

Synthesis of Polysubstituted Benzenes via the Vinylogous *Michael* Addition of Alkylidenemalononitriles to 2-(1,3-Dioxo-1*H*-inden-2(3*H*)-ylidene)-malononitrile

by **Abdolali Alizadeh**^{*a}, **Hadi Sedighian**^a, **Seyed Yasub Hosseini**^a, and **Long-Guan Zhu**^b)

^a) Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran
(phone: +98-21-88006631; fax: +98-21-88006544; e-mail: aalizadeh@modares.ac.ir,
abdol_alizad@yahoo.com)

^b) Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. China

An efficient synthesis for polysubstituted benzenes was successfully developed by the reaction of ninhydrin (=2,2-dihydroxyindane-1,3-dione), malononitrile (=propanedinitrile), and alkylidenemalononitrile. The method involves vinylogous *Michael* addition of alkylidenemalononitrile to 2-(1,3-dioxo-1*H*-inden-2(3*H*)-ylidene)malononitrile, which formed by condensation of malononitrile and ninhydrin in the presence of Et₃N, and the alcoholic solvent has participated in the reaction as a reagent. The method has the advantages of good yields and of not requiring a metal catalyst. The structures were confirmed spectroscopically (IR, ¹H- and ¹³C-NMR, and EI-MS) and by elemental analyses, and, in the case of **2c**, by X-ray crystallography. A plausible mechanism for this reaction is proposed (*Scheme*).

Introduction. – Polysubstituted benzenes are vital compounds in natural products and material sciences [1]. Several strategies are available for the construction of polysubstituted benzenes such as *Friedel–Crafts* reactions [2], coupling reactions [3], and electrophilic and nucleophilic substitutions [4][5]. However, these strategies suffer from some disadvantages such as low yields, long reaction times, and regioisomeric problems [6][7], and some of these processes have low atom economy. Moreover, applying these methods for the synthesis of benzenes bearing NH₂, C≡N, and C=O groups is difficult. These limitation led chemists to try to synthesize the aromatic backbone from acyclic precursors to avoid the problem of the formation of regioisomers and low atom economy. In this regard, other methods such as [4+2] cycloadditions, transition metal-catalyzed [2+2+2] cycloadditions, and [4+2] annulation strategy based on the *Baylis–Hillman* reaction have been developed [8][9].

The *Michael* addition reaction can be considered as one of the most firmly established methodologies in the formation of C–C bonds. In *Michael* reactions, alkylidenemalononitriles (‘vinyl malononitriles’, ‘2-ethylidenepropanedinitriles’) behave as either acceptors or vinylogous donors. Alkylidenemalononitriles have been applied as components in annulation reactions for constructions of aromatic compounds. Reaction of alkylidenemalononitriles with electrophilic C=C bonds leads to polysubstituted benzenes [10–13].

Addition of alkylidenemalononitriles to suitable conjugated acceptors such as dialkyl acetylenedicarboxylate was studied; the reported examples in this area are confined to synthesize polysubstituted benzene derivatives [14].

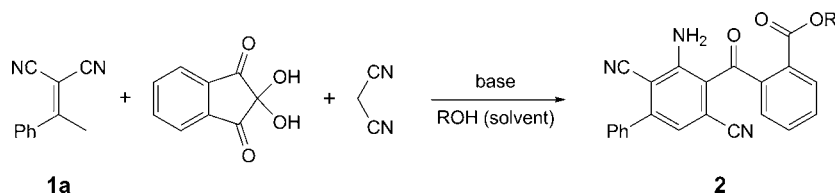
Results and Discussion. – On the basis of the above-mentioned features, we considered the addition of (1-phenylethylidene)malononitrile (**1a**) to ninhydrin (=2,2-dihydroxyindane-1,3-dione) and malononitrile (= propanedinitrile) in EtOH. The ^1H - and ^{13}C -NMR spectra of the product indicated that EtOH has participated in the reaction as a reagent. We, therefore, screened various bases and solvents for their efficiency in the reaction of **1a** with ninhydrin, malononitrile, and solvent as nucleophile (*Table 1*).

With the optimal conditions established (EtOH and Et_3N), we then examined the scope of the reaction for the formation of various polysubstituted benzenes, and the results are compiled in *Table 2*.

The structures of compounds **2a–2g** were deduced by means of IR, ^1H - and ^{13}C -NMR, and mass spectra, and elemental analyses. The molecular structure of **2c** was further established by a single-crystal X-ray diffraction analysis (*Fig.*). For example, the mass spectrum of **2a** showed a molecular-ion peak at m/z 395, in agreement with the structure. In the IR spectrum of **2a**, absorption bands at 3418 and 3308, 2223, and 1714 and 1657 cm^{-1} , were attributed to NH_2 , CN, and C=O stretching frequencies, respectively, indicating of the functional groups in the product. The ^1H -NMR spectrum of **2a** exhibited two sharp *singlets* at $\delta(\text{H})$ 7.19 and 7.81 ppm for the CH group of the formed aromatic ring and the NH_2 group, respectively, one *triplet* and one *quartet* for Et H-atoms ($\delta(\text{H})$ 1.15 ($J=7.2$) and 4.16 ppm ($J=7.2$)), and the ten aromatic H-atoms gave rise to characteristic resonances in the aromatic region of the spectrum. The detection of 22 distinct signals in the ^{13}C -NMR spectrum of **2a** confirmed the proposed structure.

A plausible reaction mechanism was proposed in the *Scheme*. The initial condensation of malononitrile and ninhydrin in the presence of Et_3N leads to the formation of compound **3** [15]. Alkylidenemalononitrile **1** in the presence of Et_3N is converted to the vinylogous carbanion **4**. Then, addition of **4** to **3** gives intermediate **5**, which is converted to intermediate **6** by attack of the carbanion at the $\text{C}\equiv\text{N}$ group

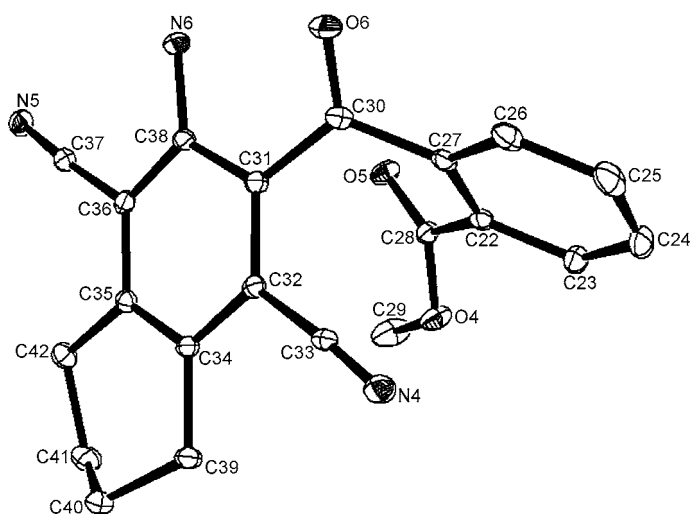
Table 1. Optimization of the Synthesis of Polysubstituted Benzenes **2**



Entry	ROH (Solvent)	Base	Time [h]	Yield [%]
1	EtOH	Et_3N	9	78
2	MeOH	Et_3N	9	65
3	EtOH	NaOH	12	56
4	MeOH	NaOH	12	45
5	PrOH	Et_3N	24	0
6	BuOH	Et_3N	24	0
7	EtOH	Na_2CO_3	12	25
8	MeOH	Na_2CO_3	12	17

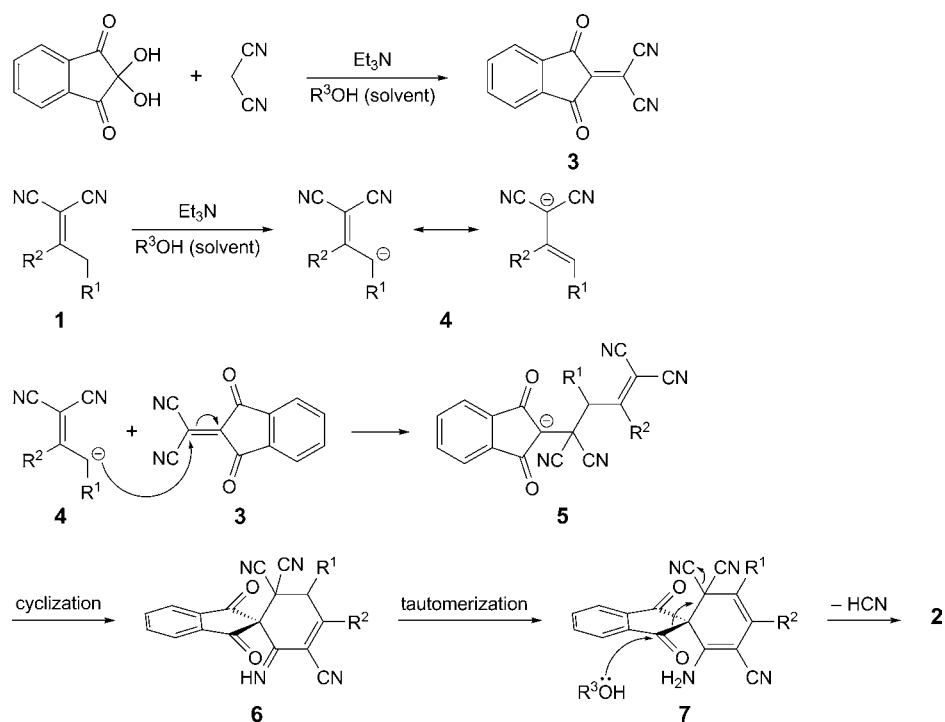
Table 2. Synthesis of Substituted Benzenes **2a–2g**

Entry	R ¹	R ²	R ³	Product	Yield [%]
1	H	Ph	Et	2a	78
2	H	4-Me-C ₆ H ₄	Et	2b	77
3	-CH ₂ CH ₂ CH ₂ CH ₂ -		Me	2c	70
4	-CH ₂ CH ₂ CH ₂ -		Et	2d	78
5			Et	2e	80
6			Et	2f	75
7	H		Et	2g	80


 Figure. ORTEP Diagram of **2c**

[16][17]. A tautomerization affords intermediate **7**. The final product **2** is formed from the addition of EtOH to the C=O group and opening of the cyclopentanedione moiety, followed by dehydrocyanation.

Scheme. Mechanistic Rationalization for the Formation of Substituted Benzenes



In summary, we described a novel approach to the synthesis of new polysubstituted benzene derivatives by a one-pot reaction between ninhydrin, malononitrile, alkylidenemalononitrile, and EtOH as nucleophile. Advantages of this protocol include good yields and operational simplicity.

Experimental Part

General. All starting materials were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. M.p.: *Electrothermal 9100* apparatus. IR Spectra: *Shimadzu IR-460* spectrometer, in KBr; $\bar{\nu}$ in cm^{-1} . ^1H - and ^{13}C -NMR spectra: *Bruker DRX 400-AVANCE* FT-NMR instrument, at 400 and 100 MHz, resp., in CDCl_3 , if not stated otherwise; δ in ppm rel. to Me_4Si as internal standard; J in Hz. EI-MS: *FINNIGAN-MATT 8430* mass spectrometer operating at an ionization potential of 70 eV; in m/z . Elemental analyses for C, H, and N: *Heraeus CHN-O-Rapid* analyzer; in %.

General Procedure (exemplified for **2a**). A mixture of malononitrile (0.066 g, 1.0 mmol), ninhydrin (0.16 g, 1.0 mmol), and Et_3N (one drop) in EtOH (6 ml) was stirred at r.t. for 1 h. A soln. of *benzylidenemalononitrile* (**1a**; 0.154 g, 1.0 mmol) and Et_3N (one drop) in EtOH (4 ml), stirred at r.t. for 20 min, was then added. When the reaction was complete (TLC), the solvent was evaporated under reduced pressure, and the product was isolated by column chromatography (silica gel; hexane/AcOEt 1:7).

Ethyl 2-[(3-Amino-2,5-dicyano[1,1'-biphenyl]-4-yl)carbonyl]benzoate (**2a**). Yield: 310 mg (78%). Yellow powder. M.p. 280–283°. IR: 3418 and 3308 (NH_2), 2223 (CN), 1714 (COOEt), 1657 and 1603

(arom.), 1273 (C–O). ¹H-NMR: 1.15 (*t*, *J* = 7.2, MeCH₂O); 4.16 (*q*, *J* = 7.2, MeCH₂O); 7.12 (*t*, *J* = 4.5, 2 *m*-H_m); 7.19 (*s*, 1 arom. H); 7.53–7.58 (*m*, 4 arom. H); 7.63–7.68 (*m*, 2 arom. H); 7.81 (*s*, NH₂); 7.93 (*t*, *J* = 4.5, 1 *p*-H_p). ¹³C-NMR: 13.7; 61.5; 100.6; 115.5; 115.6; 117.7; 117.9; 122.7; 128.3; 128.6; 128.8; 129.9; 130.0; 130.2; 131.4; 132.6; 136.0; 141.1; 150.2; 152.7; 165.9; 195.7. EI-MS: 395 (57, *M*⁺), 378 (25), 350 (80), 332 (16), 321 (75), 293 (85), 266 (56), 246 (55), 191 (75), 164 (75), 149 (100), 104 (55), 93 (57), 76 (66), 65 (51). Anal. calc. for C₂₄H₁₇N₃O₃ (395.41): C 72.90, H 4.33, N 10.63; found: C 72.80, H 4.28, N 10.54.

Ethyl 2-[(3-Amino-2,5-dicyano-4'-methyl[1,1'-biphenyl]-4-yl)carbonyl]benzoate (2b). Yield: 310 mg (77%). Yellow powder. M.p. 282–284°. IR: 3447 and 3335 (NH₂), 2214 (CN), 1716 (COOEt), 1596 and 1550 (arom.), 1278 (C–O). ¹H-NMR: 1.15 (*t*, *J* = 7.2, MeCH₂O); 2.37 (*s*, Me); 4.16 (*q*, *J* = 7.2, MeCH₂O); 7.16 (*s*, 1 arom. H); 7.35 (*d*, *J* = 8.1, 2 arom. H); 7.54 (*d*, *J* = 7.8, 3 arom. H); 7.70 (*t*, *J* = 6.6, 2 arom. H); 7.81 (*s*, NH₂); 7.93 (*t*, *J* = 4.5, 1 arom. H). ¹³C-NMR: 13.7; 20.9; 61.5; 100.4; 115.61; 115.63; 117.3; 117.9; 122.7; 128.3; 128.6; 129.2; 129.9; 130.1; 131.3; 132.6; 133.1; 139.9; 141.2; 150.2; 152.8; 165.9; 195.7. EI-MS: 409 (65, *M*⁺), 378 (75), 365 (75), 335 (75), 319 (50), 306 (77), 279 (37), 260 (30), 205 (32), 183 (100), 168 (50), 149 (76), 93 (32), 77 (40), 65 (50). Anal. calc. for C₂₅H₁₉N₃O₃ (409.44): C 73.34, H 4.68, N 10.26; found: C 73.27, H 4.61, N 10.17.

Methyl 2-[(3-Amino-1,4-dicyano-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]benzoate (2c). Yield: 290 mg (82%). Yellow powder. M.p. 264–266°. IR: 3417 and 3321 (NH₂), 2220 (CN), 1721 (COOMe), 1651 and 1616 (arom.), 1263 (C–O). ¹H-NMR: 1.65–1.84 (*m*, 2 CH₂); 2.51–2.61 (*m*, CH₂); 2.77–2.90 (*m*, CH₂); 3.37 (*s*, NH); 3.67 (*s*, MeO); 7.23 (*s*, NH); 7.44–7.50 (*m*, 1 arom. H); 7.65–7.74 (*m*, 2 arom. H); 7.84–7.92 (*m*, 1 arom. H). ¹³C-NMR: 21.0; 21.5; 27.1; 28.8; 52.6; 102.0; 114.1; 114.9; 117.4; 118.6; 128.4; 129.6; 129.9; 130.3; 131.5; 132.4; 141.2; 148.0; 149.5; 166.7; 195.5. EI-MS: 359 (60, *M*⁺), 312 (68), 385 (70), 358 (32), 229 (30), 210 (31), 182 (25), 149 (100), 128 (33), 115 (13), 104 (28), 93 (28), 76 (30), 65 (28), 50 (10). Anal. calc. for C₂₁H₁₇N₃O₃ (359.38): C 70.18, H 4.77, N 11.69; found: C 70.07, H 4.69, N 11.59.

Crystallographic Data for 2c. C₂₁H₁₇N₃O₃, *M*_r 359.38, monoclinic, *a* = 8.3730(3), *b* = 18.1633(6), *c* = 23.466(1) Å, β = 95.895(4)°, *V* = 3549.9(2) Å³, *Z* = 8, *D*_x = 1.3245 g cm⁻³, *F*(000) = 384, radiation, MoK_α (λ = 0.71073 Å), 2.85 ≤ 2θ ≤ 25.10; intensity data were collected at 170(2) K with a Bruker APEX area-detector diffractometer, and employing ω/2θ scanning technique, in the range of −8 ≤ *h* ≤ 9, −21 ≤ *k* ≤ 18, −28 ≤ *l* ≤ 27; the structure was solved by a direct method; all non-H-atoms were positioned, and anisotropic thermal parameters were refined from 6277 observed reflections with *R*(into) = 0.0713 by a full-matrix least-squares technique converged to *R* = 0.0454 and *R*_w = 0.1129 [*I* > 2σ(*I*)]. CCDC No.: 981453.

Ethyl 2-[(6-Amino-4,7-dicyano-2,3-dihydro-1H-inden-5-yl)carbonyl]benzoate (2d). Yield: 280 mg (78%). Yellow powder. M.p. 152–154°. IR: 3417 and 3321 (NH₂), 2220 (CN), 1721 (COOMe), 1651 (C=O), 1616 and 1550 (arom.), 1263 (C–O). ¹H-NMR: 1.12 (*t*, *J* = 7.2, MeCH₂O); 2.07 (*m*, CH₂); 2.83 (*t*, *J* = 7.2, CH₂); 3.07 (*t*, *J* = 7.2, CH₂); 4.13 (*q*, *J* = 7.2, MeCH₂O); 7.41–7.46 (*m*, 1 arom. H); 7.64–7.70 (*m*, 2 arom. H); 7.74 (*s*, NH₂); 7.89–7.95 (*m*, 1 arom. H). ¹³C-NMR: 13.6; 23.4; 32.1; 33.6; 61.3; 98.6; 113.8; 114.4; 114.8; 116.4; 128.0; 129.9; 130.0; 131.0; 132.5; 137.9; 141.6; 151.5; 156.1; 165.8; 195.6. EI-MS: 359 (58, *M*⁺), 312 (62), 285 (62), 258 (34), 229 (36), 210 (37), 182 (29), 149 (100), 128 (29), 115 (18), 104 (924), 93 (24), 76 (30), 65 (24), 50 (10). Anal. calc. for C₂₁H₁₇N₃O₃ (359.38): C 70.18, H 4.77, N 11.69; found: C 70.08, H 4.69, N 11.60.

Ethyl 2-[(3-Amino-1,4-dicyano-9H-fluoren-2-yl)carbonyl]benzoate (2e). Yield: 325 mg (80%). Yellow powder. M.p. 212–215°. IR: 3456 and 3347 (NH₂), 2216 (CN), 1720 (COOEt), 1642 (C=O), 1602 and 1545 (arom.), 1281 (C–O). ¹H-NMR: 1.10 (*t*, *J* = 6.7, MeCH₂O); 3.87 (*s*, CH₂); 4.13 (*q*, *J* = 6.7, MeCH₂O); 7.53 (*s*, NH₂); 7.54–7.59 (*m*, 2 arom. H); 7.65–7.73 (*m*, 3 arom. H); 7.92–7.96 (*m*, 2 arom. H); 8.26–8.28 (*m*, 1 arom. H). ¹³C-NMR: 13.6; 35.9; 61.3; 92.9; 114.0; 114.5; 115.2; 116.0; 122.4; 125.8; 127.8; 128.2; 129.9; 130.0; 130.9; 131.0; 132.6; 136.5; 136.7; 141.6; 145.7; 147.2; 152.6; 165.7; 195.6. EI-MS: 407 (42, *M*⁺), 360 (60), 333 (60), 304 (44), 278 (22), 258 (26), 203 (60), 176 (54), 149 (100), 121 (30), 104 (33), 93 (34), 76 (34), 65 (32), 50 (18). Anal. calc. for C₂₅H₁₇N₃O₃ (407.42): C 73.70, H 4.21, N 10.31; found: C 73.61, H 4.15, N 10.23.

Ethyl 2-[(3-Amino-1,4-dicyano-9,10-dihydrophenanthren-2-yl)carbonyl]benzoate (2f). Yield: 316 mg (75%). Yellow powder. M.p. 287–289°. IR: 3456 and 3347 (NH₂), 2216 (CN), 1720 (COOEt), 1642 and 1602 (arom.), 1281 (C–O). ¹H-NMR: 1.14 (*t*, *J* = 6.9, MeCH₂O); 2.65–2.80 (*m*, 2 CH₂); 4.14 (*q*,

$J = 6.9$, MeCH_2O); 7.39–7.45 (m , 2 arom. H); 7.47 (s , NH_2); 7.49–7.58 (m , 2 arom. H); 7.64–7.70 (m , 2 arom. H); 7.88–7.92 (m , 1 arom. H); 8.18 (d , $J = 6.6$, 1 arom. H). $^{13}\text{C-NMR}$: 13.7; 26.4; 27.8; 61.5; 102.0; 114.5; 116.2; 116.8; 125.3; 127.0; 127.4; 128.3; 128.5; 129.8; 129.9; 130.7; 131.1; 131.4; 131.5; 132.4; 140.3; 141.2; 143.0; 151.8; 166.2; 195.5. EI-MS: 421 (8, M^+), 402 (100), 386 (14), 374 (60), 358 (22), 346 (15), 331 (15), 303 (27), 277 (14), 215 (10), 193 (9), 166 (7), 138 (6), 104 (4), 76 (8). Anal. calc. for $\text{C}_{26}\text{H}_{19}\text{N}_3\text{O}_3$ (421.45): C 74.10, H 4.54, N 9.97; found: C 74.01, H 4.49, N 9.91.

Ethyl 2-[2-Amino-3,6-dicyano-4-(2-oxo-2H-1-benzopyran-3-yl)benzoyl]benzoate (2g). Yield: 370 mg (80%). Yellow powder. M.p. $> 300^\circ$. IR: 3400 and 3295 (NH_2), 2217 (CN), 1706 (COOEt), 1602 and 1542 (arom.), 1279 (C–O). $^1\text{H-NMR}$: 1.16 (t , $J = 6.9$, MeCH_2O); 4.16 (q , $J = 6.9$, MeCH_2O); 7.30 (s , 1 arom. H); 7.44 (t , $J = 7.5$, 1 arom. H); 7.51 (d , $J = 8.4$, 1 arom. H); 7.58 (t , $J = 4.5$, 1 arom. H); 7.70–7.75 (m , 3 arom. H); 7.80 (s , NH_2); 7.81 (d , $J = 8.4$, 1 arom. H); 7.92 (t , $J = 4.5$, 1 arom. H); 8.43 (s , 1 CH). $^{13}\text{C-NMR}$: 13.7; 61.5; 102.1; 114.7; 115.4; 116.4; 117.9; 118.4; 119.0; 123.3; 123.5; 125.2; 128.4; 129.3; 129.9; 130.2; 131.5; 132.6; 133.4; 140.8; 144.1; 144.8; 151.9; 153.6; 158.3; 165.9; 195.5. EI-MS: 463 (54, M^+), 390 (16), 366 (81), 278 (90), 178 (100), 166 (63), 140 (40), 128 (50), 105 (81), 77 (63). Anal. calc. for $\text{C}_{27}\text{H}_{17}\text{N}_3\text{O}_5$ (463.44): C 69.98, H 3.70, N 9.07; found: C 69.91, H 3.62, N 8.95.

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