A Conceptually New Approach to the Synthesis of Secondary Amides and Thioamides[1]

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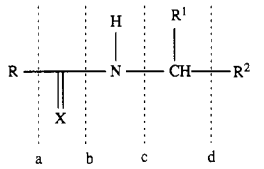
Amides and thioamides of type $RC(=X)NHCHR^1R^2$ are prepared in high yield with the formation of a new C-R^2 bond by the action of a Grignard reagent (R^2MgX) on the readily available adducts from an amide $RCONH_2$ (or thioamide $RCSNH_2$), aldehyde R^1CHO, and benzotriazole.

Amides of type **1** and thioamides of type **2** can be prepared in conceptually different ways according to which of the alternative bonds (a–d) is constructed (Scheme I). The most important methods are the following: (i) formation of bond a using RLi or RMgHal as nucleophile and an isocyanate or isothiocyanate $R^2CHR^1N{=}C{=}X$ (X = O, S) as an electrophile,[2-4] (ii) in the most familiar method, formation of bond b by use of the amine $R^2R^1CHNH_2$ as nucleophile and a carboxylic or thiocarboxylic acid, chloride, ester, or other derivative, as an electrophile,[5] (iii) formation of bond c by the N-alkylation of an amide anion $RCONH^-$ nucleophile[6] with an alkyl halide or similar electrophile [Recently, it has become possible to construct bond c by using an amide[7] $RCONH_2$ or a thioamide[8] $RCSNH_2$ as nucleophile, with special electrophiles. Thus adducts of type **3** and **4** have been made, and the N-monoalkylation of amides and thioamides was achieved by the nucleophilic attack of sodium borohydride on adducts **3** and **4**, respectively[7,8]], and (iv) formation of bond d. Suitably sterically hindered amides of type $RC(=X)NR^3CH_2R^1$ can be deprotonated at the CH_2 group by strong bases and the conjugate base is reacted with electrophilic alkylating agents. Such base-induced reaction with an electrophile has been described by Tischler for *N*-benzylbenzamide[9] and more recently by Beak for sterically hindered amides.[10]

The alternative strategy for the construction of bond d, by reaction of nucleophilic alkylating agent at the carbon α to the amide nitrogen, has not been previously available in the literature, either for amides or for thioamides. We now report that this mode of construction of bond d is possible for amides by using the previously reported adducts **3** of amide–aldehyde–benzotriazole[7] and for thioamides by using the adducts **4** of thioamide–aldehyde–benzotriazole.[8]

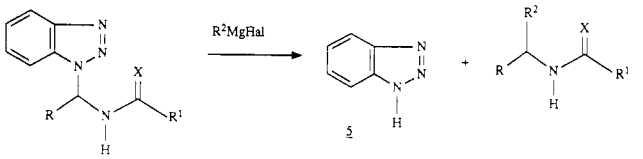
Preparation of Secondary Amides and Thioamides. The (amidoalkyl) and (thioamidoalkyl)benzotriazole derivatives **3** and **4** are easily available in previously described one-pot reactions from benzotriazole, the appropriate aldehydes, and the corresponding amides (or thioamides).[7,8]

Scheme I



1 X = O
2 X = S

Scheme II



3 X = O
4 X = S

	R of RCHO	R of R^1CXNH_2
a	Pr^i	Ph
b	Pr^n	Ph
c	Ph	Ph
d	p-Me-C_6H_4	Me
e	$Pent^n$	Ph
f	Oct^n	Ph
g	Und^n	Ph
h	H	Ph

1 X = O
2 X = S

Reactions of adducts **3** and **4** with 2.1 equiv of Grignard reagent (see Scheme II) in a mixture of tetrahydrofuran and diethyl ether gave the secondary amides and thioamides in a very good yields. Benzotriazole, a side product of the reaction, was removed easily by extraction with alkali in a simple workup and is potentially available for recovery. This reaction can be carried on a large scale and provides good overall yields in the two-step sequence (see Table I).

Spectral Characterization (for full details see Table 2, supplementary material). The structures of all the amides and thioamides synthesized are supported by their analytical and spectral data. The ^{13}C NMR spectra of the amides show the absorption peak for the carbonyl carbon atom in the region of 169.3–165.5 ppm and for the carbon atom directly attached to the amide nitrogen atom at 56.8–53.1 ppm. Typical downfield peaks were observed for the thiocarbonyl carbon atom at 199.1–198.0 ppm, and the signal for carbon α to the nitrogen atom in the secondary thioamides appeared in the region of 61.3–47.4 ppm.

Examination of the ^1H NMR spectra of the amides **1** and the thioamides **2** shows that all contain a doublet at 8.8–6.8 ppm, for the proton attached to the nitrogen. The proton attached to the tertiary carbon atom, which appears in the spectrum as a multiplet at 6.8–4.8 ppm, clearly indicates the proposed structures of the amides and thioamides. Both ^{13}C NMR and ^1H NMR chemical shifts are in good accordance with literature data for this class of compounds.[11-13]

(1) This report constitutes paper 10 in our series The Chemistry of Benzotriazole; for paper 9, see ref 8.
(2) Singleton, H. M.; Edwards, W. R., Jr. *J. Am. Chem. Soc.* **1938**, *60*, 540.
(3) McElvain, S. M.; Venerable, J. T. *J. Am. Chem. Soc.* **1950**, *72*, 1661.
(4) LeBel, N. A.; Cherluck, R. M.; Curtis, E. A. *Synthesis* **1973**, 678.
(5) Reynaud, P.; Moreau, R. C.; Samama, J.-P. *Bull. Chem. Soc. Fr.* **1965**, 3623.
(6) Hepp, P. *Ber.* **1877**, *10*, 327. Pictet, A. *Ber.* **1987**, *20*, 3422. Isele, G. L.; Luttringhaus, A. *Synthesis* **1971**, 266. Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169. Fones, W. S. *J. Org. Chem.* **1949**, *14*, 1099. Park, J. D.; Englert, R. D.; Meek, J. S. *J. Am. Chem. Soc.* **1952**, *74*, 1010.
(7) Katritzky, A. R. Drewniak, M. *J. Chem. Soc., Perkin Trans. 1*, in press.
(8) Katritzky, A. R.; Drewniak, M. *Tetrahedron. Lett.* **1988**, *29*, 1755.
(9) Tischler, A. N.; Tischler, M. H. *Tetrahedron Lett.* **1978**, 3.
(10) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275. Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471.
(11) Breitmaier, E.; Voelter, W. *^{13}C NMR Spectroscopy*, 2nd ed.; Verlag Chemie: Weinheim, 1978; p 187.

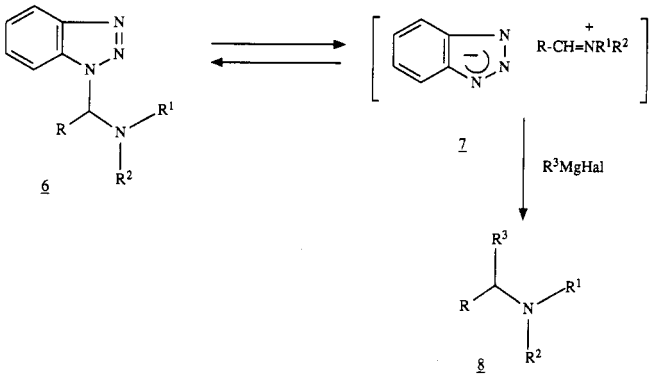
0022-3263/88/1953-5854$01.50/0

Table I. Preparation of the Secondary Amides 1 and Thioamides 2[a]

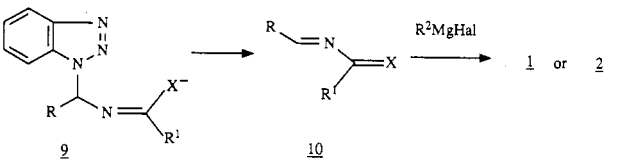
no.	starting adduct	R^2 of R^2MgX	yield, %	recryst solvent	mp, °C	mol form
1a	**3a**	$PhCH_2$	95	ethanol	146–148	$C_{18}H_{21}NO$
1b	**3b**	Ph	92	85% ethanol	124–125	$C_{17}H_{19}NO$
1c	**3c**	Bu^n	85	85% ethanol	129–130	$C_{18}H_{21}NO$
1d	**3d**	Ph	93	EtOAc/P.Et	124–125	$C_{16}H_{17}NO$
1f	**3f**	$PhCH_2$	91	ethanol	117–119	$C_{23}H_{31}NO$
1i	**3a**	PhCC	81	EtOAc/P.Et.	94–95	$C_{19}H_{19}NO$
1j	**3b**	PhCC	86	95% EtOH	84–85	$C_{19}H_{19}NO$
2a	**4a**	$PhCH_2$	87		oil	$C_{18}H_{21}NS$
2b	**4b**	Bu^n	89		oil	$C_{15}H_{23}NS$
2e	**4e**	Ph	88		oil	$C_{19}H_{23}NS$
2g	**4g**	$PhCH_2$	81		oil	$C_{26}H_{37}NS$
2h	**4h**	$PhCH_2$	84		oil	$C_{15}H_{15}NS$

[a] Correct C, H, N analyses were obtained for products **1a–d** and **1i,j**; compound **1e** had melting point identical with the reported in the literature [Solomon, P. W. US Pat. 3.256, 245]; *Chem. Abstr.* **1966**, *65*, 7100. For products **2a–h** M^+ were determined by high resolution mass spectroscopy. P.Et. = petroleum ether.

Scheme III



Scheme IV



The carbonyl frequency of the synthesized amides (amide I band) occurs in the region of 1625–1635 cm^{-1} when examined in the solid state. The amide II band (N–H bending vibrations) at 1570–1520 cm^{-1} is partially under the envelope of the ring vibrations of the phenyl groups. Fine structure usually appears on the low frequency side of the expected N–H stretching band near 3300 cm^{-1}, arising from dimers with a cis amide conformation and polymers with a trans amide conformation. The thioamides show a moderate intensity thiocarbonyl band at 1508–1520 cm^{-1} and the N–H stretch at 3220 cm^{-1}, with slightly higher intensities in comparison to those of the amides.

Reaction Mechanism. The reaction presently described is similar to the previously reported methods for the construction of secondary[14] and tertiary amines,[15] **6** → **8** (Scheme III). However, the mechanism of the new reaction is different, at least from that for the preparation of tertiary amines. The tertiary amines are formed by ionization to ion pairs **7**, the existence of which has been proved by cross-over isomerization experiments.[16] The formation of a similar ion pair (**9**) for an amide is considerably less likely and indeed variable temperature NMR spectra of the intermediate adducts **3** and **4** in toluene-d_8 did not show any changes in the spectral picture on raising the temperature to 80 °C. Hence it is likely that the reaction proceeds via initial deprotonation of the amide to give **9**, which then expells benzotriazole anion to give the acylated imine **10**, which is rapidly trapped by the second mole of Grignard (Scheme IV).

In summary, the use of benzotriazole–aldehyde adducts derived from primary amides and and thioamides allows an exclusive monoalkylation α to the amide (thioamide) nitrogen, yielding the corresponding secondary amides and thioamides in good overall yields.

Experimental Section

Column chromatography was carried out on MCB silica gel (230–400 mesh). Melting points were determined with a Kofler hot stage apparatus and are uncorrected. The IR spectra were recorded on a Perkin–Elmer 238B spectrophotometer. ^1H NMR (200 MHz) spectra were recorded on a Varian XL 200 (FT mode) spectrometer. ^{13}C NMR (50 MHz) spectra were recorded on a Varian XL 200 (FT mode) spectrometer. Tetrahydrofuran and diethyl ether were predried and 4A molecular sieves and distilled from sodium. The benzotriazole adducts **3** and **4** were prepared according to the earlier described methods.[7,8] A typical procedure is given below.

Reaction with Grignard Reagent; Typical Procedure. To the Grignard reagent prepared from magnesium turnings (10.5 mmol) and alkyl or aryl halide (10.5 mmol) in diethyl ether (20 mL) was added the benzotriazole adduct **3** or **4** (5 mmol) in tetrahydrofuran (15 mL) dropwise. After the addition was completed, the reaction mixture was refluxed for 1 h and then poured into ice–water (20 g) and NH_4Cl (15 mL, saturated solution). The organic layer was washed with NaOH (2 × 15 mL, 1 N) and water (2 × 20 mL) and dried with $MgSO_4$ (5 g). Evaporation of the solvent (25 °C/35 mmHg) gave the crude products, which were purified by crystallization (for **1a–j**) (for details see Table I) or by column chromatography (for **2a–h**) and characterized by IR and ^1H and ^{13}C NMR spectra (see Table 2, supplementary material).

Preparation of the *N*-[1-(Benzotriazol-1-yl)alkyl]amides 3; Typical Procedure. Benzotriazole (11.9 g, 0.1 mol), an aldehyde (0.1 mol), and an amide (0.1 mol) were refluxed for 24–48 h in 40 mL of dry toluene in a Dean–Stark apparatus. Water (about 1.5 mL) was formed. Toluene was then removed at 60 °C/30 mmHg, the residue was treated with 200 mL of diethyl ether, and resulting solid was recrystallized from the appropriate solvent.

Preparation of the *N*-[1-(Benzotriazol-1-yl)alkyl]thioamides 4; Typical Procedure. Benzotriazole (11.9 g, 0.1 mol), an aldehyde (0.1 mol), and thioamide (0.1 mol) were refluxed for

(12) Piccini-Leopardi, C.; Fabre, O.; Zimmermann, D.; Reisse, J.; Cornea, F.; Fulea, C. *Org. Magn. Reson.* **1976**, *8*, 536.
(13) Dunina, V. V.; Potapov, V. M.; Rukhadze, E. G.; Kazakova, E. I. *Zhur. Org. Khim.* **1978**, *14*(10), 2064.
(14) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 799, 805.
(15) Katritzky, A. R.; Yannakopoulou, K.; Kuzmierkiewicz, W.; Aurrecoechea, J. M.; Palenik, G. J.; Koziol, A. E.; Szczesniak, M.; Skarjune, R. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 2673.
(16) Katritzky, A. R.; Yannakopoulou, K., manuscript in preparation.

5–48 h in 40 mL of dry toluene in a Dean–Stark apparatus. Water (about 1.5 mL) was removed. Toluene was removed at 60 °C/30 mmHg and the residue was treated with 200 mL of diethyl ether. The crude product was recrystallized from the appropriate solvent or purified by column chromatography.

Registry No. **1a**, 82894-56-2; **1b**, 116368-50-4; **1c**, 66730-27-6; **1d**, 5267-50-5; **1f**, 6583-59-1; **1i**, 117067-56-8; **1j**, 117067-57-9; **2a**, 117067-58-0; **2b**, 117067-59-1; **2e**, 117067-60-4; **2g**, 117067-61-5; **2h**, 97469-74-4; **3a**, 117067-46-6; **3b**, 117067-47-7; **3c**, 117067-48-8; **3d**, 117067-49-9; **3f**, 117067-50-2; **4a**, 117067-51-3; **4b**, 117067-52-4; **4e**, 117067-53-5; **4g**, 117067-54-6; **4h**, 117067-55-7.

Supplementary Material Available: Table of ^{13}C NMR spectral data for compounds 1 and 2 (1 page). Ordering information is given on any current masthead page.

Oxidation of Amines with 2-Sulfonyloxaziridines (Davis' Reagents)

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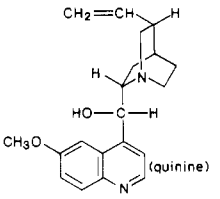
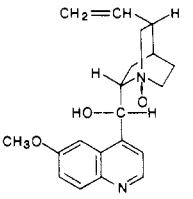
2-(Phenylsulfonyl)-3-aryloxaziridines (Davis' Reagents) react rapidly with amines that are more basic than pyridine to give products that are dependent upon the structure of the amine. Tertiary aliphatic amines are oxidized to the corresponding *N*-oxides in high yields, while secondary aliphatic amines give the N,N-disubstituted hydroxylamines and corresponding nitrones in variable, stoichiometrically dependent ratios. Primary aliphatic amines give 10–35% yields of nitroso compounds and 50–65% yields of *N*-arylideneamines formed by the transimination reaction of the amine with the *N*-arylidenebenzenesulfonamide generated following oxygen transfer from the 2-(phenylsulfonyl)-3-aryloxaziridine.

Numerous reagents have been used to oxidize primary amines to nitro compounds,[1] among them the small ring heterocycle dimethyldioxirane.[2] Our need to effect the amine to nitro transformation under convienent, mild, and anhydrous reaction conditions prompted us to explore the use of another class of heterocyclic oxidants, the 2-(phenylsulfonyl)-3-aryloxaziridines (Davis' Reagents). These easy to prepare and handle solids are useful aprotic and neutral oxidizing reagents, which have been employed for the oxidation of a wide variety of functionalities.[3] Although it had been demonstrated that pyridine was not oxidized to pyridine *N*-oxide by 2-(phenylsulfonyl)-3-(4-nitrophenyl)oxaziridine,[4] we hypothesized that amines more basic than pyridine would prove sufficiently nucleophilic to be oxidized by these reagents. We now report our study on the oxidation of a wide variety of amines with 2-(phenylsulfonyl)-3-aryloxaziridines.

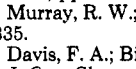
Although our primary interest was the conversion of primary amines into nitro compounds, we first examined the oxidation of tertiary amines more basic than pyridine to test the aforementioned basicity hypothesis. The oxidations were carried out by adding the sulfonyloxaziridine in a single portion to a deuteriochloroform solution of the amine. Any precipitate that formed was removed by filtration, and a ^{13}C NMR analysis of the filtrate was performed. In some instances the reactions were carried out on a preparative scale, the products were isolated and characterized, and the yields were determined. The results

Table I. Percent Yield of Tertiary Amine *N*-Oxide from Oxidation of Tertiary Amine

R_3N	R_3NO, %	ref
triethylamine	>95[a]	5
pyridine	0[a]	
N-methylpiperidine	>95[a]	6
1-azabicyclo[2.2.2]octane[b]	>95[a]	7
(1*R*,2*S*)-$C_6H_5CH(OH)CH(CH_3)N(CH_3)_2$[c]	>95,[a] 67[d]	8
 (quinine)	 >95,[a] 94[d]	7

[a] Estimated from the ^{13}C NMR spectra. The *N*-oxides were observed to be the only amine derived products present in the crude reaction mixtures where oxidation had occurred. [b] Quinuclidine. [c] (−)-*N*-Methylephedrine. [d] Isolated by preparative-layer chromatography.

Table II. ^{13}C NMR Chemical Shifts of *tert*-Butylamine Oxidation Products

	δ in ppm		
compd (R = *tert*-butyl)	*C*N	*C*H$_3$	*C*H
RN=O	95.9	25.2	
RNO_2	84.9	27.7	
$(RNO)_2$	76.3	23.0	
$RN(O)=CHC_6H_5$	70.6	28.1	*a*
	58.3	25.1	73.5
$RN=CHC_6H_5$	56.9	29.5	154.8
RNH_2	47.2	32.4	

[a] In aromatic region, 126–132.

(1) Rosenblatt, D. H.; Burrows, E. P. In "*The Chemistry of Functional Groups*; Supplement F: The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives; Patai, S., Ed.; Interscience: New York, 1982; pp 1085–1149.
(2) Murray, R. W.; Jeyaraman, R.; Mohan, L. *Tetrahedron Lett.* **1986**, *27*, 2335.
(3) Davis, F. A.; Billmers, J. M.; Gosciniak, D. J.; Towson, J. C.; Bach, R. D. *J. Org. Chem.* **1986**, *51*, 4240 and references cited therein.
(4) Davis, F. A.; Stringer, O. D.; Billmers, J. M. *Tetrahedron Lett.* **1983**, *24*, 1213.
(5) Bravo, R.; Laurent, J.-P. *J. Chem. Res., Miniprint* **1983**, 711.
(6) Leung, J.; Jones, A. *Org. Magn. Reson.* **1977**, *9*, 333.
(7) Wenkert, E.; Bindra, J. S.; Chang, C.-J.; Cochran, D. W.; Schell, F. M. *Acc. Chem. Res.* **1974**, 17, 46.
(8) Sharpless, K. B.; Miyano, S.; Lu, L. D.-L.; Viti, S. M. *J. Org. Chem.* **1985**, *50*, 4350.

0022-3263/88/1953-5856$01.50/0