_2O_3 as a new catalyst. *J. Org. Chem.* **1984**, *49*, 5195; (c) Prajapati, D.; Lekhok, K.; Sandhu, J. S.; Ghosh, A. C. Lithium bromide as a new catalyst for carbon–carbon bond formation in the solid state. *J. Chem. Soc., Perkin. Trans. 1* **1996**, 959; (d) Zhang, S.; Chen, J.; Shi, D. Q.; Zhuang, Q. Y.; Zhang, Q. S. The condensation of aromatic aldehyde with active methylene compounds in water. *J. Xuzhou Normal Uni. (Natural Sciences)* **2003**, *21*, 42.
15. (a) Mongilaiah, K.; Prashanthi, G. Microwave-assisted Knoevenagel condensation using sodium fluoride and lithium chloride as a catalyst under solvent-free conditions. *Synth. Commun.* **2003**, *33*, 2309; (b) Bogdal, D. Fast synthesis by Knoevenagel condensation reaction under microwave irradiation. *J. Chem. Res., Synop.* **1998**, 468.

16. Cao, Y. Q.; Dai, Z.; Zhang, R.; Chen, B. H. A practical Knoevenagel condensation catalyzed by PEG400 and anhydrous K_2CO_3 without solvent. *Synth. Commun.* **2004**, *34*, 2965.
17. Ren, Z. J.; Cao, W. G.; Tong, W. Q. The Knoevenagel condensation reaction of aromatic aldehydes with malonontrile by grinding in the absence of solvents and catalysts. *Synth. Commun.* **2002**, *32*, 3475.