The Conversion of Secondary into Tertiary Amides Using Benzotriazole Methodology

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N-Alkyl-*N*-[1-(benzotriazol-1-yl)alkyl]amides, easily prepared from benzotriazole, an aldehyde, and a secondary amide, react readily with organozinc reagents to give tertiary amides in moderate to good yields. They are also reduced by $LiAlH_4$ to afford tertiary amines.

Introduction

The tertiary amide moiety is an important constituent of many biologically significant compounds,[1] and tertiary amides have frequently been used as precursors to unsymmetrical tertiary amines having different substituents.[2] Tertiary amides have usually been prepared by acylation of a secondary amine or by alkylation of a secondary amide. The alkylation of primary and secondary amides has been well investigated and reviewed:[3] it has been carried out under neutral, acidic, and basic conditions. Under neutral conditions, only reactive electrophiles such as alkyl sulfate,[4a] oxonium salts,[4b] and diazoalkanes[4c] are synthetically useful, and mixtures of the O- and N-alkylated products are frequently obtained.[4d] Alkylation of amides under acidic conditions is rare, but has been reported for some alcohols[5a] and acetals.[5b] The alkylations under basic conditions are synthetically the most important. A variety of electrophilic species usually react predominantly at the amide nitrogen atom,[6] and intramolecular alkylation yields lactams and other heterocyclic nitrogen compounds.[7] However, strongly basic conditions are required such as KOH in DMSO[8a] or in EtOH,[8b] lithium amide in toluene,[9] and sodium hydride in THF,[10a] in *p*-xylene,[10b] in toluene,[10c] or in DMF,[10d] often with phase-transfer reagents.[11a-d] Such alkylations with *sec*-alkyl halides proceed with difficulty and with *tert*-alkyl halides not at all.[12] The strong basic conditions required along with the limitations for the alkylating reagents sometimes preclude this classical N-alkylation of *sec*-amides. The more general electroreductive N-alkylation of amides[13] is not convenient in many laboratories.

Previous work from our group has demonstrated the versatility of benzotriazole as a synthetic auxiliary in synthesis.[14] The benzotriazole anion is a good leaving group and can be used in place of a halogen or other substituent in many transformations. In particular, primary amides $RCONH_2$ are readily converted by treatment with benzotriazole and an aldehyde into intermediates RCONHCHR'Bt which react smoothly with Grignard reagents or $NaBH_4$ to give secondary amides and with $LiAlH_4$ to give secondary amines.[15,16] These same RCONHCHR'Bt intermediates have also been shown to be effective amidoalkylating reagents: they react readily with active aromatic compounds,[17] CH acids,[18] thiols,[19] and alcohols[20] to give the corresponding amidoalkylated products. The original procedure is also applicable to effect similar transformations with primary thioamides[16,21] and with primary sulfonamides.[22] However, no successful reactions were reported for secondary amides. Indeed, compounds of type RCONHR', in which neither R nor R' are hydrogen, do not condense with an aldehyde and benzotriazole under the procedure previously reported (i.e. refluxing in dry toluene with azeotropic removal of water). However, we have recently achieved condensations of such secondary amides by the use of catalytic amounts of *p*-toluenesulfonic acid in toluene or by carrying out the reactions in acetic acid. This has led to a significant expansion of the range of applicability of our published procedure in the form of a two-step convergent method commencing with the condensation of a secondary amide

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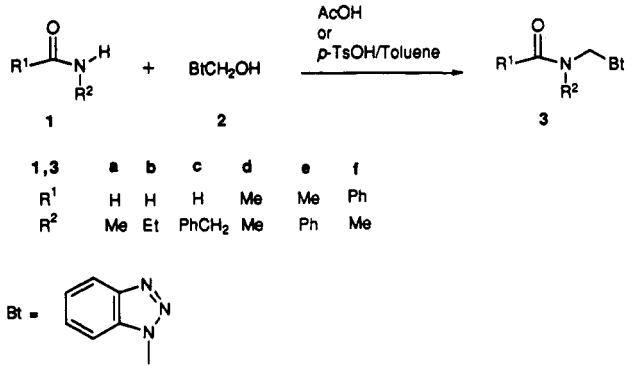
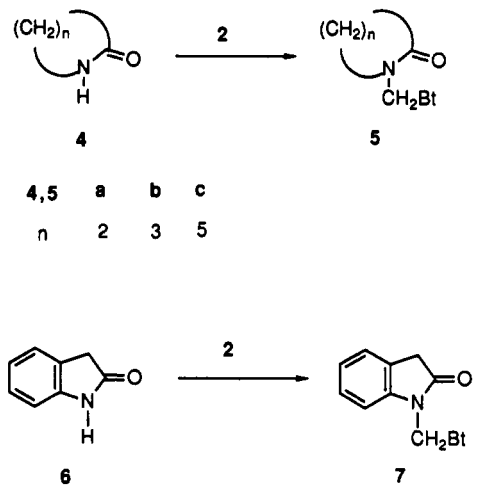
Scheme I



Scheme II

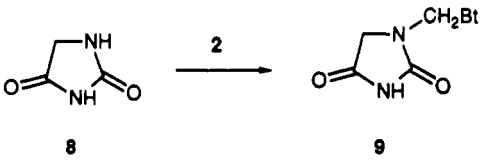


with benzotriazole and an aldehyde followed by displacement of the benzotriazolyl group in the resulting adducts by organozinc reagents to afford tertiary amides or by reduction with $LiAlH_4$ to give tertiary amines.

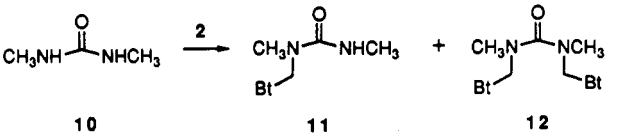
Results and Discussion

Preparation of Secondary Amide–Benzotriazole Adducts (3, 5, 7, 9, 11, 12, 14, 15, 17, 19, and 21). Heating a mixture of *N*-alkylformamides **1a–c** with 1-(hydroxymethyl)benzotriazole (**2**) in toluene in the presence of *p*-toluenesulfonic acid under reflux for an appropriate time, with azeotropic removal of water by a Dean–Stark trap, gave the *N*-alkyl-*N*-(benzotriazol-1-ylmethyl)amides **3a–c** in good yields (Scheme I). Use of acetic acid as both the solvent and the acid catalyst was also investigated and it was found to afford comparable yields of the desired products. This procedure succeeded with the other secondary amides **1d–f** and with cyclic secondary amides **4** and **6** (Schemes I, II). However, further extension to imides such as phthalimide and succimide failed, probably due to their lower nucleophilicity. This limitation was also demonstrated by the reaction of hydantoin (**8**) with **2** where only the 3-monoalkylated hydantoin product **9** was obtained (Scheme III). The product of the reaction of dimethylurea with **2** depends on the number of equivalents of **2** used. With 1 equiv of **2**, the monoalkylated urea **11** was obtained in 60% yield, and the disubstituted product **12** was not observed. A mixture of **11** and **12** was obtained in 52% and 14% yields, respectively, when **2** equiv of **2** were used. With 4 equiv of **2**, only the disubstituted product **12** was obtained in 80% yield (Scheme IV).

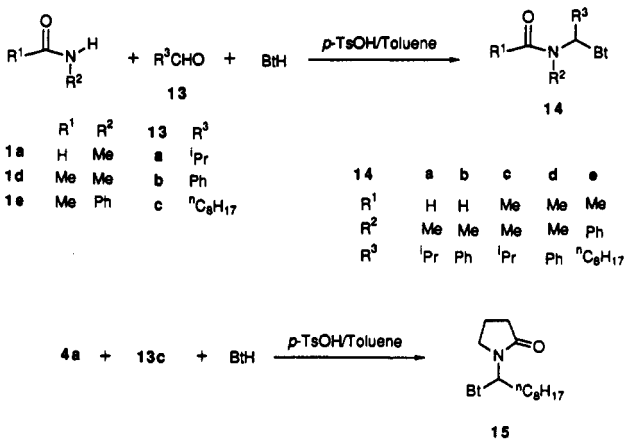
Scheme III



Scheme IV



Scheme V



We examined similar condensations with benzotriazole and aldehydes other than formaldehyde. We found that heating a mixture of a secondary amide, an aldehyde (**13**; $R^3 \neq H$) and benzotriazole with a catalytic amount of *p*-toluenesulfonic acid in toluene afforded the desired derivatives **14** and **15** in 29–73% yields (Scheme V). Both aliphatic (**13**; $R^3 = {}^iPr, {}^nC_8H_{17}$) and aromatic (**13**; $R^3 = Ph$) aldehydes were employed. The yields were lower than for the products from **2** probably in part because side reactions occurred between the aldehydes. We also examined similar reactions with the secondary thioamides, thioacetanilide (**16**), and thiohydantoin (**18**) and with the secondary *N*-methylbenzenesulfonamide (**20**) and found that the desired products **17**, **19**, and **21** were obtained in good to excellent yields in condensations with **2** (Scheme VI). Again, the reaction of the thiohydantoin (**18**) gave only the monoalkylated product **19**. The preparative data and NMR spectral data of the products are given in Tables I–III.

The new benzotriazole derivatives were characterized by their ^1H and ^{13}C NMR spectra and elemental analysis. The four characteristic multiplets between 7.3 and 8.1 ppm (^1H NMR) and the six characteristic carbon signals between 108 and 146 ppm show that they are all benzotriazole-1 isomers.[23] This is in accord with the benzotriazole derivatives from primary amides.[15] For the derivatives of *N*-alkylformamide **3a–c** and **14a,b**, two sets of signals were observed in both the ^1H and ^{13}C NMR spectra. This is expected for the rotational isomers which slowly interconvert at room temperature due to the well-established partial double bond character of the C–N bond

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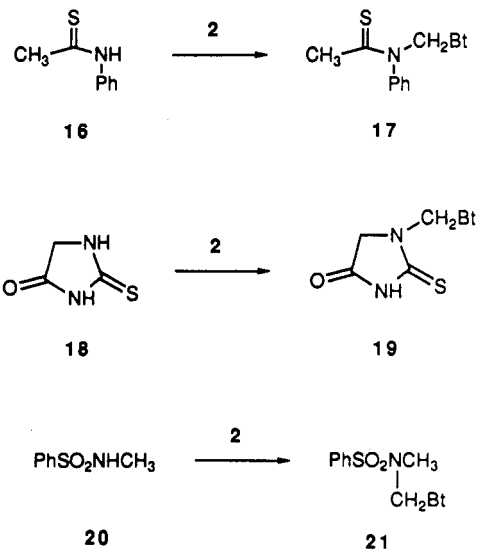
Table I. Preparation of Condensation Products 3, 5, 7, 9, 11, 12, 14, 15, 17, 19, and 21

compd	solvent	time (h)	yield (%)	mp (°C)	molecular formula	calcd/found C	calcd/found H	calcd/found N	purification[a]
3a	toluene	6	62	84–86	$C_9H_{10}N_4O$	56.84/57.21	5.26/5.30	29.47/29.89	Et_2O
3b	toluene	8	60	oil	$C_{10}H_{12}N_4O$	MS (HR): 204.1011/104.1006 (calcd/found)			Et_2O
3c	toluene	12	73	109–10	$C_{15}H_{14}N_4O$	67.67/67.36	5.36/5.21	21.05/21.09	Et_2O
3d	HOAc	24	77	76–8	$C_{10}H_{12}N_4O$	59.01/58.61	5.89/5.87	27.30/27.52	hexane–EtOAc[b]
3e	HOAc	96	80	134–5	$C_{15}H_{14}N_4O$	67.65/67.70	5.30/5.32	21.04/21.29	hexane–EtOAc (1:1)
	toluene	48	77						
3f	HOAc	48	80	111–2	$C_{15}H_{14}N_4O$	67.65/67.65	5.30/5.24	21.04/21.25	Et_2O
5a	toluene	48	43	94–5	$C_{10}H_{10}N_4O$	59.40/58.98	4.98/4.94	27.71/28.04	hexane–EtOAc (1:4)
5b	HOAc	24	96	78–80	$C_{11}H_{12}N_4O$	61.10/61.33	5.59/5.63	25.91/26.25	hexane–EtOAc (1:2)
5c	HOAc	96	62	74–5	$C_{13}H_{16}N_4O$	63.92/64.07	6.60/6.73	22.93/22.85	–
7	HOAc	48	95	178–80	$C_{15}H_{12}N_4O$	68.16/68.23	4.58/4.54	21.20/21.23	hexane–EtOAc (1:2)
9	HOAc	96	76	235–6	$C_{10}H_8N_5O_2$	51.95/51.68	3.92/3.91	30.29/30.37	HOAc[b]
11	toluene	24	60	101–2	$C_{10}H_{13}N_5O$	54.78/54.72	5.98/5.93	31.94/32.32	acetone
12	toluene	24	80[c]	143–4	$C_{17}H_{18}N_8O$	58.28/58.16	5.18/5.15	31.98/32.30	Et_2O[b]
14a	toluene	12	73	86–98	$C_{12}H_{16}N_4O$	62.05/61.69	6.94/6.96	24.12/23.84	$CHCl_3$
14b	toluene	24	33	112–5	$C_{15}H_{14}N_4O$	67.65/67.77	5.30/5.31	21.04/21.21	$CHCl_3$
14c	toluene	24	67	123–5	$C_{13}H_{18}N_4O$	63.39/63.59	7.37/7.44	22.75/23.06	hexane–EtOAc (4:1)
14d	toluene	24	34	106–110	$C_{16}H_{16}N_4O$	68.55/68.62	5.75/5.76	19.99/20.15	hexane–EtOAc (6:1)
14e	toluene	72	29	oil	$C_{23}H_{30}N_4O$	72.98/72.86	7.99/8.11	14.80/14.77	hexane–EtOAc (1:1)
15	toluene	72	67	84–5	$C_{19}H_{28}N_4O$	69.48/69.56	8.59/8.68	17.06/16.89	Et_2O–CH_2Cl_2 (1:1)
17	toluene	72	42	96–97	$C_{15}H_{14}N_4S$	63.81/63.52	5.00/4.92	19.84/19.79	hexane–Et_2O (1:1)
19	HOAc	20	61	266–8	$C_{10}H_9N_5OS$	48.57/48.52	3.67/3.67	28.32/28.16	HOAc[b]
21	toluene	16	94	97–8	$C_{14}H_{14}N_4O_2S$	55.62/55.94	4.67/4.67	18.53/18.67	Et_2O[b]

[a] Eluent used for column chromatography. [b] Recrystallization solvent. [c] Four equivalents of **2** was used. When 2 equiv of **2** was used, a mixture of **11** and **12** was obtained in 52 and 14%, respectively. The mixture was separated by column chromatography with Et_2O.

Scheme VI



of amides[24a–d] and of thioamides.[24e–g] For products from other secondary amides, only one preferred rotational isomer is observed in the NMR spectra due to steric hindrance which increases the energy of the other. ^{13}C NMR spectra show the amide carbonyl for formamide in the region of 162.2–163.8 ppm and other open-chain carbonyl resonances in the region of 170.7–172.1 ppm and for the cyclic amide carbonyl in the region of 175.0–176.3 ppm except for strained ring **5a** at 167.6 ppm. The ^{13}C resonances for the thioamide are observed for **17** and **19** at 205.0 and 183.3 ppm, respectively. No significant changes were observed for the carbonyl resonances as compared with those of the starting amides. For formaldehyde derivatives, the methylene groups directly attached to the amide nitrogen atom resonated between 5.95–6.52 ppm for protons and between 51.0–61.6 ppm for carbons. While no significant differences are observed for the ^1H shifts, the ^{13}C shifts for strained rings, **5a,b**, **7**, and **9**, are in the region 51.0–53.7 ppm, which is upfield compared to the corresponding open-chain derivatives due to the ring strain. The methylene carbons for the thio derivatives **17** and **19** are downfield compared to their oxygen analogues **3e** and **9**. For derivatives of other aldehydes, the ^1H and ^{13}C chemical shifts of the methine groups are in the region 5.78–8.67 and 63.2–77.2 ppm, respectively, due to additional group.

Preparation of Tertiary Amides. We have previously demonstrated that the benzotriazole group in 1-(benzotriazol-1-yl)alkyl esters can be displaced by organozinc reagents to give esters without attack at the carbonyl group.[25] We have now found that the *N*-(benzotriazolylalkyl)-*N*-alkylamides obtained above react similarly with organozinc reagents to give the desired tertiary amides in moderate to good yields. Thus, a mixture of the benzotriazole adduct (dissolved in THF before addition) and the appropriate organozinc reagent in toluene is refluxed for the appropriate time. THF was essential for a satisfactory suspension, otherwise solids stuck to the bottom of the flask and failed to react. The reactions and results are shown in Scheme VII and Table IV, respectively. The benzotriazole byproduct is easily removed with dilute alkali during workup. This makes the isolation and purification of the desired products very simple.

The reaction worked successfully with both aromatic and aliphatic carbanions from organozinc reagents (R^4 = Ph, $PhCH_2$, PhC≡C) with benzotriazole derivatives from both formaldehyde and other aldehydes (R^3 = H, ^iPr, Ph) as shown in Scheme VII. In this way, the H atom in the secondary amide NH was replaced with a R^3R^4CH group where R^3 was derived from the aldehyde in the condensation and R^4 from the organozinc reagent. Since various

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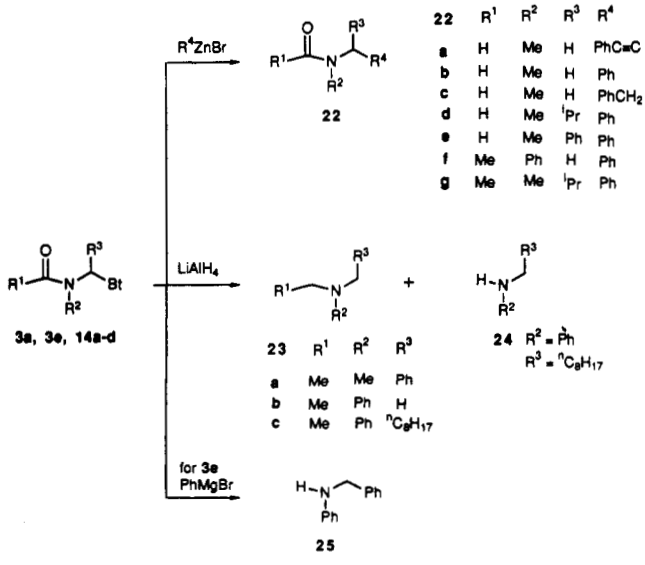
Table II. ^{1}H NMR Spectral Data of Compounds 3, 5, 7, 9, 11, 12, 14, 15, 17, 19, and 21 (δ, ppm)

compd	benzotriazolyl[a] 4	5	6	7	NCH_2Bt or NCHBt	other groups
3a[b,c]	8.11 (8.07) (d, 8.3)	7.4–7.9 (m)	7.4–7.9 (m)	7.4–7.9 (m)	6.37 (6.39) (s, 2 H)	2.76 (2.96) (s, 3 H), 8.23 (8.79) (s, 1 H)
3b[b,c]	8.10 (8.13) (d, 8.3)	7.44 (7.47) (t, 7.9)	7.60 (7.64) (t, 7.4)	7.93 (8.03) (d, 8.3)	6.22 (6.35) (s, 2 H)	0.79 (1.08) (t, 3 H, J = 7.0), 3.23 (3.34) (q, 2 H, J = 7.0), 8.26 (8.71) (s, 1 H)
3c[b,c]	8.02 (8.08) (d, 8.4)	*d*	*d*	7.86 (7.89) (d, 8.4)	6.03 (5.95) (s, 2 H)	4.36 (4.43) (s, 2 H), 8.38 (8.79) (s, 1 H) 7.26–7.55 (m, 8 H)
3d	8.01 (d, 8.3)	7.39 (t, 7.9)	7.49 (t, 7.9)	7.90 (d, 8.3)	6.20 (s, 2 H)	2.13 (s, 3 H), 3.11 (s, 3 H)
3e	8.05 (d, 8.3)	*d*	7.54 (t, 7.1)	7.97 (d, 8.3)	6.50 (s, 2 H)	1.88 (s, 3 H), 6.84–6.87 (m, 2 H), 7.27–7.43 (m, 4 H)
3f	8.06–8.09 (m)	*d*	*d*	8.06–8.09 (m)	6.40 (s, 2 H)	3.05 (s, 3 H), 7.39–7.44 (m, 7 H)
5a	8.08 (d, 8.3)	7.43 (d, 8.3)	7.55 (t, 7.1)	7.83 (d, 8.3)	5.97 (s, 2 H)	3.00 (t, 2 H, J = 4.3), 3.32 (t, 2 H, J = 4.3)
5b	8.04 (d, 8.3)	7.41 (t, 7.1)	7.51 (t, 7.1)	7.86 (d, 8.3)	6.10 (s, 2 H)	1.98–2.10 (m, 2 H), 2.41 (t, 2 H, J = 8.0), 3.46 (t, 2 H, J = 7.2)
5c	8.04 (d, 8.3)	7.40 (t, 7.1)	7.50 (t, 7.1)	7.92 (d, 8.3)	6.23 (s, 2 H)	1.20–1.38 (m, 2 H), 1.59–1.61 (m, 4 H), 2.48–2.61 (m, 2 H), 3.56–3.59 (m, 2 H)
7	8.02 (d, 8.3)	*d*	*d*	7.92 (d, 8.3)	6.52 (s, 2 H)	3.60 (s, 2 H), 7.06 (t, 1 H, J = 6.7), 7.21 (d, 1 H, J = 7.4), 7.23–7.50 (m, 4 H)
9	8.09 (d, 8.3)	7.46 (t, 7.4)	7.62 (t, 7.4)	7.94 (d, 8.3)	6.21 (s, 2 H)	4.06 (s, 2 H), 11.20 (s, br, 1 H)
11	7.97–8.03 (m)	7.28–7.50 (m, 2 H)		7.97–8.03 (m)	6.19 (s, 2 H)	2.85 (d, 3 H, J = 4.6), 2.99 (s, 3 H), 4.85 (s, br, 1 H)
12	8.06 (d, 8.2, 2 H)	7.38–7.46 (m, 4 H)		7.91 (d, 8.2, 2 H)	6.10 (s, 4 H)	2.94 (s, 6 H)
14a[b]	8.06 (8.11) (d, 8.3)	7.40–7.50 (m)	7.50–7.60 (m)	7.79 (d, 8.3)	6.72 (5.78) (d, 1 H, J = 11.0)	0.91 (0.93) (d, 3 H, J = 6.5), 1.15 (1.17) (d, 3 H, J = 6.5), 2.92 (2.88) (s, 3 H), 3.29–3.33 (3.39–3.41) (m, 1 H), 8.13 (8.59) (s, 1 H)
14b[b]	8.10–8.20 (m)	*d*	*d*	*d*	8.29 (7.60) (s, 1 H)	3.06 (2.97) (s, 3 H), 7.15–7.64 (m, 8 H), 8.39 (8.66) (s, 1 H)
14c	8.04 (d, 8.3)	7.38 (t, 7.3)	7.50 (t, 7.3)	7.82 (d, 8.3)	7.00 (d, 1 H, J = 11.0)	0.89 (d, 3 H, J = 6.5), 1.12 (d, 3 H, J = 6.5), 2.11 (s, 3 H), 2.99 (s, 3 H), 3.2–3.3 (m, 1 H)
14d	8.09 (d, 8.3)	*d*	7.48 (t, 7.1)	7.67 (d, 8.3)	8.67 (s, 1 H)	2.20 (s, 3 H), 3.10 (s, 3 H), 7.1–7.2 (m, 2 H), 7.3–7.4 (m, 4 H)
14e	8.06 (d, 8.3)	7.52–7.65 (m, 2 H)		7.97 (d, 8.3)	5.9–6.0 (m, 1 H)	0.82–1.00 (m, 3 H), 1.20–1.60 (m, 12 H), 1.79 (s, 3 H), 2.20–2.36 (m, 1 H), 2.42–2.60 (m, 1 H) 7.02–7.52 (m, 5 H)
15	8.04 (d, 8.3)	7.37 (t, 6.9)	7.49 (t, 6.9)	7.83 (d, 8.3)	6.78 (t, 1 H, J = 7.7)	0.82–1.00 (m, 3 H), 1.20–1.55 (m, 12 H), 1.80–2.18 (m, 2 H), 2.24–2.78 (m, 4 H), 3.2–3.4 (m, 1 H), 3.6–3.7 (m, 1 H)
17	8.01–8.06 (m)	*d*	*d*	8.01–8.06 (m)	6.77 (d, 2 H, J = 7.8)	2.39 (s, 3 H), 7.21–7.33 (m, 7 H)
19	8.11 (d, 8.3)	7.45 (t, 7.3)	7.62 (t, 7.3)	8.07 (d, 8.3)	6.59 (s, 2 H)	4.27 (s, 2 H), 12.10 (s, br, 1 H)
21	8.06 (d, 8.2)	*d*	*d*	8.01 (d, 8.2)	6.03 (s, 2 H)	2.88 (s, 3 H), 7.41–7.51 (m, 3 H), 7.56–7.61 (m, 2 H), 7.72–7.75 (m, 2 H)

[a] The data in the brackets indicates multiplicity and coupling constant, J. Each represents one proton unless stated otherwise. [b] Mixtures of two rotamers and signals appear in pairs. The numbers in the brackets are the chemical shifts for another rotamer. [c] DMSO-d_6 solvent. [d] Overlapped with the phenyl signals.

Scheme VII



R^3 and R^4 groups could be used, this method is general for the preparation of tertiary amides. Compared to the previous procedures for alkylation under basic conditions, the R^3R^4CH group introduced by the present method corresponds to primary alkyl halides when R^3 = H and to secondary halides when $R^3 \neq$ H. It is in respect of secondary alkyl groups that our new method shows great advantages.[12]

The tertiary amides **22a–g** thus prepared all appear to be novel: compound **22e** was mentioned in the literature[24c] for calculation of its rotational barrier, but no physical data is available. Structures **22a–g** were confirmed by their ^{1}H and ^{13}C NMR spectra and by elemental analysis or high resolution MS data. The chemical shifts and assignments are listed in Table V and VI. Chemical shifts for the amide carbonyl and the carbons of R^1, R^2, and R^3 groups were as expected. The principal differences from the precursors were in the chemical shifts of the characteristic C-α which, in the absence of the electron-withdrawing benzotriazole residue, has shifted upfield by about 7 ppm to 33.7–69.4 ppm. The protons were also shifted upfield to the region 3.98–6.82 ppm. Two sets of signals derived from the two rotational isomers were observed for formamide derivatives **22a–e**. Such rotational

Table III. ^{13}C NMR Spectral Data of Compounds 3, 5, 7, 9, 11, 12, 14, 15, 17, 19, and 21 (δ, ppm)

compd	benzotriazolyl 4	5	6	7	3a	7a	C(=O)	NCH_2Bt or NCHBt	other groups
3a[a,b]	119.2 (119.5)	124.3 (124.4)	127.7 (128.1)	110.9 (110.3)	145.2 (145.4)	132.2 (132.3)	163.7 (163.3)	54.5 (60.7)	28.5 (33.0)
3b[a,b]	119.2 (119.5)	124.4 (124.5)	127.8 (128.1)	111.0 (110.4)	144.3 (145.5)	132.1 (132.2)	163.8 (163.1)	52.5 (59.2)	14.3 (12.2), 40.8 (36.6)
3c[a,b]	119.6 (120.3)	124.4 (124.5)	128.0 (127.9)	110.5 (108.7)	145.9 (146.0)	134.3 (134.4)	162.9 (162.2)	51.7 (58.6)	49.6 (44.6), 128.2 (128.4), 128.6 (128.5), 128.9 (128.7), 134.3 (134.4)
3d	119.0	123.9	127.4	110.7	145.6	131.9	171.2	57.1	21.3, 34.5
3e	119.5	124.1	127.8	110.8	145.9	132.2	171.1	58.5	22.4, 127.9, 128.9, 129.9, 140.2
3f	119.7	124.4	127.0	111.0	146.1	132.4	172.1	58.0	36.3, 128.0, 128.5, 130.4, 134.5
5a	119.8	124.5	128.2	109.7	146.1	131.9	167.6	52.4	37.6, 38.9
5b	119.5	124.4	127.9	110.4	145.9	132.1	175.5	53.7	17.4, 30.3, 45.7
5c	119.3	124.1	127.7	110.8	145.8	131.9	176.3	57.8	22.9, 27.8, 29.3, 36.6, 47.9
7	119.8	124.4	128.2[c]	110.4	146.0	132.1	175.0	51.0	35.5, 109.9, 123.41, 123.43, 123.5, 128.3,[c] 142.1
9	119.2	124.3	127.8	110.7	145.3	132.3	157.0	53.5	50.1, 171.0
11	119.3	124.2	127.7	111.2	146.0	132.3	157.9	59.8	27.6, 33.1
12	120.0	124.6	128.2	111.2	146.5	132.9	162.8	61.6	36.3
14a	119.6 (120.4)	124.4 (124.5)	127.8 (128.2)	110.2 (108.6)	145.4 (145.8)	133.3 (132.5)	163.4 (162.0)	68.3 (77.2)	18.3 (19.0), 18.9 (19.2), 27.5 (25.7), 29.5 (28.7)
14b	119.8 (120.4)	124.4 (124.5)	127.9 (128.1)	109.9 (109.8)	145.1 (146.1)	133.1 (132.4)	163.5 (163.0)	65.1 (74.3)	31.2 (28.5), 127.2 (126.8), 128.9 (129.0), 129.2 (129.5), 132.9 (132.8)
14c	119.2	124.1	127.5	110.3	145.1	133.2	171.5	69.5	18.2, 18.8, 21.7, 28.1, 29.7
14d	119.5	124.1	127.6	109.9	145.0	133.2	171.9	66.5	21.7, 32.4, 126.9, 128.5, 128.6, 134.2
14e	119.3	123.8	127.4	110.4	145.3	132.8	170.7	64.8	13.7, 22.1, 22.7, 25.1, 28.7, 28.9, 31.0, 31.3, 128.8, 129.2, 129.5, 136.6
15	119.5	124.3	127.7	110.3	145.6	132.8	175.3	63.2	14.0, 17.7, 22.5, 25.3, 28.9, 29.0, 29.2, 30.3, 30.8, 31.7, 42.0
17	119.8	124.3	128.0	111.0	145.8	132.2	205.0	64.1	34.7, 126.4, 129.4, 130.1, 140.8
19	119.2	124.3	127.7	111.2	145.2	132.4	183.3	56.2	52.5, 171.6
21	119.8	124.5	127.0	110.5	146.1	133.2	-	61.4	34.1, 126.9, 128.2, 129.3, 137.7

[a] Mixtures of two rotamers and signals appear in pairs. The numbers in the bracket are the chemical shifts for another rotamer. [b] DMSO-d_6 solvent. [c] Exchangeable signals.

Table IV. Preparation of Compounds 22–24

compd	substrate	reagent[a]	time (h)	yield (%)	mp (°C)	molecular formula	calcd/found C	H	N	purification[b]
22a	**3a**	PhC≡CZnBr	16	55	oil	$C_{11}H_{11}NO$	MS (HR): 173.0841/173.0838			Et_2O
22b	**3a**	PhZnBr	16	30	oil	$C_9H_{11}NO$	MS (HR): 149.0841/149.0839			Et_2O
22c	**3a**	$PhCH_2ZnBr$	16	41	oil	$C_{10}H_{13}NO$	MS (HR): 163.0997/163.1001			Et_2O
22d	**14a**	PhZnBr	19	43	65–69	$C_{12}H_{17}NO$	75.35/75.61	8.96/9.07	7.32/7.32	hexane–Et_2O (1:1)
22e	**14b**	PhZnBr	19	52	82–86	$C_{15}H_{15}NO$	79.97/79.67	6.71/6.69	6.22/6.31	hexane–Et_2O (1:1)
22f	**3e**	PhZnBr	96	64	oil	$C_{15}H_{15}NO$	79.97/79.88	6.71/6.76	6.22/6.19	hexane–EtOAc (1:1)
22g	**14c**	PhZnBr	16	44	61–63	$C_{13}H_{19}NO$	76.06/76.07	9.33/9.41	6.82/6.79	Et_2O
23a	**14d**	$LiAlH_4$	15	82	oil	$C_{10}H_{15}N$	lit.[28] bp 103.5 °C/36 mm			
23b	**3e**	$LiAlH_4$	24	96	oil	$C_9H_{13}N$	lit.[29] bp 202.5 °C			hexane–EtOAc (2:1)
23c	**14e**	$LiAlH_4$	24	40	oil	$C_{17}H_{29}N$	82.53/82.43	11.81/11.81	5.66/5.63	hexane
24	**14e**	$LiAlH_4$	24	37	oil	$C_{15}H_{25}N$	lit.[30] bp 178 °C/9 mm			hexane

[a] The reactions were carried out in toluene except for **23a** where THF was used as solvent. [b] Eluent for column chromatography.

isomers were also observed in the case of acetamide **22g**, but not in the more sterically hindered *N*-phenylacetamide **22f**.

Preparation of Tertiary Amines. We previously demonstrated that *N*-(benzotriazolylalkyl)amides derived from primary amides react with $LiAlH_4$ or $NaBH_4$ to give secondary amines and secondary amides respectively in good yields.[15] We have now shown that the benzotriazole group in *N*-alkyl-*N*-(benzotriazolylalkyl)amides derived from secondary amides is also removed by $LiAlH_4$, with the concomitant reduction of the carbonyl to a methylene group. Thus, heating a mixture of the benzotriazole derivative and an excess of $LiAlH_4$ in THF or toluene under reflux gave the desired tertiary amines **23a–c** in good yields. In the case of **3e**, the expected product **23c** was accompanied by the secondary amine **24** derived from the removal rather than reduction of the amido group. The isolation of the amines was simple since the benzotriazole byproduct was easily extracted in aqueous alkaline solution. The reactions are shown in Scheme VII and the preparative data along with the ^1H and ^{13}C NMR data are given in Tables IV–VI. These conversions are believed to involve initial reduction of the amide group to a methylene group. The resulting intermediate reacts readily with $LiAlH_4$ to remove the benzotriazole and give tertiary amines as previously described.[26]

The structures of the tertiary amines **23** obtained were confirmed by the NMR spectra, by elemental analysis (for **23c**), or by comparison with literature data. The C-α groups, now appear upfield due to the loss of the electron-withdrawing benzotriazole group, in the regions of 2.89–

(26) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 805.

Table V. ^{1}H NMR Spectral Data of Compounds 22–24 (δ, ppm)

compd	R^1	R^2	R^3	R^4	NCH_2R^1 or NH	$NCHR^3R^4$ or NCH_2R^3
22a[a]	8.04 (8.14) (s, 1 H)	2.99 (3.05) (s, 3 H)	–	7.3–7.4 (m, 5 H)	–	4.21 (4.38) (s, 2 H)
22b[a]	8.10 (8.22) (s, 1 H)	2.72 (2.78) (s, 3 H)	–	7.2–7.4 (m, 5 H)	–	4.33 (4.48) (s, 2 H)
22c[a]	7.77 (7.98) (s, 1 H)	2.81 (2.87) (s, 3 H)	–	2.81–2.87 (m, 2 H), 7.11–7.32 (m, 5 H)	–	3.44 (3.55) (t, 2 H, J = 7.6)
22d[a]	8.05 (8.32) (s, 1 H)	2.68 (2.65) (s, 3 H)	0.85–0.95 (m, 3 H), 1.00–1.05 (m, 3 H), 2.4–2.6 (m, 1 H)	7.2–7.4 (m, 5 H)	–	5.20 (3.98) (d, 1 H, J = 11.0)
22e[a]	8.20 (s, 1 H)	2.71 (2.66) (s, 3 H)	7.1–7.3 (m, 10 H)	see R^3	–	5.79 (6.82) (s, 1 H)
22f	1.87 (s, 3 H)	6.96–7.00 (m, 2 H) 7.17–7.31 (m, 8 H)	–	see R^2	–	4.88 (s, 2 H)
22g[a]	2.06 (2.32) (s, 3 H)	2.70 (2.71) (s, 3 H)	0.85–0.95 (m, 3 H), 0.97–1.05 (m, 3 H), 2.3–2.5 (m, 1 H)	7.2–7.4 (m, 5 H)	–	5.52 (4.38) (d, 1 H, J = 11.4)
23a	1.01 (t, 3 H, J = 7.2)	2.10 (s, 3 H)	7.1–7.3 (m, 5 H)	–	2.35 (q, 2 H, J = 7.2)	3.39 (s, 2 H)
23b	1.08 (t, 3 H, J = 7.1)	6.69–6.72 (m, 3 H), 7.18–7.24 (m, 2 H)	–	–	3.36 (q, 2 H, J = 7.1)	2.89 (s, 3 H)
23c	1.14 (t, 3 H, J = 7.0)	6.59–6.67 (m, 3 H), 7.16–7.22 (m, 2 H)	0.86–0.96 (m, 3 H), 1.20–1.60 (m, 14 H)	–	3.34 (q, 2 H, J = 7.0)	3.22 (t, 2 H, J = 7.7)
24	–	6.57–6.69 (m, 3 H), 7.12–7.18 (m, 2 H)	0.86–0.96 (m, 3 H), 1.20–1.62 (m, 14 H)	–	3.50 (s, br, 1 H)	3.08 (t, 2 H, J = 7.3)

[a] Mixtures of two rotamers and signals appear in pairs where the numbers in the bracket are the chemical shits for another rotamer.

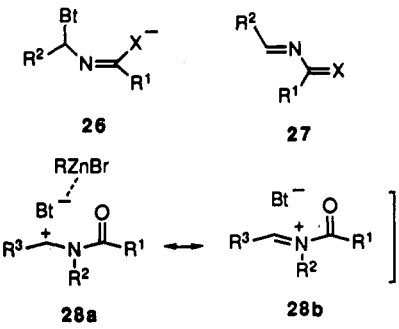
Table VI. ^{13}C NMR Spectral Data of Compounds 22–24 (δ, ppm)

compd	R^1	R^2	R^3	R^4	NCH_2R^1	$NCHR^3R^4$ or NCH_2R^3	C=O
22a[a]	–	33.66 (29.3)	–	82.7 (82.4), 85.2 (83.9), 121.9 (122.3), 128.15 (128.24), 128.7 (128.6), 131.6 (131.5)	–	33.69 (39.8)	161.9 (162.1)
22b[a]	–	28.9 (33.5)	–	127.1 (126.9), 127.5 (127.7), 128.2 (128.4), 135.6 (135.4)	–	47.2 (52.9)	162.1 (162.3)
22c[a]	–	29.5 (34.8)	–	33.0 (34.5), 126.2 (126.6), 128.3 (128.4), 128.46 (128.52), 138.4 (137.5)	–	45.8 (51.0)	162.3 (162.4)
22d[a]	–	27.0 (29.7)	19.8 (19.2), 20.2 (20.0), 25.9 (25.4)	127.9 (127.5), 128.0 (128.3), 128.6 (128.7), 137.3 (137.7)	–	69.4 (60.8)	162.3 (162.7)
22e[a]	–	29.0 (31.6)	127.9 (127.5), 128.3 (128.4), 128.6, 137.9 (137.6)	see R^3	–	66.4 (58.5)	163.4 (163.0)
22f	22.5	127.1, 127.8, 128.1, 128.4, 128.6, 129.4, 137.3, 142.6	–	see R^2	–	52.6	170.1
22g[a]	22.13 (22.18)	26.5 (29.9)	19.2 (19.6), 20.1 (20.4), 28.0 (27.1)	127.2 (127.6), 128.2 (127.9), 128.54 (128.47), 138.9 (138.3)	–	61.4 (68.1)	170.5 (170.1)
23a	12.4	41.6	126.8, 128.1, 129.0, 139.1	–	51.1	61.9	–
23b	11.2	112.4, 116.0, 129.1, 149.1	–	–	46.7	37.3	–
23c	12.3	111.7, 115.1, 129.2, 148.0	14.1, 22.7, 27.2, 27.5, 29.3, 29.5, 29.6, 31.9	–	44.8	50.4	–
24	–	112.6, 117.0, 129.1, 148.5	14.0, 22.6, 27.1, 29.2, 29.4, 29.5, 31.8	–	–	43.9	–

[a] Mixtures of two rotamers and signals appear in pairs where the numbers in the bracket are the chemical shifts for another rotamer.

3.39 ppm for protons and 37.3–61.9 ppm for carbons. The newly formed methylene groups resonated at 2.35–3.36 and 44.8–51.1 ppm for protons and carbons, respectively.

Comparison of the Reaction Mechanisms of N-Benzotriazolylalkylated Primary and Secondary Amides. Reaction of *N*-(benzotriazol-1-ylalkyl)amides from primary amides with Grignard reagents and $NaBH_4$ gave secondary amides.[15,16] Reaction of the present benzotriazole derivative with a Grignard reagent was also attempted: this succeeded, but simultaneous removal of the amido group was also observed; thus compound **3e** with phenylmagnesium bromide in refluxing toluene gave the secondary amine **25** in 69% yield. The present compounds did not react with $NaBH_4$ which left the starting material unaffected even when the reaction was carried out in refluxing toluene for 3 days. These results suggest that our derivatives from secondary amides react in a different manner to those from primary amides. It was previously postulated[16] that for the primary amide derivatives, initial deprotonation of NH by Grignard reagents or $NaBH_4$ gave **26** from which the anion expelled benzotriazole anion to give **27**. The second molecule of Grignard reagent or $NaBH_4$ then reacted with **27** to afford the desired secondary amides. In the reactions of secondary amide derivatives, the amide NH was not available and the reaction should go through initial ionization as shown by **28**. Because the cation **28** is destabilized by the carbonyl group, the reaction requires an elevated temperature in refluxing toluene, much stronger conditions than for the corresponding primary amide derivatives in refluxing THF. Additionally, organozinc reagents need to be used which do not attack the amide carbonyl group.



26 27

28a 28b

Under refluxing toluene conditions with organozinc reagents, ionization was possible by the assistance of the free electron pair on the amide nitrogen and by the chelation of benzotriazole with the zinc atom (see **28a**). Subsequent reaction with organozinc reagents gave tertiary amides. This reaction is similar in nature to that previously reported for esters.[25]

In the reaction with Grignard reagent, initial attack of the carbanion from the Grignard reagent on the amide carbonyl afforded anion **29** which activated the elimination of the benzotriazole group via the loss of acetophenone (**31**) to give **30**. Further reactions of **30** and **31** with PhMgBr gave the secondary amine **25** and presumably the tertiary alcohol **32** (Scheme VIII). With the weak reducing reagent $NaBH_4$, which is known not to reduce amides, no reaction was thus observed.

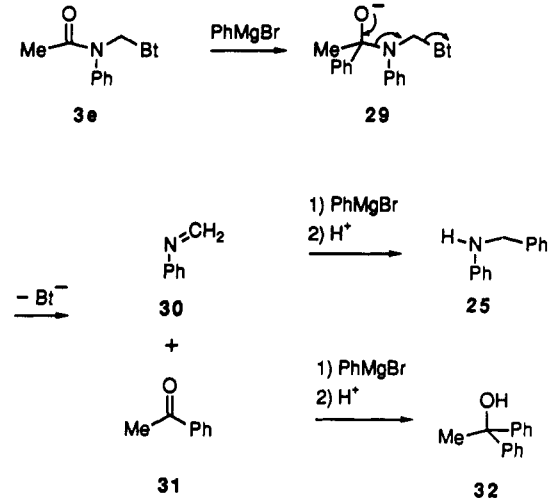
In summary, we have developed a general, two-step sequence for the N-alkylation of secondary amides to give tertiary amides. The method commences with easily available benzotriazole derivatives from a secondary amide, an aldehyde, and a benzotriazole. The overall result is the replacement of the H attached to the amide nitrogen by a R^3R^4CH group where R^3 derives from an aldehyde and R^4 from an organozinc reagent. The sequence proceeds with both aliphatic and aromatic aldehydes and with various organozinc reagents. In addition, tertiary amines were obtained by the reaction of the benzotriazole adducts with $LiAlH_4$. This method is also potentially useful for the alkylation of lactams and for the elaboration of secondary thioamides and sulfonamides. Compared to previous routes, which use strong basic conditions and are limited to primary alkyl halides, or use an inconvenient electroreductive method, our route, general in scope, employs easily accessible starting materials, mild reaction conditions, and a simple workup procedure and affords reasonable yields of tertiary amides. This work further demonstrates the utility of benzotriazole in organic synthesis.

Experimental Section

^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra[25] were recorded in $CDCl_3$ solutions unless otherwise stated.

N-Substituted-*N*-(Benzotriazol-1-ylalkyl)amides (3, 5, 7, 9, 11, 12, 14, 15, 17, 19, and 21): General Procedure. A mixture of 1-(hydroxymethyl)benzotriazole (**2**) (2.98 g, 20 mmol) [or benzotriazole (2.38 g, 20 mmol) and an aldehyde (20 mmol) for **14** and **15**] and the secondary amide (20 mmol) in acetic acid (30 mL) or in toluene (30 mL) with a catalytic amount of *p*-toluenesulfonic acid (0.19 g, 1.0 mmol) was refluxed for the time given in Table I. In the case of toluene solutions, water was removed with a Dean–Stark trap. The progress of the reaction was monitored by TLC until it indicated the starting materials had been consumed. The solvent was removed under reduced pressure. For **3a–c** and **14a,b**, the crude products were purified by flash column chromatography with ether (**3a–c**) or chloroform (**14a,b**). Other products were taken up in $CHCl_3$ (100 mL), and washed with 5% Na_2CO_3 solution (30 mL) and H_2O (30 mL). The $CHCl_3$ extracts were dried ($MgSO_4$) and the solvent was evaporated. Residues were purified by column chromatography or recrystallization as given in Table I.

Scheme VIII



3e 29 30 25 31 32

Reactions of Compounds 3a, 3e, and 14a–d with Organozinc Reagents. Preparation of Tertiary Amides: General Procedure. A solution of zinc bromide in dry Et_2O (10 mmol; 1.0 mmol/mL; 10 mL) (freshly prepared by addition of bromine to zinc powder in dry Et_2O) was added to a Et_2O solution of the Grignard reagent (10 mmol; 1.0 mmol/mL; 10 mL) (prepared from the appropriate organic halide and magnesium. PhC≡CMgBr was prepared by the exchange reaction of MeMgBr with PhC≡CH). The mixture was stirred at room temperature under N_2 for 30 min. Then a solution of the appropriate benzotriazole derivative (5.0 mmol) in THF (20 mL) was added followed by dry toluene (40 mL). The low-boiling solvents were distilled from the mixture and the residual toluene solution refluxed for the time given in Table IV. The mixture was poured into water (30 mL) and acidified to pH 5 with 2 N HCl. The aqueous layer was extracted with chloroform (3 × 40 mL). The combined extracts were washed with 2 N NaOH (30 mL) and H_2O (30 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude products were purified by flash column chromatography using the eluents given in Table IV to afford the tertiary amides.

Reaction of Compounds 3e and 14d,e with LiAlH. Preparation of Tertiary Amines: General Procedure. To a solution of the benzotriazole derivative (5 mmol) in dry THF (40 mL) or in dry toluene (40 mL) (see Table IV) under N_2 was added $LiAlH_4$ (0.50 g, 13 mmol) portionwise. The resulting solution was heated under reflux until TLC indicated that the starting material had been consumed. The reaction mixture was cooled, ice (5 g) added, and the solvent evaporated. The residue was taken up in $CHCl_3$ and H_2O, the $CHCl_3$ layer was separated, and the aqueous layer extracted with $CHCl_3$ (3 × 60 mL). The combined $CHCl_3$ solution was washed with H_2O (30 mL), dried ($MgSO_4$), the solvent removed to give the crude product. Compound **23a** thus obtained was pure. Column chro-

matography purification using eluents given in Table IV afforded compounds **23b,c** and **24**.

Reaction of Compound 3e with PhMgBr: Preparation of *N*-Benzylaniline 25. To a Et_2O solution of PhMgBr (40 mmol; 2.0 mmol/mL; 20 mL) (freshly prepared from reaction of bromobenzene and magnesium) was added a solution of **3e** (1.33 g, 5 mmol) in THF (50 mL) dropwise. Et_2O was distilled off and the residual THF solution heated under reflux for 2 days. It was cooled and poured into H_2O (50 mL) and the solid filtered off. The organic layer was separated and the aqueous solution extracted with Et_2O (2 × 60 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed to give the crude product. Purification by column chromatography (hexane–Et_2O = 10:1) afforded compound **25** (0.75 g, 69%): mp 34–35 °C (lit.[27] mp 37–39 °C); ^{1}H-NMR 3.97 (s, br, 1 H), 4.28 (s, 2 H), 6.56–6.70 (m, 3 H), 7.1–7.4 (m, 7 H); ^{13}C-NMR 48.2, 112.7, 117.4, 127.1, 127.4, 128.5, 129.2, 139.4, 148.1.

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Supplementary Material Available: Copies of NMR spectra of **3b** and **22a–c** (10 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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