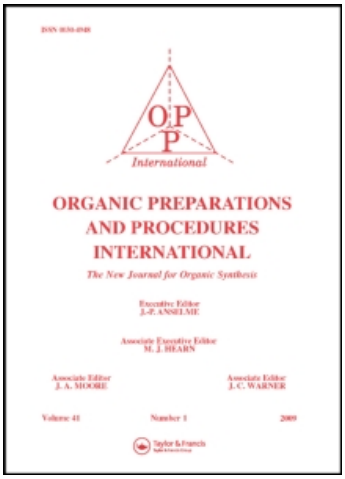

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SYNTHESIS OF SUBSTITUTED AROMATIC COMPOUNDS USING BTC/DMF AS VILSMEIER REAGENT

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20. C. H. Schiesser and M. A. Skidmore, *J. Chem. Soc. Perkin Trans. 1*, 2689 (**1997**).

21. M. A. Lucas and C. H. Schiesser, *J. Org. Chem.*, **61**, 5754 (1996).

22. L. Wang and Y. Zhang, *Synth. Commun.*, **29**, 3107 (1999).

23. B. Movassagh and A. Fazeli, *Monatsh. Chem.*, **138**, 863 (2007).

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SYNTHESIS OF SUBSTITUTED AROMATIC COMPOUNDS USING BTC/DMF AS VILSMEIER REAGENT

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The wide synthetic potential of the Vilsmeier reaction has been known for years and its utility for achieving different transformations has been amply demonstrated.[1] It has been reported that some aliphatic substances could be annulated to aromatic compounds by treatment of $POCl_3$/DMF as the Vilsmeier reagent, such as acyclic ketones,[2] cyclohexenones,[3] and α,β-epoxy ketones[4] and etc.[5] Generally, the traditional Vilsmeier-Haack reagent employs toxic reagents such as phosgene and phosphorus oxychloride.[6] Recently, the utilization of Vilsmeier salts derived from *bis*-(trichloromethyl) carbonate (triphosgene, BTC) and N,N-dimethylformamide (DMF) has been explored extensively.[7] In previous papers, we reported organic reactions involving by BTC/DMF as the Vilsmeier reagent.[8] In continuation of our studies on a variety of applications of BTC, we herein report a convenient method for the preparation of some substituted aromatic compounds using BTC/DMF as Vilsmeier reagent under mild conditions.

We initially investigated various conditions for the annulation of 3-benzoylpentane-2,4-dione with BTC/DMF to aromatic compound as the model reaction for the optimal conditions. The postulated mechanism indicates that the formation of the aromatic ring is quite complex with the generation of some by-products.[9] The reaction was monitored by TLC until the starting material was consumed. The residue was purified by flash chromatography on silica gel. The assignments of structure was confirmed by ^1H NMR, ^{13}C NMR, MS, IR and elemental analysis or comparison with literature data.[10] The results are shown in *Table 1*.

Table 1. Effect of Reagent, Solvent and Temperature on the annulation of **1a**.[a]

1a **2a**

Entry	Ratio of BTC:DMF:**1a**	Solvent	Conditions	Yield (%)
1	1:3:1	DMF	40°C, 6h	48
2	1.67:5:1	CH_2Cl_2	reflux., 6h	50
3	1:3:1	CH_2Cl_2	reflux., 6h	50
4	1:3:1	THF	reflux, 6h	40
5	1:3:1	$(CH_2Cl)_2$	reflux, 6h	37
6	1:3:1	DMF	100°C, 6h	- -[b]
7	1:3:2	CH_2Cl_2	reflux, 10h	35

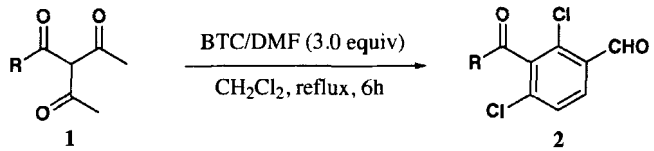
a) See general procedure. b) No product was obtained.

As shown in *Table 1*, different solvents affect the yield under reflux for the same reaction time (*Table 1, Entry 1, 3-5*). Apparently with increasing reaction temperature, the reaction became complex and the yield decreased, especially at 100°C in DMF where no product was obtained (*Table 1, Entry 6*). Study of the amounts of Vilsmeier reagent (*Table 1, Entry 2, 3, 7*) suggests that the use of 3 equiv. of BTC/DMF as Vilsmeier reagent is sufficient to effect this reaction in CH_2Cl_2 under reflux for 6 h. Subsequently, the above optimal protocol was utilized for the annulation of a variety of 3-substituted benzoylpentane-2, 4-dione derivatives (*Table 2*).

As shown in *Table 2*, the product yield is influenced by different substituents on the aromatic ring. With substrates bearing electron-withdrawing groups (*Table 2, Entries 7-9*), lower yields were obtained (25-30%). On the other hand, higher yields were obtained for substrates bearing electron-donating group (*Table 2, Entry 2, 5, 6, 10*). Interestingly, 3-(2-chlorobenzoyl)pentane-2,4-dione and 3-(4-chlorobenzoyl)pentane-2,4-dione (*Table 2, Entry 3 and 4*) proceeded efficiently, possibly due to the conjugate effect of chlorine atom which overcome its inductive effect. Furthermore, the reaction with electron-rich heterocyclic substituted carbonyl pentane-2,4-dione (*Table 2, Entry 11 and 12*) gave the corresponding products in relatively good yields. The ^1H NMR, ^{13}C NMR and IR data are given in *Table 3*. The MS and analytical data for all unknown compounds are shown in *Table 4*.

In conclusion, a convenient method for the preparation of some substituted aromatic compounds using BTC/DMF as Vilsmeier reagent has been developed. Compared to $POCl_3$/DMF the present protocol has such advantages such as being environmentally benign, mild reaction conditions and reasonable yields.

Table 2. Synthesis of Aromatic Compounds under Vilsmeier Conditions [a]



1 2

Entry	R	Product [b]	Yield (%)	m.p. (°C) (*lit.* m.p.)
1	C_6H_5	**2a**	50	88-91(93-95[11])
2	4-$CH_3C_6H_4$	**2b**	58	105-107
3	2-ClC_6H_4	**2c**	53	83-85
4	4-ClC_6H_4	**2d**	55	132-133
5	2-$MeOC_6H_4$	**2e**	52	96-97
6	4-$MeOC_6H_4$	**2f**	60	117-120
7	4-$NO_2C_6H_4$	**2g**	30	102-105
8	3-$NO_2C_6H_4$	**2h**	25	164-166
9	2-Cl-4-$NO_2C_6H_3$	**2i**	28	117-119
10	3,4-$(MeO)_2C_6H_3$	**2j**	66	136-139
11	2-thienyl	**2k**	55	86-87
12	2-furyl	**2l**	53	99-102

a) Reaction conditions: 1 (3 mmol), BTC (3 mmol), DMF (9 mmol), 6.0 h. The reaction was carried out under reflux CH_2Cl_2. b) All the unknown products were characterized by ^1H NMR, ^{13}C NMR, MS, IR and elemental analysis.

Table 3. ^1H NMR, ^{13}C NMR, and IR Spectral Data of All Products

Compound (color)	IR (cm^{-1})	^1H NMR (δ)	^{13}C NMR (δ)		
2a (yellow crystal)	1693, 1674, 1575	10.45 (s, 1 H, CHO), 7.99 (d, 1 H, *J* = 8.0 Hz, Ar *H*), 7.84 (d, 2 H, *J* = 7.2 Hz, Ar *H*), 7.67 (t, 1 H, *J* = 6.8 Hz, Ar *H*)7.52 (t, 3 H, *J* = 8.0 Hz, Ar *H*)	128.8, 130.2, 134.8, 138.9,	129.0, 131.1, 135.2, 187.8,	129.4, 134.6, 137.6, 191.4
2b (yellow crystal)	1694, 1671, 1601	10.45 (s, 1 H, CHO),7.98 (d, 1 H, *J* = 8.4 Hz, Ar *H*), 7.73 (d, 2 H, *J* = 8.4 Hz, Ar *H*), 7.52 (d, 1 H, *J* = 8.4 Hz, Ar *H*), 7.31 (d, 2 H, *J* = 8.0 Hz, Ar *H*), 2.45 (s, 3 H, CH_3)	21.8, 129.8, 132.7, 139.3, 190.9	128.8, 130.2, 135.6, 145.9,	129.6, 131.3, 137.7, 187.9,
2c (yellow crystal)	1688, 1674, 1585	10.44 (s, 1 H, CHO), 7.96 (d, 1 H, *J* = 8.4 Hz, Ar *H*), 7.79 (d, 1 H, *J* = 8.4 Hz, Ar *H*), 7.49-7.55 (m, 3 H, Ar *H*), 7.39-7.42 (m, 1 H, Ar *H*)	127.2, 131.3, 134.0, 135.4, 187.9,	129.0, 131.8, 134.2, 137.7, 189.8	130.4, 132.4, 134.3, 140.0,

Table 3. Continued...

Compound (color)	IR (cm^{-1})	^1H NMR (δ)	^{13}C NMR (δ)		
2d (yellow crystal)	1706, 1670, 1586	10.44 (s, 1 H, CHO), 8.00 (d, 1 H, *J* = 8.8 Hz, Ar *H*), 7.78 (d, 2 H, *J* = 6.8 Hz, Ar *H*), 7.54 (d, 1 H, *J* = 8.0 Hz, Ar *H*), 7.50 (d, 2 H, *J* = 6.8 Hz, Ar *H*)	129.0, 130.8, 135.2, 141.4,	129.5, 131.3, 137.7, 187.8,	130.5, 133.4, 138.6, 190.3
2e (yellow crystal)	1691, 1649, 1593	10.45 (s, 1 H, CHO), 8.02 (d, 1 H, *J* = 7.6 Hz, Ar *H*), 7.89 (d, 1 H, *J* = 8.0 Hz, Ar *H*), 7.60 (t, 1 H, *J* = 8.0 Hz, Ar *H*), 7.45 (d, 1 H, *J* = 8.4 Hz, Ar *H*), 7.10 (t, 1 H, *J* = 7.6 Hz, Ar *H*), 6.97 (d, 1 H, *J* = 8.0 Hz, Ar *H*), 3.70 (s, 3 H, OCH_3)	55.9, 124.7, 130.9, 136.2, 188.3,	112.2, 128.3, 131.8, 136.8, 189.6	121.0, 129.0, 134.4, 142.8,
2f (yellow crystal)	1694, 1663, 1593	10.45 (s, 1 H, CHO), 7.97 (d, 1 H, *J* = 8.4 Hz, Ar *H*), 7.81 (d, 2 H, *J* = 8.8 Hz, Ar *H*), 7.52 (d, 1 H, *J* = 8.4 Hz, Ar *H*), 6.98 (d, 2 H, *J* = 9.2 Hz, Ar *H*), 3.90 (s, 3 H, OCH_3)	55.6, 128.8, 131.9, 139.3	114.4, 130.0, 135.2,	128.0, 131.1, 137.7,
2g (yellow crystal)	1693, 1599, 1561	10.45 (s, 1 H, CHO), 8.37 (d, 2 H, *J* = 8.0 Hz, Ar *H*), 8.01-8.07 (m 3 H, Ar *H*), 7.60 (d, 1 H, *J* = 8.8 Hz, Ar *H*)	124.4, 131.1, 137.6, 151.2,	129.2, 131.5, 137.9, 187.4,	130.4, 135.1, 139.3, 190.0
2h (yellow crystal)	1705, 1676, 1609	10.45 (s, 1 H, CHO), 8.64 (s, 1 H, Ar *H*), 8.53 (d, 1 H, *J* = 7.2 Hz, Ar *H*), 8.18 (d, 1 H, *J* = 7.6 Hz,Ar *H*), 8.06 (d, 1 H, *J* = 8.4 Hz, Ar *H*), 7.76 (t, 1 H, *J* = 8.0 Hz, Ar *H*), 7.59 (d, 1 H, *J* = 8.8 Hz, Ar *H*)	124.0, 130.5, 134.7, 137.6, 187.4,	128.7, 131.2, 135.1, 137.7, 189.5	129.2, 131.5, 136.4, 148.8,
2i (yellow crystal)	1697, 1574, 1523	10.44 (s, 1 H, CHO), 8.36 (s, 1 H, Ar *H*), 8.23 (d, 1 H, *J* = 8.8 Hz, Ar *H*), 8.00 (dd, 2 H, J_1 = 8.0 Hz, J_2 =8.4 Hz, Ar *H*), 7.54 (d, 1 H, *J* = 8.4 Hz, Ar *H*)	122.0, 131.2, 135.1, 138.8, 187.5,	126.7, 131.5, 135.4, 139.1, 188.6	129.3, 132.9, 137.7, 150.1,
2j (yellow crystal)	1698, 1662, 1596	10.45 (s, 1 H, CHO), 7.97 (d, 1 H, *J* = 8.4 Hz, Ar *H*), 7.64 (s, 1 H, Ar *H*), 7.52 (d, 1 H, *J* = 8.4 Hz, Ar *H*), 7.17 (d, 1 H, *J* = 8.0 Hz, Ar *H*), 6.86 (d, 1 H, *J* = 8.4 Hz, Ar *H*), 3.96 (s, 3 H, OMe), 3.94 (s, 3 H, OMe)	56.0, 125.6, 130.0, 137.7, 154.7,	109.9, 128.2, 131.1, 139.1, 187.9,	110.2, 129.0, 135.3, 149.6, 189.9
2k (yellow crystal)	1700, 1650, 1573	10.45 (s, 1 H, CHO), 7.98 (d, 1 H, *J* = 7.6 Hz, Ar *H*), 7.84 (d, 1 H, *J* = 5.2 Hz, Ar *H*), 7.53 (d, 1 H, *J* = 8.4 Hz, Ar *H*), 7.44 (d, 1 H, *J* = 4.4 Hz, Ar *H*), 7.16-7.18 (m, 1 H, Ar *H*)	128.7, 131.3, 137.8, 183.3,	129.0, 135.4, 138.9, 187.9	130.5, 136.6, 142.3,
2l (yellow crystal)	1697, 1656, 1578	10.45 (s, 1 H, CHO), 7.98 (d, 1 H, *J* = 8.8 Hz, Ar *H*), 7.71 (s, 1 H, Ar *H*), 7.52 (d, 1 H, *J* = 8.0 Hz, Ar *H*), 7.19 (d, 1 H, *J* = 3.2 Hz, Ar *H*), 7.63-7.64 (m, 1 H, Ar *H*)	113.1, 130.6, 138.0, 151.3,	121.2, 131.2, 138.1, 178.4,	128.9, 135.7, 148.6, 187.9

Table 4. MS and Analytical Data for All Unknown Compounds

Cmpd	MS (EI)	Mol. Formula (Mol. Weight)	Analysis/% Found (Calcd)		
			C	H	N
2a	278 (M^+, 9), 280 (M^+ + 2, 6), 282 (M^+ + 4, 1),105 (100)	$C_{14}H_8Cl_2O_2$ (279)	----	----	----
2b	292 (M^+, 35), 294 (M^+ + 2, 20), 296 (M^+ + 4, 3), 119 (100)	$C_{15}H_{10}Cl_2O_2$ (293)	61.58 (61.46)	3.66 (3.44)	---- (-)
2c	312 (M^+, 45), 314 (M^+ + 2, 37), 316 (M^+ + 4, 14), 318 (M^+ + 6, 2), 139 (100)	$C_{14}H_7Cl_3O_2$ (313.5)	53.57 (53.63)	2.48 (2.25)	---- (-)
2d	312 (M^+, 45), 314 (M^+ + 2, 37), 316 (M^+ + 4, 14) , 318 (M^+ + 6, 2), 139 (100)	$C_{14}H_7Cl_3O_2$ (313.5)	53.71 (53.63)	2.49 (2.25)	---- (-)
2e	308 (M^+, 21), 310 (M^+ + 2, 12), 312 (M^++4, 2), 135 (100)	$C_{15}H_{10}Cl_2O_3$ (309)	58.39 (58.28)	3.44 (3.26)	---- (-)
2f	308 (M^+, 36), 310 (M^+ + 2, 21), 312 (M^+ + 4, 3), 135 (100)	$C_{15}H_{10}Cl_2O_3$ (309)	58.17 (58.28)	3.43 (3.26)	---- (-)
2g	323 (M^+, 48), 325 (M^+ + 2, 23), 327 (M^+ + 4, 4), 150 (100)	$C_{14}H_7Cl_2NO_4$ (324)	51.96 (51.88)	2.29 (2.18)	4.55 (4.32)
2h	323 (M^+, 43), 325 (M^+ + 2, 26), 327 (M^+ + 4, 4), 150(100)	$C_{14}H_7Cl_2NO_4$ (324)	51.99 (51.88)	2.39 (2.18)	4.21 (4.32)
2i	357 (M^+, 53), 359 (M^+ + 2, 34), 361 (M^+ + 4, 12), 363 (M^+ + 6, 2), 184 (100)	$C_{14}H_6Cl_3NO_4$ (358.5)	46.81 (46.90)	1.78 (1.69)	3.83 (3.91)
2j	338 (M^+, 66), 340 (M^+ + 2, 40), 342 (M^+ + 4, 7), 165 (100)	$C_{16}H_{12}Cl_2O_4$ (339)	56.78 (56.66)	3.69 (3.57)	---- (-)
2k	284 (M^+, 42), 286 (M^+ + 2, 24), 288 (M^+ + 4, 6), 111 (100)	$C_{12}H_6Cl_2O_2S$ (285)	50.59 (50.55)	2.33 (2.12)	---- (-)
2l	268 (M^+, 41), 270 (M^+ + 2, 27), 273 (M^+ + 4, 4), 95 (100)	$C_{12}H_6Cl_2O_3$ (269)	53.48 (53.56)	2.38 (2.25)	---- (-)

EXPERIMENTAL SECTION

Melting points were obtained on a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer. ^1H NMR spectra were measured on a Varian Mercur plus-400 spectrometer (400 MHz) in $CDCl_3$ using TMS as internal standard. ^{13}C NMR spectra were obtained in $CDCl_3$ on Varian Mercur plus-100 spectrometer (100 MHz) with TMS as internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants *J* are given in Hz. Mass spectra were determined on a Trace DSQ mass spectrometer. Elemental analysis was performed on a VarioEL-3 instrument. The starting material 3-substituted benzoylpentane-2, 4-dione derivatives were prepared according to the literature.[12] Organic solvents were obtained from commercial sources.

Typical Procedure.- A solution of 3-benzoylpentane-2,4-dione (3 mmol) in CH_2Cl_2 (5 mL) was added dropwise to an ice-cooled magnetically stirred mixture of Vilsmeier reagent prepared from DMF (9 mmol) and BTC (3 mmol) in 15 mL CH_2Cl_2 for 15 min. The reaction mixture was gradually allowed to reach room temperature and heated under reflux condition for 6 h. The residual solution was poured onto crushed ice, stirred for 3 h, and extracted with ethyl acetate. The organic layer was separated, washed with water, saturated $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent, purification of the residue by silica gel column chromatography (petroleum ether/AcOEt 10:1) gave 3-benzoyl-2, 4-dichlorobenzaldehyde (**2a**).

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REFERENCES

1. (a) C. Jutz, *"Topics in Current Chemistry"*. **73**, 125 (1978). (b) O. Meth-Cohn and B. Tarnowski, *"Advances in Heterocyclic Chemistry"*. **31**, 207 (1982). (c) M. C. Marson, *Tetrahedron*, **48**, 3659 (1992). (d) M. C. Marson and P. R .Giles, *"Synthesis using Vilsmeier Reagents"*. CRC Press (**1994**).

2. (a) A. Holy and Z. Arnold, *Collect. Czech. Chem. Commun.* **30**, 53 (1965). (b) A. R. Katritzky and M. C. Marson, *J. Org. Chem.*, **52**, 2726 (1987). (c) M. Sreenivasulu and G. S. Krishna Rao, *Indian J. Chem., Sec. B*, **28B**, 494 (1989). (d) S. Selvi and P. T. Perumal, *Synth. Commun.*, **30**, 3925 (2000). (e) J. Khiari, A. M. A Hadj and H. B. Ben, *Tetrahedron Lett.*, **47**, 2973 (2006).

3. (a) B. Raju and G. S. Krishna Rao, *Indian J. Chem., Sec. B*, **26B**, 177 (1987). (b) A. R. Katritzky, M. C. Marson and Z. Q. Wang, *J. Org. Chem.*, **52**, 2730 (1987).

4. M. Sreenivasulu and G. S. Krishna Rao, *Tetrahedron Lett.*, **36**, 5819 (1995).

5. (a) B. Raju and G. S. Krishna Rao, *Synthesis*, **08**, 779 (1985). (b) B. Raju and G. S. Krishna Rao *Synthesis*, **02**, 197 (1987). (c) M. Sreenivasulu and G. S. Krishna Rao, *Indian J. Chem., Sec. B*, **26B**, 1187 (1987). (d) B. Raju and G. S. Krishna Rao, *Indian J. Chem., Sec. B*, **26B**, 175 (1987). (e) A. D. Thomas, Josemin and C. V. Asokan, *Tetrahedron*, **60**, 5069 (2004).

6. W. Ziegenbein and W. Franke, *Angew. Chem.*, **71**, 573 (1959).

7. I. A. Rivero, K. A Espinoza and A.Ochoa, *J. Comb. Chem.*, **6**, 270 (2004).

8. (a) W. K. Su and C. Jin, *Org. Lett.*, **9**, 993 (2007). (b) W. G. Shan, X. J. Shi and W. K. Su, *Org. Prep. Proced. Int.*, **36**, 337 (2004); (c) X. J. Shi, W. K. Su and W. G. Shan, *J. Indian Chem. Soc.*, **82**, 1019 (2005); (d) W. K. Su, W. H. Zhong, G. F. Bian, X. J. Shi and J. P. Zhang, *Org. Prep. Proced. Int.*, **36**, 499 (2004).

9. M. C. Marson, *Tetrahedron*, **48**, 3659 (1992).

10. (a) S. Kenso, W. Masami and K. Masashi, *J. Chem. Soc., Chem. Commun.*, **9**, 534 (1989).
(b) S. Kenso, W. Masami and K. Masashi, *Bull. Chem. Soc. Jpn*, **62**, 2124 (1989).

11. W. J. Houlihan, US Patent 3898275 (**1975**); *Chem. Abstr.*, **83**,147305a (1975).

12. D. L. Lee (Martinez, CA), US Patent 4741769 (**1988**); *Chem. Abstr.*, **109**,144620u (1988).

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AN EFFICIENT SYNTHESIS OF 3,5-*bis*(2-CYANOISOPROPYL)TOLUENE

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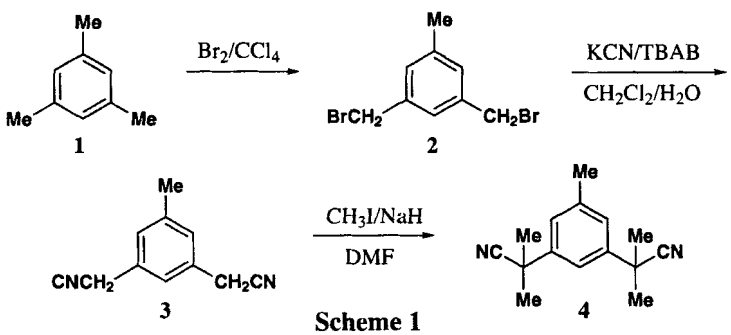
3,5-*bis*(2-Cyanoisopropyl)toluene (**4**) is a key intermediate for the preparation of *anastrozole*, an anti-tumor drug for the treatment of breast cancer. So far, the only synthetic route to **4** involves three steps from mesitylene (*Scheme 1*).[1,2] However, this patented approach suffers from low yield, environmentally unfriendly chemicals (CCl_4 and benzoyl peroxide) and high cost (expensive iodomethane).



Scheme 1

As a part of our exploration of a facile synthesis of *anastrozole*, we have developed an efficient preparation of 3,5-*bis*(2-cyanoisopropyl)toluene (**4**) from commercially available 5-methylisophthalic acid (**5**) (*Scheme 2*).