Novel Routes to 1-Aryl-1,4-dihydro-3(2*H*)-isoquinolinones and 2-Substituted or 2,3-Disubstituted Benzofurans by Intramolecular Cyclizations

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N-(α-Benzotriazolylalkyl)arylacetamides, readily available from an arylacetamide, an aldehyde and benzotriazole, undergo intramolecular cyclization under acidic conditions to give 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones in good to excellent yields. Similarly, 2-(benzotriazol-1-yl)-2-(*o*-hydroxyphenyl)ethanols, obtained by lithiation of 2-(benzotriazol-1-ylmethyl)phenols followed by quenching with aldehydes or ketones, eliminate a molecule of water and a molecule of benzotriazole yielding 2-substituted and 2,3-disubstituted benzofurans.

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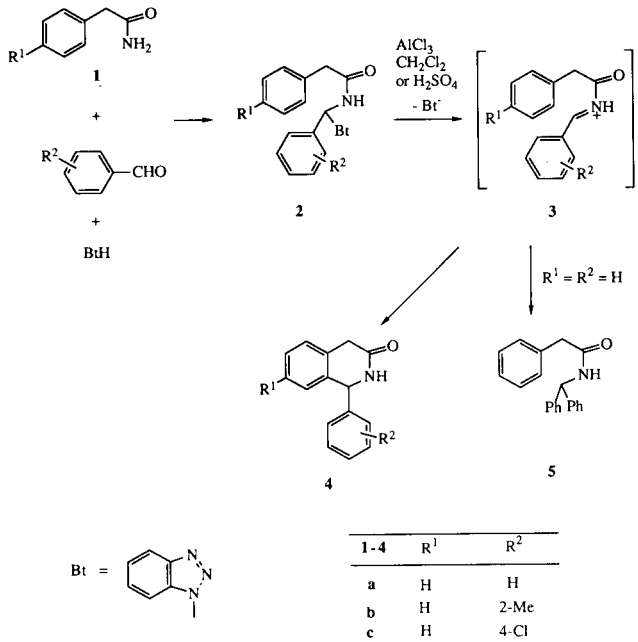
Benzotriazole as a synthetic auxiliary has been well investigated in this laboratory [1]. In particular, *N*-(benzotriazol-1-ylalkyl)amides, readily available from an amide, an aldehyde and benzotriazole [2], have been used as efficient amidoalkylation reagents with advantages compared to classical amidoalkylation techniques [3-7]. Thus, they react smoothly with active aromatic compounds [8], thiols [9], CH acids [10], and alcohols [11] under mild conditions to give the corresponding amidoalkylation products by intermolecular reactions. We anticipated that for suitable ring sizes, this type of reaction should occur intramolecularly thus providing an attractive route to certain heterocycles. We now report such ring-closures: under acidic conditions, *N*-(1-benzotriazolylalkyl)arylacetamides eliminate a molecule of benzotriazole to give 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones, and 2-(benzotriazol-1-yl)-2-(*o*-hydroxyphenyl)ethanols cyclize to benzofurans. Almost all the reactions concerning the use of benzotriazole as a synthetic auxiliary previously reported are intermolecular. The results in the present work represent the first examples of intramolecular benzotriazole eliminations to form useful heterocycles.

1-Aryl-1,4-dihydro-3(2*H*)-isoquinolinones.

Phenylacetamide (**1a**) condensed with benzaldehyde and benzotriazole to give the derivative **2a** in a modification of our literature procedure [2]. Treatment of **2a** in dichloromethane with aluminum chloride under reflux gave the desired cyclized product **4a** in 95% yield. The by-product benzotriazole was easily removed by alkali during workup. When benzene was used as the solvent, an intermolecular reaction occurred to give **5**. We have previously reported amidoalkylation for activated aromatic compounds [8], but this intermolecular reaction demonstrates a suitable procedure for unactivated aromatic rings which should be capable of considerable generalization. Stirring the benzotriazolyl derivative **2a** in concentrated sulfuric acid at room temperature for 3 hours also gave **4a** in 81% yield. The reactions presumably involve the formation of *N*-acyliminium ion **3** after loss of benzotriazole from **2**. The ion **3** then reacts with aromatic rings intra- or intermolecularly to give **4** and **5**, respectively (Scheme 1).

Scheme 1



Bt =

1-4	R^1	R^2
a	H	H
b	H	2-Me
c	H	4-Cl
d	OMe	H
e	OMe	4-Cl

We next examined reactions with other aldehydes and with other amides. Condensation of phenylacetamide (**1a**) with 2-methylbenzaldehyde and 4-chlorobenzaldehyde afforded the benzotriazolyl derivatives **2b,c**. Further cyclization reactions gave good yields of the cyclized products **4b,c**. 4-Methoxyphenylacetamide (**1b**) and 1-naphthaleneacetamide (**6**) reacted similarly with benzotriazole and aromatic aldehydes to give benzotriazolyl derivatives **2d,e** and **7**. These derivatives were then cyclized in dichloromethane in the presence of aluminum chloride to yield the desired products **4d,e** and **8** respectively (Schemes 1, 2). For 4-methoxyphenylacetamide, relatively low yields of the desired products were obtained because the cyclization

Table I

Preparation of *N*-(α-Benzotriazolylalkyl)arylacetamides **2** and **7**

Product	Solvent	Time (hours)	Yield (%)	Mp (°C)	Molecular Formula	Analysis Calcd./Found C	H	N
2a	toluene	48	61	158-160	$C_{21}H_{18}N_4O$	73.67/73.82	5.30/5.40	16.36/16.46
2b	toluene	48	65	192-194	$C_{22}H_{20}N_4O$	74.14/74.51	5.66/5.65	15.72/15.99
2c	toluene	48	60	173-176	$C_{21}H_{17}ClN_4O$	66.93/67.29	4.55/4.59	14.87/14.48
2d	benzene	24	63	126-128	$C_{22}H_{20}N_4O_2$	70.95/71.07	5.41/5.41	15.04/15.20
2e	benzene	20	63	145-147	$C_{22}H_{19}ClN_4O_2$	64.95/64.51	4.71/4.66	13.77/13.35
7	benzene	24	53	162-164	$C_{25}H_{20}N_4O$	76.51/76.78	5.14/5.14	14.28/14.35

Table II

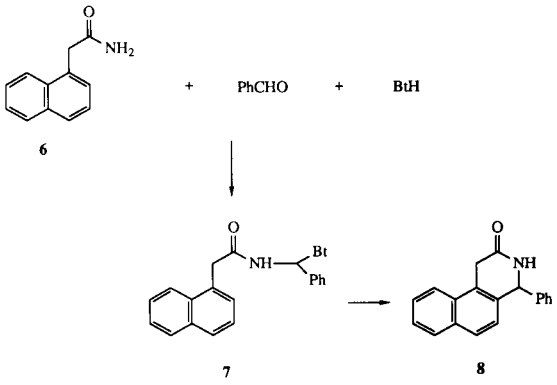
Preparation of 1-Aryl-1,4-dihydro-3(2*H*)-isoquinolinones **4** and **8**

Product	Method	Time hours	Yield (%)	Mp (°C)	Lit mp or Molecular Formula	Analysis Calcd./Found C	H	N
4a [a]	A(B)	4(3)	95(81)	165-167	164-165° [18]	-	-	-
4b	B	5.5	76	163-165	164° [22]	-	-	-
4c [a]	A(B)	2(4)	95(85)	158-160	$C_{15}H_{12}ClNO$	69.51/69.61	4.69/4.76	5.43/5.31
4d	A	2.5	47	135-137	$C_{16}H_{15}NO_2$	75.87/76.02	5.97/5.97	5.53/5.36
4e	A	2	60	111-113	$C_{16}H_{14}ClNO_2$	66.79/66.01	4.90/5.03	4.87/4.61
8	B	3	56	209-211	$C_{19}H_{15}NO$	83.49/83.75	5.53/5.54	5.12/5.07

[a] Included in parenthesis are relative data by method B.

had to occur at the unreactive position *meta* to the methoxy group.

Scheme 2



1,4-Dihydro-3(2*H*)-isoquinolinones, which possess significant biological activity [12,13] and can easily be reduced to the useful tetrahydroisoquinolines [14,15], have previously been prepared by various methods. Arylacetonitriles and aromatic aldehydes in polyphosphoric acid form 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones [16-20] *via* arylidenebis(phenylacetamides) which cyclize intramolecularly with loss of a molecule of amide. Alternatively, arylidenebisamides are isolated in a two-step sequence from the reaction of aldehydes and primary amides [12,20-22]. In both cases, a molecule of the by-product amide is generated which can complicate the isolation of the product and the yield calculated on the amide or nitrile component can not exceed 50%. The direct reaction of amides (both primary and secondary) to 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones is reported only with benzaldehyde and in yields of 21-54% [14,18,20]. Reductive amination of *o*-acylphenylacetic acid gives 1-substituted 1,4-dihydro-3(2*H*)-isoquinolinones [15] in a three-step procedure and involves the use of high pressure and temperature (70 atmospheres, 110°). *N*-Hydroxymethylarylacetamides are cyclized by polyphosphoric acid to give 1,4-dihydro-3(2*H*)-isoquinolinones [23] under vigorous conditions, no examples are reported with other aldehydes. The cyclization of *N*-(α-alkoxyalkyl)-amides, obtained by the anodic oxidation of amides [24,25] requires specialized equipment. Compared to these previous routes, our two-step sequence for the synthesis of 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones offers comparable yields, mild reaction conditions, stable intermediates, and easy workup procedure. A recent paper [26] has reported a somewhat similar synthesis of tetrahydroisoquinolines by intramolecular ring-closure of *N*-alkoxycarbonyl-*N*-α-methoxyalkyl-β-arylethylamines.

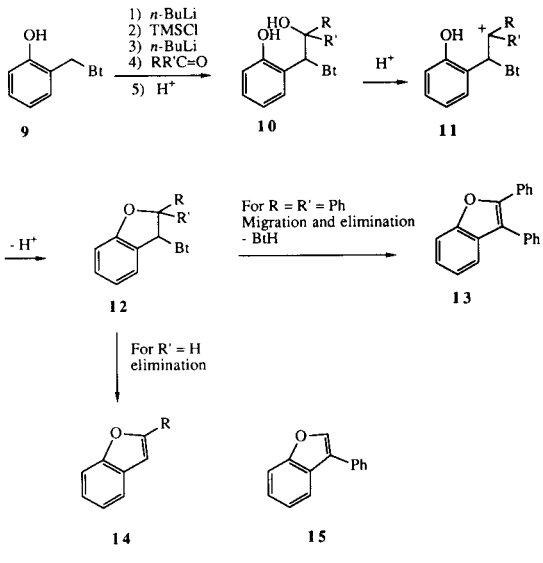
Benzofurans.

We previously demonstrated that 2-(benzotriazol-1-ylmethyl)phenols, easily obtained from condensation of phe-

nols with 1-hydroxymethylbenzotriazole, undergo lithiation at the methylene group α to the benzotriazolyl and the lithium salt can be trapped with various electrophiles such as alkyl halides, aldehydes, ketones, and carbon dioxide [27]. The benzotriazole group is then displaceable by carbanions from Grignard reagents or by hydride from lithium aluminum hydride. We have now found that derivatives **10**, obtained by using aldehydes or ketones as electrophiles, undergo intramolecular cyclization and thus provide a new route to 2-substituted or 2,3-disubstituted benzofurans.

Compounds **10** are obtained according to our previously reported procedure [27]. Heating **10** in acetic acid in the presence of *p*-toluenesulfonic acid for an appropriate time gives the 2-substituted or 2,3-disubstituted benzofurans as shown in Scheme 3. Protonation of the alcoholic hydroxy group was followed by elimination of a molecule of water to give cation **11**, which was immediately attacked by the phenolic hydroxy group in an intramolecular reaction to give **12**. For compounds **10** derived from aromatic or aliphatic aldehydes, *i.e.* where R' = H, elimination of a molecule of benzotriazole and the formation of an aromatic benzofuran ring gave **14a-c**. For compound **10d** derived from quenching the lithiated derivative of **9** with benzophenone (R = R' = Ph), scission of the benzotriazole group from **12d** was followed by the migration of a phenyl group to give 2,3-diphenylbenzofuran **13** in 63% yield. Migration of a phenyl group from the 2- to 3-position was also observed for compound **10a** (derived from benzaldehyde): heating **10a** under the above described conditions gave a mixture of the expected 2-phenylbenzofuran (**14a**) and the rearranged product 3-phenylbenzofuran (**15**), in a 48:52 ratio as confirmed by gc/ms data. In another experiment, compound **10a** was heated with a catalytic amount of *p*-toluenesulfonic acid without any solvent in a closed sample vial, again, a mixture of compound **14a** and compound **15** was obtained in a ratio of 47:53 according to gc/ms data.

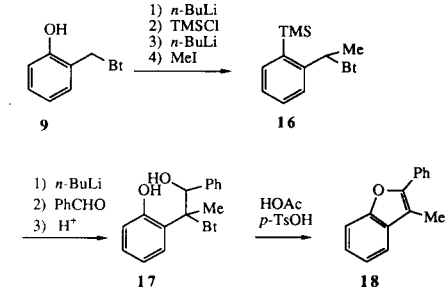
Scheme 3



10-12,14	R	R'
a	Ph	H
b	^{i}Pr	H
c	n-C_8H_{17}	H
d	Ph	Ph

We also examined a one-pot sequence which employed two consecutive lithiations. Initial treatment of **9** under the normal lithiation conditions followed by quenching with methyl iodide gave compound **16**. Further lithiation and treatment with benzaldehyde afforded compound **17**. Heating **17** under the above described conditions afforded 2-phenyl-3-methylbenzofuran (**18**) in 55% yield (Scheme 4).

Scheme 4



The benzofuran nucleus is present in natural products and benzofurans have been widely used, particularly in pharmacology [28]. Benzofurans are usually prepared by the cyclodehydration of aryloxy ketones with sulfuric acid or polyphosphoric acid [29,30]. Le Corre *et al.* [31,32] reported the use of *o*-hydroxybenzyl triphenylphosphonium bromide in reaction with acid chlorides or acid anhydrides, in the presence of triethylamine, to give 2-substituted benzofurans in moderate to good yields. Chromium(III) complexes have also been used for the synthesis of 2-substituted benzofurans [33]. Brady [34,35] reported intramolecular [2+2] cycloaddition reactions of ketene and carbonyl groups to afford benzofurans. Although our yields of 2-substituted and 2,3-disubstituted benzofurans are variable, the alternative approach presented here commences from easily available starting materials and offers easy purification of the product in the cyclization step.

Structural Characterization.

The structures of all intermediates and products obtained were characterized by their ^{1}H and ^{13}C nmr spectra, by elemental analyses, or where appropriate, by comparison with literature data. The benzotriazole derivatives **2** and **7** are all benzotriazol-1-yl isomers as evidenced by nmr spectra. This is in accordance with the results previously reported for primary amides [2].

Table III

^1H and ^{13}C NMR Spectral Data for *N*-(α-Benzotriazolylalkyl)arylacetamides **2** and **7**

	^1H			^{13}C		
	$ArCH_2$	Others	C=O	CHBt	$ArCH_2$	Others
2a	3.60 (*s*, 2 H)	7.1-7.3 (m, 10 H), 7.34 (t, 1 H, J = 7.1), 7.42 (t, 1 H, J = 6.9), 7.75 (d, 1H, J = 9.0), 7.88 (d, 1 H, J = 9.0), 8.01 (d, 1 H, J = 8.1)	171.0	64.5	42.8	109.8, 119.7, 124.2, 126.2, 127.2, 127.8, 128.7, 128.8, 128.9, 129.2, 132.6, 133.9, 135.9, 145.7
2b [a]	3.62 (AB, 2 H, J = 14.2)	2.21 (*s*, 3 H), 7.0-7.5 (m, 11 H), 7.64 (d, 1 H, J = 7.6), 8.00 (t, 2 H, J = 8.5), 9.73 (d, 1 H, J = 8.6)	169.3	62.2	40.6	17.3, 109.2, 118.0, 122.6, 124.6, 125.1, 126.0, 126.7, 127.5, 127.6, 129.4, 130.8, 133.1, 133.9, 134.5, 144.1
2c [a]	3.62 (AB, 2 H, J = 14.3)	7.15-7.50 (m, 11 H), 7.69 (d, 1 H, J = 8.3), 7.93 (d, 1 H, J = 8.7), 8.01 (d, 1 H, J = 8.2), 9.85 (d, 1 H, J = 8.5)	170.4	63.6	41.4	109.6, 118.6, 123.3, 125.8, 126.8, 127.4, 127.8, 128.1, 131.5, 133.6, 134.1, 134.2, 144.7
2d	3.50 (*s*, 2 H)	3.71 (*s*, 3 H), 6.76 (d, 2 H, J = 8.1), 7.07 (d, 2 H, J = 8.3), 7.1-7.4 (m, 6 H), 7.55 (d, 1 H, J = 7.6), 7.89 (d, 1 H, J = 8.8), 7.97 (d, 1 H, J = 8.2), 8.08 (d, 1 H, J = 9.0)	171.5	64.5	41.8	55.0, 109.8, 114.1, 119.6, 124.2, 125.8, 126.2, 127.7, 128.7, 128.9, 130.2, 132.5, 135.9, 145.4, 158.6
2e [a]	3.54 (AB, 2 H, J = 14.4)	3.72 (*s*, 3 H), 6.76 (d, 2 H, J = 8.5), 7.15 (d, 2 H, J = 8.4), 7.2-7.5 (m, 6 H), 7.68 (d, 1 H, J = 8.5), 7.92 (d, 1 H, J = 8.5), 8.00 (d, 1 H, J = 8.2), 9.72 (d, 1 H, J = 8.8)	170.5	63.4	40.2	53.9, 109.5, 112.6, 118.4, 123.1, 126.0, 126.5, 127.3, 127.6, 128.9, 131.2, 133.3, 133.9, 144.5, 157.2
7 [a]	4.10 (*s*, 2 H)	7.25-7.45 (m, 11 H), 7.65-7.75 (m, 2 H), 7.79 (d, 1 H, J = 8.1), 7.94 (d, 1 H, J = 4.6), 7.97 (d, 1 H, J = 4.2), 8.01 (d, 1 H, J = 8.4), 9.94 (d, 1 H, J = 8.4)	170.3	64.3	38.8	109.6, 118.5, 123.0, 123.1, 124.4, 124.6, 124.9, 125.6, 126.5, 126.8, 127.4, 127,7, 127.8, 130.6, 131.0, 131.4, 132.5, 135.3, 144.6

[a] The nmr spectra were run in solutions of a mixture of deuteriochloroform and DMSO-d_6.

Table IV

^1H and ^{13}C NMR Spectral Data for 1-Aryl-1,4-dihydro-3(2*H*)-isoquinolinones **4** and **8**

	^1H			^{13}C			
	$ArCH_2$	HNC*H*	Others	C=O	HNCH	$ArCH_2$	Others
4a	3.60 (AB, 2 H, J = 19.7)	5.60 (*s*, br, 1 H)	6.98 (d, 1 H, J = 7.5), 7.1-7.3 (m, 8 H), 7.67 (*s*, br, 1 H)	171.4	59.8	36.3	126.5, 126.6, 127.1, 127.4, 127.7, 127.9, 128.8, 131.2, 134.5, 141.4,
4b	3.64 (*s*, 2 H)	5.84 (*s*, 1 H)	2.31 (*s*, 3 H), 6.72 (d, 1 H, J = 7.8), 7.0-7.3 (m, 9 H)	170.8	57.2	36.3	19.3, 126.0, 126.6, 126.7, 127.4, 127.6, 128.2, 128.5, 131.1, 131.4, 134.3, 136.1, 138.6
4c	3.62 (*s*, 2 H)	5.61 (*s*, 1 H)	6.96 (d, 1 H, J = 7.5), 7.1-7.3 (m, 7 H), 7.56 (*s*, 1 H)	171.6	58.9	36.1	126.4, 126.7, 127.6, 127.8, 128.3, 128.8, 131.0, 133.6, 133.9, 140.0
4d	3.53 (AB, 2 H, J = 20.0)	5.54 (*s*, 1 H)	3.67 (*s*, 3 H), 6.52 (d, 1 H, J = 2.5), 6.7-6.8 (m, 1 H), 7.04 (d, 1 H, J = 8.3), 7.2-7.3 (m, 5 H), 7.80 (*s*, br, 1 H)	171.7	59.8	35.4	55.1, 112.0, 113.1, 123.1, 126.9, 127.8, 128.6, 128.7, 135.5, 141.4, 158.1
4e	3.56 (*s*, 2 H)	5.55 (*s*, 1 H)	3.71 (*s*, 3 H), 6.48 (d, 1 H, J = 2.5), 6.75-6.85 (m, 1 H), 7.09 (d, 1 H, J = 8.6), 7.18 (d, 2 H, J = 8.6), 7.30 (d, 2 H, J = 8.5), 7.49 (*s*, br, 1 H)	171.8	59.3	35.4	55.2, 112.1, 113.4, 123.1, 128.5, 128.9, 129.0, 133.8, 135.0, 139.9, 158.3
8 [a]	3.99 (AB, 2 H, J = 21.0)	5.79 (d, 1 H, J = 2.2)	3.27 (*s*, 1 H), 7.1-7.3 (m, 6 H), 7.50 (t, 1 H, J = 8.0), 7.58 (t, 1 H, J = 6.6), 7.66 (d, 1 H, J = 8.5), 7.81 (d, 1 H, J = 8.0), 7.93 (d, 1 H, J = 8.5), 8.53 (*s*, br, 1 H)	167.5	58.9	30.6	121.4, 123.4, 124.2, 124.6, 125.4, 125.7, 125.8, 126.3, 127.0, 127.3. 129.2, 129.6, 130.7, 142.1

[a] The nmr spectra were run in solution of a mixture of deuteriochloroform and DMSO-d_6.

For compounds **2** and **7**, the benzylic methylene groups resonated in the ^1H nmr spectra in the region of 3.50-4.10 ppm as singlets or as AB patterns with coupling constants of 14.2-14.4 Hz and in the ^{13}C nmr spectra in the region of 38.8-42.8 ppm. The benzotriazolyl α methine group showed the expected proton signals in the aromatic region and the carbons resonated between 62.2-64.5 ppm. The amide carbonyl carbons appeared between 169.3-171.5 ppm.

For the isoquinolinones **4** and **8**, the chemical shifts of

protons for the benzylic methylene groups and of carbons for the amide carbonyls were quite similar to their precursors. The benzylic methylene groups, contained in the dihydroisoquinolinone six membered ring, displayed their protons as singlets or as AB patterns with coupling constants of 19.5-21.0 Hz and their carbons in the region 30.6-36.3 ppm. For the methine groups directly attached to the amide nitrogen, the protons were found at 5.54-5.84 ppm and their carbons at 57.2-59.8 ppm, respectively. These upfield shifts are due to the loss of the electron withdrawing benzotriazole group.

The structures of derivatives **10a-d** were also confirmed by their ^1H and ^{13}C nmr spectra. The nmr spectra of the benzofurans **13-15** and **18** clearly indicated the disappearance of the benzotriazole signals. The characteristic signals for the 3 position in 2-substituted benzofurans **14a-c** were their protons in the region 6.32-6.33 ppm as singlets (at 6.98 ppm for compound **14a**) and their carbons in the region 99.7-101.7 ppm, respectively.

EXPERIMENTAL

Melting points were determined on a Kolfler hot-stage microscope and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Varian VXR 300 spectrometer in deuteriochloroform solutions unless otherwise stated. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer in this Department. Commercially available reagent grade solvents were thoroughly dried by standard methods prior to use. Preparative chromatography was performed by flash column chromatography with silica gel (Merck silica gel 60, mesh 240-400).

General Procedure for the Preparation of *N*-(α-Benzotriazolylalkyl)arylacetamides **2** and **7**.

A mixture of an arylacetamide (20 mmoles), an aryl aldehyde (20 mmoles), benzotriazole (2.38 g, 20 mmoles) and 0.19 g of *p*-toluenesulfonic acid (1 mmole) in toluene (80 ml) or benzene (80 ml) was heated under reflux for the appropriate time. Water was removed azeotropically by a Dean-Stark trap. The solvent was removed under reduced pressure. For **2a-c** and **2e**, the residue was triturated with diethyl ether to give the desired product. For **2d** and **7**, the residue was taken up into chloroform (100 ml), washed with 5% sodium hydroxide solution (20 ml), and dried (magnesium sulfate). Evaporation of the solvent gave a residue which was chromatographed with hexane/ethyl acetate (3:1) to give **2d**, or triturated with diethyl ether to give **7**. The preparative data and nmr spectral data are given in Table I and Table III.

General Procedure for the Preparation of 1-Aryl-1,4-dihydro-3(2*H*)-isoquinolinones **4** and **8**.

Method A.

To a solution of the *N*-(α-benzotriazolylalkyl)arylacetamide (5 mmoles) in dry dichloromethane (30 ml) was added 2.66 g of anhydrous aluminum chloride (20 mmoles). The resulting solution was heated under reflux for an appropriate time and poured into water (30 ml). The mixture was made basic with 20% of sodium hydroxide solution and extracted with chloroform (3 x 30 ml). The combined extracts were washed with water (30 ml) and dried (magnesium sulfate). Evaporation of the solvent gave the desired product **4a** and **4c**. For **4d-e**, the pure products were obtained by column chromatography with hexane/ethyl acetate (1:1).

Method B.

To concentrated sulfuric acid (3 ml) cooled to 0° was added the appropriate *N*-(α-benzotriazolylalkyl)arylacetamide (1.5 mmoles) portionwise. The resulting mixture was then stirred at 0° for **4b** and **8** or at room temperature for **4a** and **4c** for the time given in Table II. It was poured onto ice (30 g), rendered basic with 50% sodium hydroxide solution and extracted with chloroform (3 x 20 ml). The combined extracts were dried (magnesium sulfate) and evaporated to give the desired products. The preparative data and the nmr spectral data are given in Table II and Table IV.

N-Diphenylmethylphenylacetamide (**5**).

To a solution of *N*-(α-benzotriazol-1-ylmethyl)phenylacetamide (**2a**) (0.66 g, 1.93 mmoles) in dry benzene (15 ml) under nitrogen was added 0.54 g of anhydrous aluminum chloride (4 mmoles). The mixture was heated under reflux for 1.5 hours, cooled and poured into water (30 ml). The resulting solution was rendered basic with 10% sodium hydroxide solution, extracted with chloroform (3 x 30 ml) and dried (magnesium sulfate). Evaporation of the solvent gave the desired product **5** (0.47 g, 81%), mp 161-163° (lit [36] mp 162-163°); ^1H nmr: 3.57 (s, 2 H), 6.2-6.3 (m, 2 H), 7.0-7.1 (m, 4 H), 7.2-7.4 (m, 11 H); ^{13}C nmr: 43.6, 56.7, 127.2, 127.3, 128.5, 128.9, 129.2, 129.3, 134.8, 141.3, 170.0.

General Procedure for the Preparation of 2-(Benzotriazol-1-yl)-2-(*o*-hydroxyphenyl)ethanols **10a-d**.

To a stirred solution of 2-(benzotriazol-1-ylmethyl)phenol (**9**) (2.26 g, 10 mmoles) in dry THF (60 ml) under nitrogen at −78° was added *n*-BuLi (2.5 *M* in hexane, 4.0 ml, 10 mmoles). The solution was stirred at −78° for 1 hour, then trimethylsilyl chloride (1.26 ml, 10 mmoles) was added. The resulting solution was stirred at −78° for 0.5 hour and at room temperature for 0.5 hour. It was then cooled to −78° and *n*-BuLi (2.5 *M* in hexane, 4.0 ml, 10 mmoles) was added. After stirring at −78° for 2 hours, the appropriate aldehyde or ketone (10 mmoles) was added. The resulting solution was allowed to warm to room temperature and stirred overnight. The THF was evaporated and to the residue was added 95% ethanol (45 ml) and concentrated hydrochloric acid (0.5 ml). The solution was stirred at room temperature for 0.5 hour and the ethanol was evaporated. The residue was taken up into chloroform (50 ml) and water (40 ml) and the mixture was rendered acidic with 2 *N* hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with chloroform (2 x 40 ml). The combined extracts were washed with water (40 ml) and dried (magnesium sulfate), and the solvent evaporated to give the crude product. The crude products were chromatographed with hexane/ethyl acetate (4:1) to give the pure compounds **10a-c**. For **10d**, trituration of the crude product with chloroform afforded the pure product.

2-(Benzotriazol-1-yl)-2-(*o*-hydroxyphenyl)-1-phenylethanol (**10a**) was prepared as previously reported [27].

1-(Benzotriazol-1-yl)-1-(*o*-hydroxyphenyl)-3-methyl-2-butanol (**10b**).

This compound was prepared (74%) by quenching with iso-

butyraldehyde, mp 199-200°; ^{1}H nmr (DMSO-d_6): 0.94-0.99 (m, 6 H), 1.64-1.69 (m, 1 H), 4.80-4.84 (m, 1 H), 5.01 (d, 1 H, J = 6.1), 6.33 (d, 1 H, J = 9.8), 6.80-6.90 (m, 2 H), 7.09 (t, 1 H, J = 7.4), 7.32 (t, 1 H, J = 7.0), 7.48 (t, 1 H, J = 8.1), 7.60 (d, 1 H, J = 7.6), 7.84 (d, 1 H, J = 8.0), 8.00 (d, 1 H, J = 7.7), 10.05 (s, br, 1 H); ^{13}C nmr (DMSO-d_6): 14.4, 20.6, 29.0, 58.8, 74.8, 110.9, 115.6, 118.9, 119.4, 123.5, 123.7, 126.9, 129.0, 129.2, 133.8, 144.9, 154.7.

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.68; H, 6.49; N, 13.92.

1-(Benzotriazol-1-yl)-1-(*o*-hydroxyphenyl)-2-decanol (**10c**).

This compound was prepared (35%) by quenching with 1-nonanal, mp 99-100°; ^{1}H nmr: 0.85 (t, 3 H, J = 7.0), 1.17-1.40 (m, 10 H), 1.40-1.70 (m, 4 H), 4.80 (s, br, 1 H), 5.09 (q, 1 H), J = 4.5), 5.97 (t, 1 H, J = 4.4), 6.87 (t, 1 H, J = 7.4), 6.94 (d, 1 H, J = 8.0), 7.2-7.4 (m, 5 H), 7.94 (d, 1 H, J = 7.7), 9.0 (s, br, 1 H), ^{13}C nmr: 14.0, 22.6, 25.7, 29.2, 29.4, 29.5, 31.8, 33.3, 63.9, 72.9, 110.5, 117.4, 119.3, 120.4, 121.5, 124.5, 127.6, 130.3, 130.9, 133.3, 145.0, 155.0.

Anal. Calcd. for $C_{22}H_{25}N_3O_2$: C, 71.90; H, 7.95; N, 11.43. Found: C, 72.10; H, 8.08; N, 11.19.

2-(Benzotriazol-1-yl)-2-(*o*-hydroxyphenyl)-1,1-diphenylethanol (**10d**).

This compound was prepared (85%) by quenching with benzophenone, mp 221-223°; ^{1}H nmr (DMSO-d_6): 6.51 (s, 1 H), 6.66-6.98 (m, 2 H), 7.0-7.4 (m, 14 H), 7.49 (s, 1 H), 7.61 (d, 2 H, J = 7.6), 7.82 (d, 1 H, J = 8.6), 7.89 (d, 1 H, J = 8.3), 8.08 (d, 1 H, J = 7.8), 9.89 (s, 1 H); ^{13}C nmr (DMSO-d_6): 61.0, 81.2, 111.7, 114.9, 118.5, 118.8, 122.3, 123.7, 125.5, 126.1, 126.6, 126.7, 126.9, 127.7, 129.1, 131.5, 133.4, 144.3, 144.5, 145.9, 155.2.

Anal. Calcd. for $C_{26}H_{21}N_3O_2$: C, 76.64; H, 5.19; N, 10.31. Found: C, 76.30; H, 5.17; N, 10.27.

2-(Benzotriazol-1-yl)-2-(*o*-hydroxyphenyl)-1-phenyl-1-propanol (**17**).

To a stirred solution of 2-(benzotriazol-1-ylmethyl)phenol (**9**) (3.39 g, 15 mmoles) in dry THF (90 ml) under nitrogen at −78° was added *n*-BuLi (2.5 *M* in hexane, 6.0 ml, 15 mmoles). The solution was stirred at −78° for 1 hour, then trimethylsilyl chloride (1.89 ml, 15 mmoles) was added. The resulting solution was stirred at −78° for 0.5 hour and at room temperature for 0.5 hour. It was re-cooled to −78° and *n*-BuLi (2.5 *M* in hexane, 6.0 ml, 15 mmoles) was added. After stirring at −78° for 2 hours, methyl iodide (2.13 g, 15 mmoles) was added and the mixture stirred at −78° for 2 hours and at room temperature for a further 2 hours. It was again cooled to −78° and *n*-BuLi (2.5 *M* in hexane, 6.0 ml, 15 mmoles) was added. After stirring at −78° for 2 hours, benzaldehyde (1.61 g, 15 mmoles) was added. The solution was allowed to warm to room temperature and stirred overnight. The reaction was worked up similarly to those for the preparation of compounds **10**. The crude product was purified by trituration with hexane/diethyl ether to give 0.76 g of the pure product (15%), mp 198-199°; ^{1}H nmr (DMSO-d_6): 2.18 (s, 3 H), 3.45 (s, 1 H), 5.92 (s, 1 H), 6.63-7.23 (m, 11 H), 7.88-7.96 (m, 2 H), 9.19 (s, 1 H); ^{13}C nmr (DMSO-d_6): 19.4, 69.1, 75.7, 111.4, 116.9, 118.9, 119.1, 123.0, 126.0, 127.2, 127.3, 127.5, 128.7, 129.3, 132.6, 140.5, 145.7, 156.0.

Anal. Calcd. for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 73.05; H, 5.64; N, 12.05.

General Procedure for the Preparation of 2-Substituted **14** or 2,3-Disubstituted benzofurans **13** and **18**.

A solution of the appropriate 2-(benzotriazol-1-yl)-2-(*o*-hydroxyphenyl)ethanol **10** or **17** (3 mmoles) and a catalytic amount of *p*-toluenesulfonic acid in acetic acid (15 ml) was refluxed for 24 hours. The residue obtained after evaporation of acetic acid was taken into diethyl ether (30 ml) which was washed with saturated sodium bicarbonate solution (15 ml). The aqueous solution was extracted with diethyl ether (2 x 20 ml) and the combined extracts washed with water (20 ml) and dried (magnesium sulfate). Evaporation of the solvent gave the crude product which was passed through a silica gel column with hexane to give the pure product.

2,3-Diphenylbenzofuran (**13**).

This compound was obtained (63%) from compound **10d**, mp 124-125° (lit [37] mp 121-122°); ^{1}H nmr: 7.20-7.55 (m, 12 H), 7.63-7.66 (m, 2 H); ^{13}C nmr: 111.1, 117.5, 120.0, 122.9, 124.7, 126.9, 127.6, 128.3, 128.4, 128.9, 129.7, 130.2, 130.6, 132.8, 150.5, 153.9.

2-Phenylbenzofuran (**14a**) and 3-Phenylbenzofuran (**15**).

These two compounds were obtained (52% total yield) by the general procedure as a mixture of compound **14a** and compound **15** with a ratio of 48:52 by gc/ms. The same mixture of compound **14a** and compound **15** was obtained in a total yield of 52% with a ratio of 47:53 according to gc/ms data when compound **10a** was heated with a catalytic amount of *p*-toluenesulfonic acid in a closed sample vial at 156° for 22 hours. The mixture has a very low melting point and appears as a semi-solid, (lit [35] mp 120-121° for compound **14a** and lit [38] mp 41-43° for compound **15**); ^{1}H nmr: 6.97 (s, 1 H), 7.20-7.65 (m, 15 H), 7.74 (s, 1 H), 7.8-7.9 (m, 3 H); ^{13}C nmr: 101.2, 101.3, 111.1, 111.7, 120.4, 120.9, 122.2, 122.89, 122.94, 124.2, 124.5, 124.9, 126.4, 127.4, 127.5, 128.5, 128.7, 128.9, 129.2, 130.4, 132.0, 141.3, 154.9, 155.8, 155.9. Recrystallization of the mixture from hexane gave the pure 2-phenylbenzofuran, mp 120-121° (lit [35] mp 120-121°); ^{1}H nmr: 6.98 (s, 1 H), 7.18-7.57 (m, 7 H), 7.83-7.86 (m, 2 H); ^{13}C nmr; 101.25 (101.29), 111.1, 120.9, 122.9, 124.2, 124.9, 128.5, 128.7, 129.1, 130.4, 154.9, 155.9. The filtrate from the recrystallization was concentrated to give again a mixture of compound **14a** and compound **15** as indicated by the nmr spectra.

2-Isopropylbenzofuran (**14b**).

This compound was obtained (37%) from compound **10b** as an oil (lit [32] bp 104-105°/15 mm); ^{1}H nmr: 1.32 (d, 6 H, J = 3.6), 3.02-3.04 (m, 1 H), 6.32 (s, 1 H), 7.14-7.18 (m, 2 H), 7.38-7.41 (m, 2 H); ^{13}C nmr: 20.9, 28.2, 99.7, 110.7, 120.3, 122.3, 123.0, 128.9, 154.6, 164.9.

2-Octylbenzofuran (**14c**).

This compound was obtained (32%) from compound **10c** as an oil; ^{1}H nmr: 0.87 (t, 3 H, J = 6.6), 1.26-1.35 (m, 10 H), 1.69-1.74 (m, 2 H), 2.72 (t, 2 H, J = 7.5), 6.33 (s, 1 H), 7.13-7.17 (m, 2 H), 7.37-7.46 (m, 2 H); ^{13}C nmr: 14.1, 22.7, 27.7, 28.4, 29.2, 29.3, 31.8, 101.7, 110.6, 120.1, 122.3, 123.0, 129.0, 154.6, 159.7.

Anal. Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.25; H, 9.61.

2-Phenyl-3-methylbenzofuran (**18**).

This compound was obtained (55%) from compound **17** as an oil (lit [35] mp 34-34.5°); ^{1}H nmr: 2.38 (s, 3 H), 7.21-7.45 (m, 7 H),

7.75-7.78 (m, 2 H); ^{13}C nmr: 9.36, 110.8, 111.2, 119.2, 122.3, 124.2, 126.6, 127.7, 128.5, 131.1, 131.3, 150.3, 153.9.

REFERENCES AND NOTES

[1] A. R. Katritzky, S. Rachwal and G. J. Hitchings, *Tetrahedron*, **47**, 2683 (1991) and the references cited therein.

[2] A. R. Katritzky and M. Drewniak, *J. Chem. Soc., Perkin Trans. 1*, 2339 (1988).

[3] H. Hellmann, Amidomethylation, in Newer Methods of Preparative Organic Chemistry, Vol **2**, W. Foerst, ed, Academic Press, New York, 1963, p 277.

[4] H. E. Zaugg and W. B. Martin, α-Amidoalkylation at Carbon, *Org. React.*, **14**, 52 (1965).

[5] H. E. Zaugg, *Synthesis*, 49 (1970).

[6] H. E. Zaugg, *Synthesis*, 85 (1984).

[7] H. E. Zaugg, *Synthesis*, 181 (1984).

[8] A. R. Katritzky, J. Pernak and W.-Q. Fan, *Synthesis*, 868 (1991).

[9] A. R. Katritzky, I. Takahashi, W.-Q. Fan and J. Pernak, *Synthesis*, 1147 (1991).

[10] A. R. Katritzky, J. Pernak, W.-Q. Fan and F. Saczewski, *J. Org. Chem.*, **56**, 4439 (1991).

[11] A. R. Katritzky, W.-Q. Fan, M. Black and J. Pernak, *J. Org. Chem.*, **57**, 547 (1992).

[12] Gy. Deák, K. Gáll-Istók and L. Hazai, *Acta Chim. Acad. Sci. Hung.*, **84**, 477 (1975).

[13] V. St. Georgiev, R. G. Van Inwegen and P. Carlson, *Eur. J. Med. Chem.*, **25**, 375 (1990).

[14] J. Finkelstein and A. Brossi, *J. Heterocyclic Chem.*, **4**, 315 (1967).

[15] H. Kotake, H. Kinoshita, K. Inomata and H. Masuda, *Bull. Chem. Soc. Japan*, **49**, 3365 (1976).

[16] Z. Csűrös, Gy. Deák and I. Hoffmann, *Acta Chim. Acad. Sci. Hung.*, **55**, 125 (1968).

[17] Z. Csűrös, Gy. Deák, M. Haraszthy-Papp and I. Hoffmann, *Acta Chim. Acad. Sci. Hung.*, **59**, 119 (1969).

[18] Z. Csűrös, Gy. Deák, I. Hoffmann and A. Török-Kalmár, *Acta. Chim. Acad. Sci. Hung.*, **60**, 177 (1969).

[19] Gy. Deák, K. Gáll-Istók, Zs. Kálmán and J. Haskó-Breuer, *Acta Chim. Acad. Sci. Hung.*, **76**, 299 (1973).

[20] L. Hazai and G. Deák, *Acta Chim. Hung.*, **121**, 237 (1986).

[21] U. Zehavi and D. Ben-Ishai, *J. Org. Chem.*, **26**, 1097 (1961).

[22] G. Deák, K. Gáll-Istók, L. Hazai and L. Sterk, *Synthesis*, 393 (1975).

[23] Y. Watanabe, Y. Kamochi and T. Miyazaki, *Heterocycles*, **16**, 609 (1981).

[24] T. Shono, Y. Matsumura and K. Tsubata, *J. Am. Chem. Soc.*, **103**, 1172 (1981).

[25] K. D. Moeller, P. W. Wang, S. Tarazi, M. R. Marzabadi and P. L. Wong, *J. Org. Chem.*, **56**, 1058 (1991).

[26] G. K. Cheung, M. J. Earle, R. A. Fairhurst, H. Heaney, K. F. Shuhaibar, S. C. Eyley and F. Ince, *Synlett*, 721 (1991).

[27] A. R. Katritzky, X. Lan and I. N. Lam, *Chem. Ber.*, **124**, 1809 (1991).

[28] A. Mustafa, Benzofurans, in The Chemistry of Heterocyclic Compounds, A. Weissberger and E. C. Taylor, eds, John-Wiley and Sons, New York, 1974.

[29] K. Takeda, M. Ikuta, M. Miyawaki and K. Tori, *Tetrahedron*, **22**, 1159 (1966).

[30] L. Novotny, Z. Samek and F. Šorm, *Tetrahedron Letters*, 3541 (1966).

[31] A. Hercouet and M. Le Corre, *Tetrahedron Letters*, **23**, 2145 (1979).

[32] A. Hercouet and M. Le Corre, *Tetrahedron*, **37**, 2867 (1981).

[33] B. Ledoussal, A. Gorgues and A. Le Coq, *Tetrahedron*, **43**, 5841 (1987).

[34] W. T. Brady and Y. F. Giang, *J. Org. Chem.*, **51**, 2145 (1986).

[35] W. T. Brady, Y.-s. F. Giang, A. P. Marchand and A.-h. Wu, *J. Org. Chem.*, **52**, 3457 (1987).

[36] V. C. Agwada, *J. Chem. Eng. Data*, **29**, 231 (1984).

[37] H. Inoue, Y. Kimura and E. Imoto, *Bull. Chem. Soc. Japan*, **46**, 3303 (1973).

[38] D. R. Arnold, B. J. Fahie, L. J. Lamont, J. Wierzchowski and K. M. Young, *Can. J. Chem.*, **65**, 2734 (1987).