Notes

Improved Syntheses of 3,5-Diaryl-Substituted Phenols

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Introduction

Although much less familiar than their alkyl-substituted analogues, aryl-substituted phenols have recently shown interesting potential for the preparation of "molecular harpoons".[1] Previous procedures for the syntheses of arylated phenols[2,3] are mostly of academic interest rather than solid preparative methods. Synthetic routes based on assembling the phenol backbone from "aliphatic building blocks" seem to be of most promise, generally involving intermediate aryl-substituted cyclohex-2-enones or 6-(ethoxycarbonyl)cyclohex-2-enones from the reaction of chalcones with carbonyl compounds carrying $CH_2C(O)$ or $CH_2C(O)CH_2$ fragments.[2] Aromatization of aryl-substituted cyclohexenones into phenols often requires strong conditions (treatment with Pd/C in refluxing diphenyl ether,[4] or refluxing cymene,[5] etc.). Even milder aromatization methods, e.g., oxidation by bromine,[6,7] did not guarantee improved yields or better isolation procedures. Tandem Michael addition/aldol condensation of 1-(2-oxopropyl)pyridinium chloride with chalcones forms cyclohexenones, which aromatize by the elimination of pyridinium chloride to give 3,5-diaryl-substituted phenols.[3,8] With the exception of 3-(4-nitrophenyl)-5-phenylphenol (82%), yields of 3,5-diarylphenols were poor to moderate (34−62%) via this method.

Our recent successful preparations of pyridine derivatives from 2-(benzotriazol-1-yl)acetamide and 2-(benzotriazol-1-yl)acetonitrile demonstrated the efficiency of benzotriazole as an *uncharged* leaving species leading to easier heteroaromatization of the intermediates.[9] We have now utilized this property to develop a simple and efficient preparation of 3,5-diaryl-substituted phenols.

Results and Discussion

Reactions of 1-(benzotriazol-1-yl)propan-2-one (**2**) with 1,3-diarylprop-2-enones **1a**−**g** in the presence of excess NaOH in refluxing ethanol afforded 3,5-diaryl-substituted phenols **6a**−**g** in 52−94% yield (Scheme 1). Acetone derivative **2** was readily prepared in 59% yield by reacting bromoacetone with benzotriazole in the presence of triethylamine in hot (65−70 °C) toluene. Significantly, we prepared the 3-(*ortho*-substituted-aryl)phenol **6g** in 52% yield. This type of *ortho*-substituted 3,5-diarylphenol was previously unknown and specifically could not be prepared by the method of Eichinger et al.[3] Our method thus allows access to a wider variety of phenols. Constants and NMR characteristics of phenols **6a**−**g** are shown in Tables 1 and 2.

Our suggested reaction mechanism for the formation of **6a**−**g** involves intermediate Michael adducts **3a**−**g** which undergo aldol-like condensation and dehydration to give the corresponding cyclohexenones **4a**−**g**. Loss of benzotriazole under the action of excess base leads to cyclohexadienones **5a**−**g**, which readily rearrange into 3,5-diarylphenols **6a**−**g**.

Neither phase-transfer conditions nor milder base (piperidine), in the reaction of chalcones **1b** and **1e** with benzotriazolylacetone **2**, afforded the expected phenols: instead the reaction stopped at the stage of the cyclohexenones **4b** and **4e**, respectively (Scheme 2), which were isolated by column chromatography. The ^{1}H NMR spectra of ketones **4b** and **4e** each show the expected signals: an upfield doublet for two C(4) protons, a doublet of triplets for the proton of the C(5) atom, and a wide (J = 13−14 Hz) doublet at ca. 5.9−6.5 ppm corresponding to the C(6) proton adjacent to the benzotriazole moiety. The signals typical for the benzotriazole aromatic protons were also present. The benzotriazole moiety is present as the benzotriazol-1-yl isomer in compound **4b**, whereas it appears as the benzotriazol-2-yl isomer in compound **4e**, as follows from their NMR spectra. The ^{13}C and APT NMR spectra also confirmed the suggested structure of ketones **4b** and **4e**: they contain three upfield signals (higher than 70 ppm), one secondary and two tertiary for C(4), C(5), and C(6), respectively.

Treatment of cyclohexenones **4b** and **4e** with NaOH in refluxing ethanol led to the loss of benzotriazole and formation of the corresponding phenols **6b** and **6e** in high yields (Scheme 2). The melting points and GC/MS data of the phenols prepared in this way were consistent with those of **6b** and **6e** obtained according to Scheme 1. This result supports the proposed reaction mechanism and also demonstrates that the loss of benzotriazole moiety occurs under the action of a strong base.

The structure of **4b** was confirmed by X-ray crystallography. As shown in Figure 1, this compound crystallizes with the cyclohexenone ring disordered over two, approximately equally populated, half-chair conformations. This disorder also results in some high thermal displacement parameters for certain atoms. The crystallographic analysis also determines the relative stereochemistry of the substituents, with the C-5 and C-6 aryl groups being trans. Whereas the *p*-tolyl and benzotriazolyl ring are approximately orthogonal to the cyclohexenone plane (angles between mean planes being 72.5(3) and 92.4(3), respectively), the conjugated *p*-anisyl ring is more coplanar with the cyclohexenone ring (angle

(1) Naka, K.; Sadownik, A.; Regen, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2278.
(2) Dimroth, K. In *Topics in Current Chemistry, 129: Photochemistry and Organic Synthesis*; Boschke, F. L., Ed.; Springer-Verlag: Berlin-Heidelberg, 1985; p 99.
(3) Eichinger, K.; Nussbaumer, P.; Balkan, S.; Schulz, G. *Synthesis* **1987**, 1061.
(4) Downes, A. M.; Gill, N. S.; Lions, F. *J. Am. Chem. Soc.* **1950**, *72*, 3464.
(5) Zimmerman, H. E.; Schuster, D. I. *J. Am. Chem. Soc.* **1962**, *84*, 4527.
(6) Sexsmith, D. R.; Rassweiler, J. H. *J. Org. Chem.* **1960**, *25*, 1229.
(7) Yates, P.; Hyre, J. E. *J. Org. Chem.* **1962**, *27*, 4101.
(8) The analogous use of onium salts in the formation of cyclohexenone skeleton was earlier employed by Zimmerman and Schuster.[5]
(9) Katritzky, A. R.; Belyakov, S. A.; Sorochinsky, A. E.; Henderson, S. A.; Chen, J. *J. Org. Chem.* **1997**, *62*, 6210.

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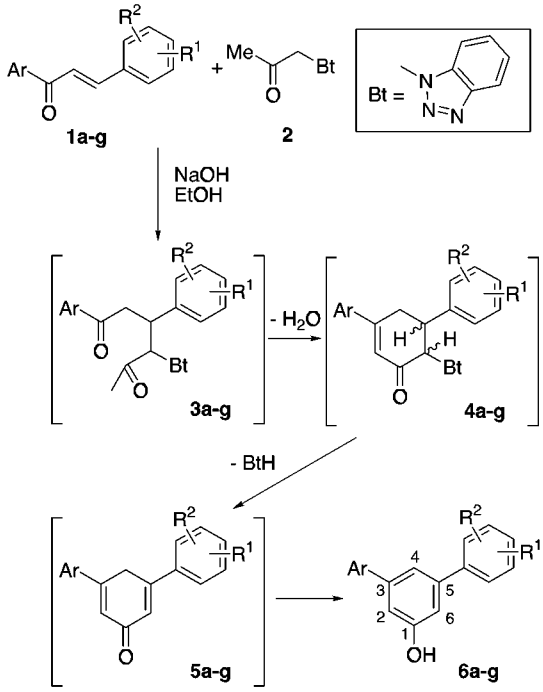
Scheme 1



a: Ar = Ph, $R^1 = R^2 = H$
b: Ar = 4-MeO-Ph, R^1 = 4-Me, $R^2 = H$
c: Ar = Ph, R^1 = 4-Cl, $R^2 = H$
d: Ar = Ph, R^1 = 4-NO_2, $R^2 = H$
e: Ar = 4-Cl-Ph, R^1 = 4-Cl, $R^2 = H$
f: Ar = 1-naphthyl, R^1 = 3-NO_2, $R^2 = H$
g: Ar = Ph, R^1 = 2-Cl, R^2 = 4-Cl

Table 1. Preparation of 3,5-Diaryl-substituted Phenols 6

phenol **6**	yield (%)	mp (°C)	lit mp (°C)	solvent for recrystallization	molecular formula
a	75	93−94	93−94[a]	hexanes	$C_{18}H_{14}O$
b	72	77−79	–	–	$C_{20}H_{18}O_2$[b]
c	91	115−116	110−112[c]	exanes	$C_{18}H_{13}ClO$
d	76	168−169 (dec)	–	MeOH	$C_{18}H_{13}NO_3$[d]
e	94	154−155	156−157[c]	hexanes/ pet. ether	$C_{18}H_{12}Cl_2O$
f	82	83−85	–	hexanes	$C_{22}H_{15}NO_3$[e]
g	52	oil			$C_{18}H_{12}Cl_2O$[f]

[a] Literature mp, ref 6. [b] MS found: 290.1264 [M^+]; calcd: 290.1307 [M^+]. [c] Literature mp, ref 3. [d] Anal. Calcd N, 4.81; Found: N, 5.13. [e] Anal. Calcd N, 4.10; Found: N, 4.08. [f] MS found: 314.0253 [M^+]; calcd: 314.0265 [M^+].

between mean planes = 29.6(3)). There are no unusually short intermolecular interactions, with the crystal packing being controlled by stacking interactions between aryl rings of adjacent molecules.

In summary, we found that [3 + 3] annulation reaction of 1-(benzotriazol-1-yl)propan-2-one (**2**) with 1,3-diarylprop-2-enones **1a**−**g** under basic conditions leads to benzotriazole-substituted cyclohex-2-enones **4** by means of tandem Michael reaction/intramolecular aldol-type condensation. Intermediates **4** under the action of strong base rapidly lose benzotriazole in situ, thus promoting formation of cyclohexadienones **5** which easily rearrange into phenols **6**. This reaction sequence was successfully used for the preparation of a series of 3,5-diaryl-substituted phenols in high yields and is suggested as a new and effective synthetic route to this class of substituted phenols. Compared to a previous method,[3] our methodology gives access to the 3-(*ortho*-substituted-aryl)phenols of type **6g**, which could not be prepared by the previous procedure.

Experimental Section

General. See refs 10 and 11. 1,3-Diarylprop-2-enones **1b,f,g** were prepared according to general literature procedure,[12] and **1a,c**−**e** were commercially available. ^{1}H NMR spectra of phenols **6a**−**c**,**e**−**g** and of cyclohexenone **4b** were recorded in $CDCl_3$, and compounds **6d** and **4e** in the mixture $CDCl_3$:DMSO-d_6 (3:1 v/v), at 300 MHz. ^{13}C NMR spectra were recorded at 75 MHz in the same solvents.

1-(Benzotriazol-1-yl)propan-2-one (2). A solution of benzotriazole (5.43 g, 46 mmol), bromoacetone (6.25 g, 46 mmol), and triethylamine (7.0 mL, 50 mmol) in toluene (100 mL) was stirred at 65−70 °C for 1 h. The precipitate was filtered, washed with toluene, dispersed in water (100 mL), stirred for 5 min, and filtered. The crude product was suspended in 10% NaOH solution, stirred for 5 min, filtered, washed with water, and air-dried to give ketone **2** (4.27 g, 53%). The analytical sample was prepared by recrystallization from toluene. Plates, mp 56−57 °C; ^{1}H NMR δ 2.21 (s, 3H), 5.44 (s, 2H), 7.40−7.45 (m, 2H), 7.48−7.50 (m, 1H), 8.07 (d, J = 8.8 Hz, 1H); ^{13}C NMR δ 27.0, 56.7, 109.0, 120.1, 124.1, 127.9, 133.3, 145.9, 199.8. Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.51; H, 5.23; N, 23.95.

3-(4-Methoxyphenyl)-5-(4-methylphenyl)-6-(benzotriazol-1-yl)cyclohex-2-enone (4b). To a mixture of chalcone **1b** (0.38 g, 1.5 mmol), ketone **2** (0.26 g, 1.5 mmol), CH_2Cl_2 (20 mL), and water (5 mL) was added a solution of tetrabutylammonium chloride (0.03 g, 0.15 mmol) in 50% NaOH (0.48 g, 6.0 mmol), and the resulting mixture was vigorously stirred at reflux for 8 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (50 mL), and the organic layer was separated, dried over anhyd Na_2SO_4, and evaporated. The resulting crude product was recrystallized from MeOH/dioxane to give **4b** (0.52 g, 84%) as yellowish crystals. The analytical sample was obtained after column chromatography of the recrystallized product (silica gel, eluent $CHCl_3$). Needles, mp 263−264 °C; ^{1}H NMR δ 2.18 (s, 3H), 3.35 (d, J = 8.0 Hz, 2 H), 3.87 (s, 3H), 4.34 (dt, J_1 = 8.1 Hz, J_2 = 15.9 Hz, 1H), 5.92 (d, J = 13.4 Hz, 1H), 6.72 (s, 1H), 6.94 (d, J = 7.8 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 7.25−7.32 (m, 1H), 7.37−7.43 (m, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.5 Hz, 1H);^{13}C NMR δ 20.9, 36.8, 45.9, 55.4, 67.6, 109.6, 114.4, 120.1, 121.8, 123.5, 126.9, 127.2, 128.0, 129.2, 129.4, 133.2, 135.7, 137.4, 145.8, 158.5, 161.9, 191.1. Anal. Calcd for $C_{26}H_{23}N_3O_2$: C, 76.26; H, 5.66; N, 10.26. Found: C, 76.41; H, 5.69; N, 10.32.

Crystal Data of the Cyclohexenone 4b. Solution and Refinement: $C_{26}H_{23}N_3O_2$, M_r = 409.5, monoclinic, space group $P2_1/n$, a = 6.391(3), b = 13.103(3), c = 26.253(6) Å, β = 96.84(2)°, V = 2183(1) Å,^{3} T = −120 °C, $F(000)$ = 864, Z = 4, D_c = 1.25 g·cm^{-3}, μ(Mo Kα) = 0.80 cm^{-1}. Data were collected using the $\omega-2\theta$ scan technique with a Nicolet P4 four-circle diffractometer to a $2\theta_{max}$ of 50°. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares procedures. Non-hydrogen atoms were made anisotropic and hydrogen atoms were included in calculated positions. In the final least-squares cycles 302 parameters were adjusted; the final R index was 0.049 for data with $I > 2\sigma(I)$ and wR 0.115 for all 3845 data.[13]

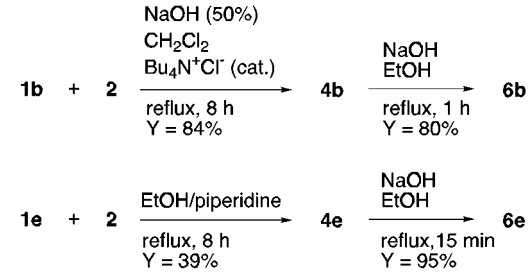
3,5-Bis(4-chlorophenyl)-6-(benzotriazol-2-yl)cyclohex-2-enone (4e). A mixture of chalcone **1e** (0.41 g, 1.5 mmol), ketone **2** (0.26 g, 1.5 mmol), and piperidine (10 drops) in EtOH (30 mL) was refluxed with stirring for 8 h. On cooling, the mixture was acidified with HCl (10%, 10 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated, washed with water (30 mL), and dried over anhyd Na_2SO_4, and the solvent was evaporated. The resulting solid was purified by column chromatography (silica gel, eluent $CHCl_3$). After evaporation of the solvent from the fractions with R_f 0.19−0.21 (silica gel TLC plates, eluent − $CHCl_3$) the product was triturated with MeOH and filtered to give **4e** (0.254 g, 39%) as white plates, mp 273−274 °C; ^{1}H NMR δ 3.24−3.34 (m, 2H), 4.51 (ddd, J_1 = 6.0 Hz, J_2 = 13.5 Hz, 1H), 6.02 (d, J = 13.5 Hz, 1H), 6.68 (s, 1H), 7.15 (d,

(10) Katritzky, A. R.; Li, J. *J. Org. Chem.* **1996**, *61*, 1624.
(11) Katritzky, A. R.; Wu, H.; Xie, L. *J. Org. Chem.* **1996**, *61*, 4035.
(12) Szmant, H. H.; Basso, A. J. *J. Am. Chem. Soc.* **1952**, *74*, 4397.
(13) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Table 2. NMR Data of 3,5-Diaryl-Substituted Phenols 6

phenol 6	^{1}H NMR δ (ppm), J (Hz)	^{13}C NMR δ (ppm)
a	5.68 (br s, 1H), 7.06 (s, 2H), 7.33−7.47 (m, 7H), 7.61 (d, J = 7.5, 4H)	113.1, 118.9, 127.2, 127.6, 128.8, 140.7, 143.4, 156.2
b	2.32 (s, 3H), 3.74 (s, 3H), 5.30 (br s, 1H), 6.86 (d, J = 8.5, 2H), 7.00 (s, 1H), 7.01 (s, 1H), 7.13 (d, J = 7.9, 2H), 7.28 (s, 1H), 7.40−7.46 (m, 4H)	21.0, 55.2, 112.5, 112.6, 114.1, 117.8, 126.9, 128.1, 129.4, 133.4, 137.1, 138.0, 142.7, 143.0, 156.6, 159.1
c	6.55 (br s, 1H), 7.01 (s, 1H), 7.08 (s, 1H), 7.25−7.48 (m, 8H), 7.51 (d, J = 6.9, 2H)	113.0, 113.5, 118.3, 127.1, 127.5,128.3, 128.7, 128.8, 133.5, 139.1, 140.6, 141.9, 143.4, 156.6
d	7.12 (s, 1H), 7.17 (s, 1H), 7.32 (s, 1H), 7.34 (t, J = 7.2, 1H), 7.46 (t, J = 7.1, 2H), 7.63 (d, J = 7.4, 2H), 7.81 (d, J = 8.8, 2H), 8.28 (d, J = 8.8, 2H), 9.45 (br s, 1H)	112.7, 114.0, 123.1, 126.2, 126.8,127.0, 128.0, 139.5, 139.8, 142.4,146.2, 146.8, 157.7
e	6.60 (br s, 1H), 6.96 (s, 2H), 7.15 (s, 1H), 7.25 (d, J = 8.5, 4H), 7.32 (d, J = 8.5, 4H)	113.4, 118.1, 128.2, 128.8, 133.7, 138.8, 142.1, 156.6
f	5.60 (br s, 1H), 7.03 (s, 1H), 7.18 (s, 1H),7.25 (s, 1H), 7.42−7.60 (m, 5H), 7.93 (d, J = 7.7, 2H), 7.87 (d, J = 9.6, 2H), 8.17 (d, J = 8.0, 1H), 8.47 (s, 1H)	113.0, 117.3, 121.5, 122.0, 122.3, 125.3, 125.7, 125.9, 126.3, 126.8, 128.1, 128.4, 129.7, 131.4, 133.1, 133.8, 139.1, 140.2, 142.3, 143.3, 148.7, 156.1
g	5.62 (br s, 1H), 6.87 (s, 1H), 7.10 (s, 1H), 7.18 (s, 1H), 7.24−7.32 (m, 2H), 7.36 (d, J = 7.1, 1H) 7.39−7.47 (m, 2H), 7.49 (s, 1H), 7.58 (d, J = 7.8, 2H)	113.7, 115.3, 120.9, 127.2, 127.7, 128.8, 129.8, 132.0, 133.2, 133.9, 138.7, 140.1, 140.4, 142.9, 155.8

Scheme 2



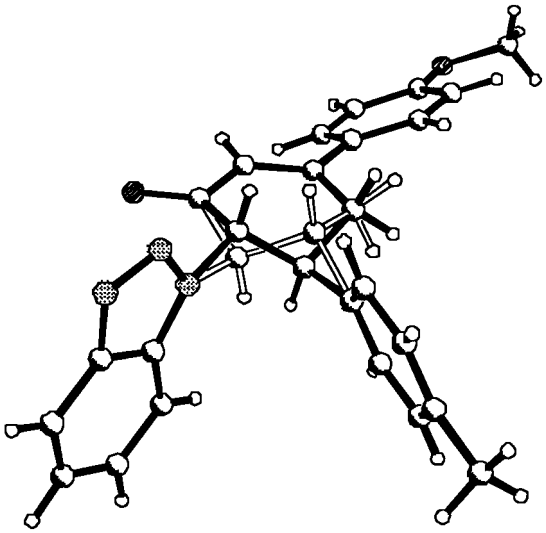


Figure 1. Perspective view of the X-ray crystal structure of **4b**.

J = 8.4 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 7.31−7.34 (m, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.75−7.80 (m, 2H); ^{13}C NMR δ 36.3, 45.7, 73.5, 117.9, 123.4, 126.2, 127.4, 128.4, 128.6, 129.0, 133.0, 135.2, 136.8, 137.0, 143.9, 157.4, 190.7. Anal. Calcd for $C_{24}H_{17}Cl_2N_3O$: C, 66.37; H, 3.95. Found: C, 66.00; H, 3.75.

General Procedure for the Preparation of 3,5-Disubstituted Phenols 6a−g. To a solution of NaOH (0.22 g, 5.44 mmol) in EtOH (10 mL) were added 1,3-diarylprop-2-enone **1a−g** (1.36 mmol) and ketone **2** (0.24 g, 1.36 mmol) at rt, and the mixture was refluxed for 1 h. The yellow-brownish solution was acidified (HCl concentrated) to pH 3−4, and water (30 mL) and CH_2Cl_2 (50 mL) were added. The organic layer was separated, washed with Na_2CO_3 (10% solution, 20 mL) and water (2 × 30 mL), separated, and dried over anhyd Na_2SO_4. After evaporation of the solvent, the crude product obtained was purified by column chromatography (silica gel; eluent − $CHCl_3$). The appropriate fraction was collected, and the solvent was removed in vacuo to give the desired phenol **6a−g**. The yields and characteristics of the phenols are given in Tables 1 and 2.

General Procedure for the Preparation of Phenols 6b,e from Cyclohexenones 4b,e. A mixture of cyclohexenone **4b** or **4e** (0.60 mmol) and NaOH (47 mg, 1.20 mmol) in EtOH (15 mL) was refluxed for 15 min (**4b**) or 1 h (**4e**). On cooling, the mixture was poured into water (50 mL) and stirred for 10 min, and the precipitate was filtered, washed with water (3 × 10 mL) and ligroine (3 × 20 mL), and air-dried to give **6b** and **6e**, respectively.

3-(4-Methoxyphenyl)-5-(4-methylphenyl)phenol (6b): Microcrystals, mp 80−82 °C (the sample prepared directly from **1b** and **2** by the general procedure above had mp 77−79 °C, Table 1). GC/MS data of the samples prepared by both methods were identical.

3,5-Bis(4-chlorophenyl)phenol (6e): Microcrystals, mp 160−161 °C (the sample prepared directly from **1e** and **2** by the general procedure above had mp 156−157 °C, Table 1). GC/MS data of the samples prepared by both methods were identical.

Supporting Information Available: ^{1}H and ^{13}C NMR and HRMS spectra for compounds **6b** and **6g** and X-ray data for compound **4b** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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