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One-pot synthesis of malononitriles by free radical reactions of ylidenemalononitrile with Et_3B and iodoalkane in a water–ether biphase medium

Zhijay Tu, Chunchi Lin, Yaochung Jang, Yeong-Jiunn Jang, Shengkai Ko, Hulin Fang, Ju-Tsung Liu and Ching-Fa Yao*

Department of Chemistry, National Taiwan Normal University, No. 88, Sec. 4, Tingchow Road, Taipei 116, Taiwan, ROC

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Abstract—The one-pot synthesis of malononitrile derivatives **4**, **6**, and **7** in moderate to high yields by the reaction of ylidenemalononitriles **3**, prepared in situ from carbonyl compounds **1** and malononitrile **2** in the presence of ammonium acetate in aqueous solution at 50–60 °C, with Et_3B or RI **5**/Et_3B in a water–diethyl ether biphase medium under an atmosphere of room temperature is reported. The reaction of Et_3B with adamantyl iodides **8** and **10** under similar conditions gave **9** and **11** in high yields, respectively. However, low yields of the monoalkylated combined with dialkylated malonates **14** were obtained when benzaldehyde **1a** was condensed with dimethylmalonate **12** followed by parallel free radical treatment in benzene solution.

The Knoevenagel reaction, the reaction of carbonyl compounds with a methylene group with increased acidity, as is found in malononitrile, malonic, and cyanoacetic esters is a special case of an aldol reaction that can be catalyzed by weak bases. Owing to their versatile and powerful application as organic synthons, various procedures and conditions for the preparation of ylidenemalononitriles have been reported.[1–3] Of importance is the development of mild and environmental-friendly strategies which have been a subject of considerable interest.[1e]

Reactions of benzylidenemalononitriles with the Grignard reagent t-BuMgX[4] or free radicals generated from different precursors such as t-Bu_2Hg,[4] t-$BuHgSiMe_3$,[4] t-BuHgX/KI,[5a,b] benzoyl peroxide/Et_3Al,[5c] Zr complex,[6a] and from organohalides/allylic stannanes[6b] to generate malononitriles have been reported. It also has been reported that Reformatsky reagents can react with various 1,1-dicyanoalkenes to give addition products.[7] Similarly, the photoinduced hydrogen abstraction from aliphatic hydrocarbons by triplet aromatic ketones in the presence of α,β-unsaturated nitriles or dinitriles affords alkylated nitriles or dinitriles.[8] The above results indicate that ylidenemalononitriles can react with a variety of organometallic reagents to yield 1,4-addition products by an ionic, SET, or free radical mechanism.

Carbon–carbon bond formation through a free radical pathway has led to a variety of useful applications in organic synthesis.[10] In view of the excellent characteristics of triethylborane as a free radical initiator in aqueous solution under aerobic conditions, we were prompted to examine the feasibility of Et_3B-mediated free radical functionalized reactions of ylidenemalononitriles at ambient temperature under economical and eco-friendly conditions. Herein we report on some of our preliminary results.

When benzylidenemalononitrile **3a** was reacted with Et_3B in diethyl ether solution under an argon atmosphere at room temperature for 15 min, the staring material was completely consumed and the expected product 1-phenylpropylmalononitrile **4a** was produced in 40% yield (Eq. 1 and entry 1 of Table 1). Similarly, **4a** was obtained in 56% yield when the reaction was conducted under a nitrogen atmosphere (entry 2). It was surprising to find that **4a** was obtained in 71% yield when 10 mol% dibenzoyl peroxide was added as a

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* Corresponding author. Tel./fax: +886 2 29309092; e-mail: cheyaocf@scc.ntnu.edu.tw

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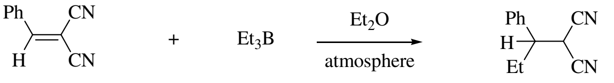
Table 1. Reaction of benzylidenemalononitrile **3a** with Et_3B in diethyl ether solution under different atmospheres at room temperature to generate 1-phenylpropylmalononitrile **4a**

Entry	Atmosphere	Additives	Time (min)	**4a**[a] (%)
1	Argon	—	15	40
2	Nitrogen	—	15	56
3	Argon	10% Bz_2O_2	15	71
4	Argon	50% Galvinoxyl	15	25
5	Pure oxygen	—	5	100
6	Air	—	5	100

[a] NMR yields.

radical initiator to the mixture under an argon atmosphere (entry 3). However, only a 25% yield of **4a** was observed and no **3a** was recovered when 50% of galvinoxyl, an efficient free radical scavenger,[9] was added to the system under similar conditions (entry 4). Oxygen is not only known to be a free radical scavenger but also to be a free radical initiator. When the reaction was conducted under an atmosphere of pure oxygen for 5 min, **4a** was obtained in quantitative yield (entry 5). To our surprise, a 100% yield of **4a** was also obtained when the reaction was conducted under an atmosphere of air at room temperature for the same period of time (entry 6). Based on these results, we conclude that the reactions proceed through a free radical pathway which can be accelerated in the presence of dibenzoyl peroxide or oxygen, and inhibited or retarded in the presence of galvinoxyl. Compared to the use of dibenzoyl peroxide or pure oxygen, the use of air to initiate the reaction is advantageous and entails no additional cost.



3a **4a**

(1)

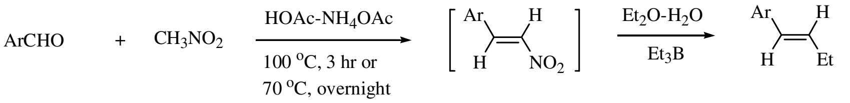
We previously reported that different *trans*-β-alkylstyrenes can be prepared under one-pot conditions by the reaction of *trans*-β-nitrostyrenes, prepared in situ from aryl aldehydes and nitromethane in an acetic acid solution, with different radicals formed from Et_3B or Et_3B/RI in a biphase medium of diethyl ether and water at room temperature (Eq. 2).[11b]

Based on literature results and our own studies,[4–8,11] we attempted to apply the above methodology to the preparation of malononitriles **4**, **6**, and **7** by reaction of ylidenemalononitrile **3**, which was prepared in situ from carbonyl compounds **1** and malononitrile **2** in the presence of ammonium acetate in aqueous solution, with Et_3B only or with RI **5**/Et_3B in the indicated biphase solvent system at room temperature in the presence of atmospheric oxygen as a free radical initiator under one-pot conditions (Eq. 3).

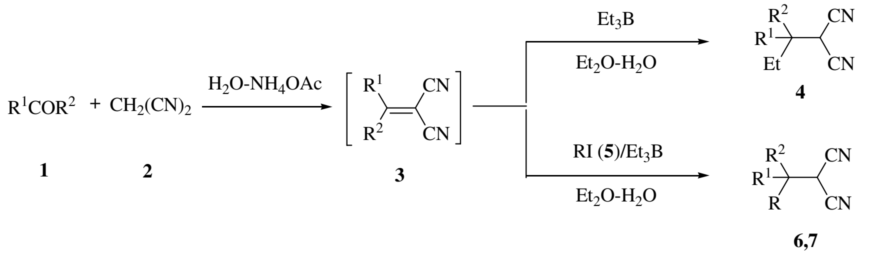
Typical experimental procedures for the one-pot synthesis of malononitriles **4**, **6**, and **7** are as follows.[13] Benzaldehyde **1a** (1.5 equiv) and malononitrile **2** (1.0 equiv) were added to an aqueous solution (10 mL) containing ammonium acetate (0.1 equiv) as a catalyst. The reaction mixture was stirred at 50–60 °C (oil bath). When the reaction started, benzylidenemalononitrile **3a** was immediately formed in the solid state. If necessary, the solid product can be isolated on a filter (100% yield) and all spectral data are consistent with the reported literature data.[12] After 20 min, the mixture was allowed to cool to room temperature and diethyl ether was added to the aqueous solution to give an ether–water biphase mixture. Triethylborane (3.0 equiv) was added to the solution under an atmosphere of air and the mixture was stirred for 5 min. The ether layer was separated, washed with dilute aqueous hydrochloric acid, dried over $MgSO_4$, filtered, and finally evaporated to give the crude product. The crude ^1H NMR of the crude product indicated that it consisted of almost entirely pure **4a**. This product could be further purified by flash column chromatography to give pure **4a** (93% yield) (Table 2, entry 1). All of the spectral data for **4a** are fully consistent with previously reported data.[4,5] Similarly, high yields of **6a** and **7a** were obtained when **3a** was reacted with Et_3B (3 equiv) and isopropyl iodide **5a** (20 equiv) or *tert*-butyl iodide **5b** (6 equiv) under similar conditions (entries 2 and 3). In addition to **1a**, valeraldehyde **1b**, and cyclohexanone **1c** were also used to synthesize **4b**,**c**, **6b**,**c**, and **7b**,**c**,[14] respectively. For substrate **1b**, the generation of intermediate **3b** was completed within

Table 2. One-pot synthesis of malononitrile derivatives **4**, **6**, and **7** from carbonyl compound **1**, malononitrile **2**, Et_3B, and *i*-PrI **5a** or *t*-BuI **5b**

Entry	Substrate	RI	Product	NMR yield (%)	Isolated yield (%)
1	**1a**	—	**4a**	100	96
2	**1a**	**5a**	**6a**	100	97
3	**1a**	**5b**	**7a**	93	85
4	**1b**	—	**4b**	100	95
5	**1b**	**5a**	**6b**	100	96
6	**1b**	**5b**	**7b**	100	96
7	**1c**	—	**4c**	88	80
8	**1c**	**5a**	**6c**	81	75
9	**1c**	**5b**	**7c**	45	40

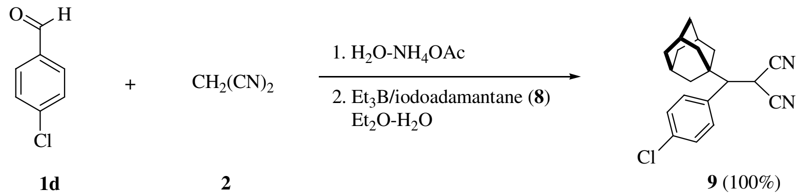


(2)

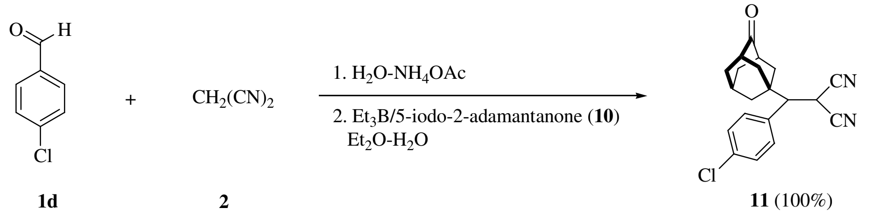


(3)

1, 3, 4	**5**	**6**	**7**
a; R^1 = Ph, R^2 = H	**a**; R = *i*-Pr	**a**; R^1 = Ph, R^2 = H, R= *i*-Pr	**a**; R^1 = Ph, R^2 = H, R= *t*-Bu
b; R^1 = C_4H_9, R^2 = H	**b**; R = *t*-Bu	**b**; R^1 = C_4H_9, R^2 = H, R= *i*-Pr	**b**; R^1 = C_4H_9, R^2 = H, R= *t*-Bu
c; R^1 + R^2 = -$(CH_2)_5$-		**c**; R^1 + R^2 = -$(CH_2)_5$-, R= *i*-Pr	**c**; R^1 + R^2 = -$(CH_2)_5$-, R= *t*-Bu



(4)



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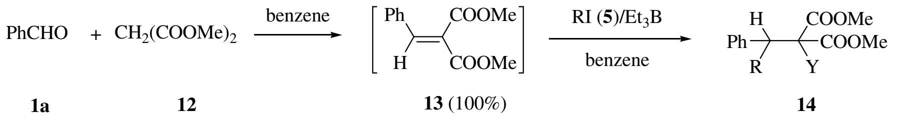

a1: R = Et, Y = H (trace)
a2: R = Et, Y = Et (38%)
b1: R = *i*-Pr, Y = H (36%)
b2: R = *i*-Pr, Y = *i*-Pr (15%)
c: R = *t*-Bu, Y = H (19%)

(6)

15 min and the free radical reactions were completed within 5 min as well. However, more than 4 h were required to generate 90% (NMR yield) of **3c** with only traces of unreacted ketone **1c** remaining when substrate **1c** was used. Likewise, more than 1 h was required for completion of the free radical reactions, and the yields of **4c**,[14] **6c**, and **7c** were 88%, 81%, and 45%, respectively, which are also lower than in the case where **1b** and **1c** were used. On the basis of these results, we conclude that steric effects play an important role in these reactions, especially in the case of **1c**.

Not only the *iso*-propyl and *tert*-butyl radicals, but other radicals which were generated from Et_3B and iodoadamantane **8** (6 equiv) or 5-iodo-2-adamantanone **10** (4 equiv) also reacted with 4-chlorobenzylidenemalononitrile **1d** to yield **9** or **11** quantitatively under analogous conditions (Eqs. 4 and 5).

In addition to malononitrile **2**, dimethylmalonate **12** was also reacted with benzaldehyde **1a** in benzene solution with a Dean–Stark apparatus under refluxing overnight to produce **13** which then underwent free radical reactions with Et$_3$B or RI **5**/Et$_3$B in the same solution at room temperature to give **14**. Although the yield of **13** was very high (NMR yield 100%), the yields of the free radical product **14** were much lower as compared with reactions using **2**. Not only the monoalkylated products **14a1**, **14b1**, and **14c1** but also the disubstituted products **14a2** and **14b2** were isolated. In the case of ethyl radical, the major product was the dialkylated compound **14a2** (38%), and only a trace amount of the monoalkylated product **14a1** was observed. Both the monoalkylated product **14b1** (36%) and the dialkylated product **14b2** (15%) were produced when isopropyl iodide was employed. Nevertheless, only a low yield of the monoalkylated product **14c1** (19%) was obtained when *tert*-butyl radical was used. All of these results are shown as Eq. 6.

In conclusion, we developed an easy and effective method for preparing medium to high yields of alkylated malononitrile or dimethyl malonate derivatives using a carbonyl compound, malononitrile or dimethyl malonate, and triethylborane or iodoalkanes/triethylborane in an ether–water biphase medium in the presence of atmospheric oxygen under one-pot conditions.

Acknowledgements

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13. Typical procedures: 4-chlorobenzaldehyde **1d** (211 mg, 1.5 equiv), malononitrile **2** (66 mg, 1.0 mmol) and NH$_4$OAc (8 mg, 0.1 equiv) were added to water (10 mL). The mixture was heated at 50–60 °C for 20 min. After cooling to room temperature, ether (10 mL) was then added to the mixture with stirring to form a biphase system. 5-Iodo-2-adamantanone **11** (1104 mg, 4.0 equiv) followed by 1 M Et$_3$B$_{(\text{hex.})}$ (3 mL, 3.0 equiv) were added to the above solution equipped with an automatic air-pumping apparatus. Several minutes later, the ether layer was washed with dilute HCl$_{(\text{aq})}$, dried over MgSO$_4$, filtered and the filtrate concentrated in vacuo to give the crude product **11**. The pure compound was obtained as a white solid by flash column chromatography on silica gel using hexane–EA (3:1) as the eluent. Mp 171–172 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.42–7.40 (d, $J = 8.5$ Hz, 2H), 7.32–7.30 (m, 2H), 4.28–4.27 (d, $J = 5.2$ Hz, 1H), 2.95–2.93 (d, $J = 5.2$ Hz, 1H), 2.58 (s, 2H), 2.23 (s, 1H), 1.96 (s, 10H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 215.5, 135.2, 132.9, 130.7, 129.2, 112.8, 112.5, 55.7, 45.7, 45.6, 41.8, 40.9, 38.8, 38.0, 37.9, 36.3, 27.5, 24.0. GC–MS (EI): m/z (%) 338 (10) [M$^+$], 163 (39), 149 (100), 121 (39), 93 (41), 79 (31), 67 (8), 55 (8), 41 (8). IR (KBr): ν (cm^{-1}) 3455, 2931 (CH stretch, vs), 2860, 2254 (CN stretch, m), 1714 (C=O stretch, vs), 1595, 1494, 1455, 1416, 1363, 1300, 1271, 1223, 1096, 1066, 1014.
14. Selected data:
    Compound **4c**: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.76 (s, 1H), 1.77–1.71 (q, $J = 7.5$ Hz, 2H), 1.67–1.52 (m, 9H), 1.42–1.36 (m, 1H), 0.95–0.91 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 112.0, 40.8, 32.2, 32.0, 26.6, 25.1, 21.2, 7.4. GC–MS (EI): m/z (%) 176 (trace) [M$^+$], 175 (trace), 147 (17), 111 (100), 81 (38),

69 (84), 55 (20), 41 (20). IR (KBr): ν (cm^{-1}) 3583, 2936 (CH stretch, vs), 2863, 2252 (CN stretch, m), 1736, 1457, 1388, 1018. Compound **7b**: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 3.94–3.93 (d, $J = 1.7$ Hz, 1H), 1.82–1.73 (m, 2H), 1.69–1.57 (m, 2H), 1.48–1.36 (m, 3H), 1.02 (s, 9H), 0.98–0.94 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 114.0, 112.5, 50.8, 34.4, 30.9, 28.2, 27.5, 23.0, 22.7, 13.7. GC–MS (EI): m/z (%) 192 (trace) [M$^+$], 191 (trace), 177 (8), 135 (6), 108 (3), 69 (4), 57 (100), 41 (19). IR (KBr): ν (cm^{-1}) 3583, 2962 (CH stretch, vs), 2875, 2253 (CN stretch, m), 1729, 1469, 1404, 1374, 1227, 1113.