g, 3.31 mmol) in dry THF (25 mL) were added water (89 μL, 4.96 mmol) and triphenylphosphine (0.868 g, 3.31 mmol). After 16 h, the solvent was removed, and the semisolid residue was triturated with ether (5 mL) and filtered. The precipitate was washed twice with 5-mL portions of ether, and the combined filtrate was evaporated. Flash chromatography of the residue (1.06 g) (20% → 25% MeOH/CH_2Cl_2), afforded **35** (0.473 g, 41%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.66–7.70 (m, 4 H, ArH), 7.34–7.45 (m, 6 H, ArH), 5.64 (m, 1 H, H6), 4.22 (br s, 2 H, OCH_2), 3.99 (br m, 1 H, H1), 2.27–2.38 (m, 2 H, CH_2), 2.14–2.20 (m, 1 H, CH), 1.82 (br s, 2 H, NH_2), 1.44–1.54 (m, 1 H, CH), 1.06 (s, 9 H, *t*-Bu); IR (CH_2Cl_2) 2970, 2865, 1111; MS *m/z* 351 M^+.

Anal. Calcd for $C_{22}H_{29}NOSi \cdot {}^1/_2H_2O$: C, 73.28; H, 8.39; N, 3.89. Found: C, 73.50; H, 8.35; N, 3.60.

(±)-*N*-[3-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1-cyclopent-2-enyl]-*N*^{1}-[(*E*)-3-methoxy-2-methylpropenoyl]-urea (36). To a stirred solution of **35** (440 mg, 1.25 mmol) in benzene (10 mL) was added dropwise a solution of 3-methoxy-2-methylacryloyl isocyanate[18] (220 mg, 1.50 mmol) in benzene (5 mL). After 1 h, the solvent was removed, and the residue (620 mg) was flash chromatographed (30% EtOAc/hexane) to give **36** (465 mg, 75%): foam; UV (EtOH) λ_{max} 254 nm, λ_{min} 229 nm; ^{1}H NMR ($CDCl_3$) δ 8.62 (br d, *J* = 7.6, 1 H, NH), 7.65–7.70 (m, 5 H, ArH, NH), 7.35–7.39 (m, 6 H, ArH), 7.32 (q, *J* = 1.1, 1 H, =CHOMe), 5.68 (q, *J* = 1.8, 1 H, H6), 4.91–5.02 (br m, 1 H, H1), 4.23 and 4.20 (AB, *J* = 15.2, 1 H, OCH_2), 3.86 (s, 3 H, OCH_3), 2.32–2.49 (m, 2 H, CH, CH), 2.14–2.27 (m, 1 H, CH), 1.78 (d, *J* = 0.9, 3 H, CH_3), 1.66–1.78 (m, 1 H, CH), 1.06 (s, 9 H, *t*-Bu).

(±)-1-[3-(Hydroxymethyl)cyclopent-2-en-1-yl]thymine (37). **36** (465 mg, 0.944 mmol), 4.0 N H_2SO_4 (10.0 mL), and 1-propanol (10.0 mL) were heated to 70 °C for 10 min, cooled to rt, and neutralized with $NaHCO_3$. The mixture was filtered and the precipitate washed with EtOH. Evaporation of the combined filtrate was followed by trituration of the residue with 5% MeOH/CH_2Cl_2 (5 mL) and filtration through a short plug of glass wool. The filtrate was evaporated and the residue (427 mg) chromatographed on preparative silica plates, eluting with 5% MeOH/CH_2Cl_2. The major band of lowest R_f afforded **37** (13 mg, 6.2%): mp 199–200 °C; UV (EtOH) λ_{max} 273 (7600); ^{1}H NMR (DMSO-d_6) δ 11.20 (br s, 1 H, NH), 7.14 (apparent d, *J* = 1.0, 1 H, H6), 5.45–5.53 (m, 2 H, H1′, H6′), 4.93 (t, *J* = 5.5, 1 H, OH), 4.07 (br s, 2 H, H5′), 2.25–2.52 (m, 3 H, CH_2, CH), 1.76 (d, *J* = 0.8, 3 H, 5 CH_3), 1.60–1.69 (m, 1 H, CH); ^{13}C NMR (DMSO-d_6) δ 163.88 (C4), 153.04 (C4′), 150.83 (C2), 137.01 (C6), 121.18 (C6′), 109.03 (C5), 60.36 (C1′), 59.89 (C5′), 30.88 (C3′), 30.24 (C2′), 12.14 (5CH_3); HRMS calcd for $C_{11}H_{14}N_2O_3$ M^+ 222.1004, found M^+ 222.1003.

Acknowledgment. The authors wish to thank Ernest Prisbe, Renee Otoski, and Edward Salaski for numerous helpful discussions, Mary Jane McRoberts and Diane Crawford-Ruth for antiviral screening of compounds, members of Syntex Analytical and Environmental Research, especially Janice Nelson and Lisa Guzzo, for NOE and other invaluable analytical data, and Nicole Grinder for flawless manuscript preparation. Thanks are also due to Dr. Gregory VanDuyne (Cornell University) for X-ray structural elucidations.

Supplementary Material Available: X-ray data for compounds **10** and **16**, including tables of atomic coordinates, thermal parameters, bond lengths, bond angles, and representations illustrating the computer-generated structures (9 pages). This material is contained in many 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.

Inexpensive Reagents for the Synthesis of Amides from Esters and for Regioselective Opening of Epoxides

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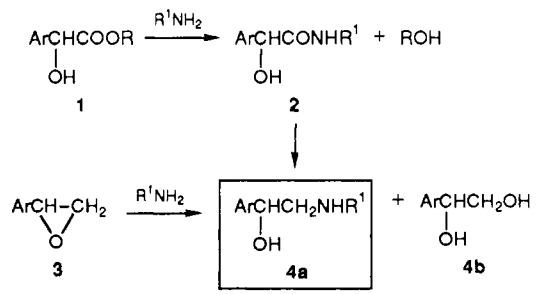
Received April 8, 1992

Lithium aluminum amides [$LiAl(NHR)_4$], **6a–6d**, easily prepared in Et_2O or THF from 1 equiv of $LiAlH_4$ and 5 equiv of amine, proved to be efficient reagents for the synthesis of secondary amides from esters (~100% with unhindered amines and 92% with $tBuNH_2$). They also open aryl epoxides with very high regioselectivity to give 97–98% of the β-amino-α-arylethanols (corresponding to the SN_2 mechanism).

During work on asymmetric synthesis of β-adrenergic compounds,[1] we became interested in the synthesis of secondary amides **2** from carboxylic esters **1** and the regioselective opening of aromatic epoxides **3** as short routes toward amino alcohols **4a**.



Since direct aminolysis of carboxylic esters with primary amines requires high temperatures and the use of an autoclave, more reactive reagents have been developed[2] such as alkali,[3] magnesium,[4] tin,[5] titanium,[6] and aluminum amides.[7] It is also well-known that the regioselectivity of the direct opening of aryl epoxides by primary amines is low and ranges between 60/40 and 85/15 in favor of regioisomer **a**.[8] Reagents such as aluminum,[9] magnesium,[10]

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0022-3263/92/1957-5831$03.00/0

Table I. Preparation of Amides 8a–8d (eq 2)

	reagent		ester 7			products	
R^1	ratio[a]	t^b (°C)	equiv[c]	t^d (°C)	t^e (h)	yield (%)	8/9
Pr	1/2.5	25	1	25	16	81[f]	86/14
Pr	1/4	25	1	25	16	82	100/0
Pr	1/5	25	1	25	16	~100	100/0
Pr	1/5	0	1	reflux	16	83[f]	75/25
Pr	1/5	25	1	reflux	4	83	100/0
iPr	1/5	25	0.7	25	16	~100	100/0
iPr	1/5	25	1	25	16	~100	100/0
tBu	1/5	25	1	25	16	92	100/0
CH_2Ph	1/5	25	1	25	16	~100	100/0

[a] Ratio of $LiAlH_4/R^1NH_2$ in mol. [b] Temperature of formation of the reagent. [c] Equivalents of ester 7 with respect to reagent 6a–6d. [d] Temperature during and after addition of ester 7. [e] Time in hours after addition of ester 7 and before the workup. [f] Yield in weight based on transformed ester.

trimethylsilyl,[11] and tetraphenylantimony amides[12] have also been developed to increase this regioselectivity.

We report here the synthesis of simple and inexpensive reagents and their use to prepare amides from esters in quantitative yields or to open epoxides and mainly aryl epoxides with regioselectivities ranging from 97% to 100%.

Synthesis of Amides from Esters. Among the reagents generally used, dimethylaluminum amides have been shown to react in satisfactory yield (70–80%) with esters[7,13,14] to produce amides. However, about 30 years ago Petit and Poisson[15] proposed the use of the amido complex of lithium and aluminum, $[LiAlH(NH_2)_2]_2NH$ (5) (synthesized in 1947 by Finholt et al.[16]), to prepare the primary amides of some fatty acids in quantitative yields.

Because $LiAlH_4$ powder is less expensive than $AlMe_3$ and because the reported yields with amido complex 5 were quantitative,[15] we extended reagent 5 to primary amines 6a–6d. The reagents were prepared by dropwise addition of the amine into a suspension of $LiAlH_4$ in anhydrous Et_2O or THF at 25 °C. The reagent derived from propylamine was prepared by addition of either 2.5 equiv or 4 and 5 equiv of the amine to 1 equiv of $LiAlH_4$ in Et_2O.

$$LiAlH_4 + 4\,R^1NH_2 \longrightarrow LiAl(NHR^1)_4 \qquad \text{(equ 1)}$$

6a, 6b, 6c, 6d

R^1 = Pr, iPr, tBu, CH_2Ph

The reaction of the lithium aluminum amide reagents with hydroxy ester 7 at 25 °C was then studied. The results are given in Table I.

$$\underset{\text{7}}{CH_3CHOOEt} \xrightarrow[Et_2O]{\text{6a–6d}} \underset{\text{8a–8d}}{CH_3CHCONHR^1} + \underset{\text{9}}{CH_3CHCH_2OH} \qquad \text{(equ 2)}$$

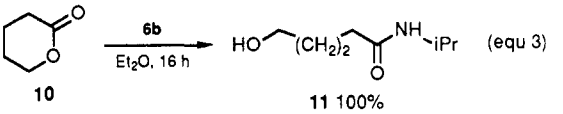
Reaction with hydroxy ester 7 showed that in the first case (Table I, line 1) the combined yield was low (81%) and that 11% of the diol 9 was obtained together with the amide 8 (70%), while in the other cases (Table I, lines 2, 3), the amide 8 was the only product obtained. The results tabulated in Table I indicate the following:

The reagents have to be prepared at about 25 °C to avoid incomplete formation of 6 and subsequent reduction of ester 7 to the diol 9 (compare lines 3 and 4).

The best ratio between $LiAlH_4$ and amine is 1/5 (compare lines 2 and 3).

An excess of reagent 6 is not necessary to obtain quantitative yields with unhindered amines (lines 3, 7, and 9).

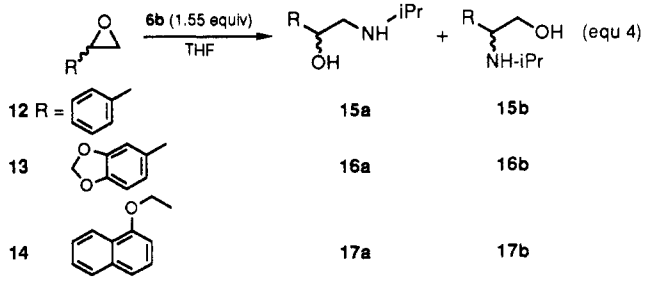
We want also to emphasize that the formation of a precipitate is indicative of formation of the reagent, and one must wait until the precipitate is completely formed before adding the ester 7 (15–30 min for unhindered amines and overnight for $tBuNH_2$). δ-Valerolactone 10 was also quantitatively converted to the corresponding hydroxy amide 11 with only 1 equiv of reagent 6b. The structures



10 11 100% (equ 3)

of the starting ester 7, diol 9, and amides 8a–8d were readily assigned, and their ratios were determined using, respectively, the ethyl signal in 7, the ABX system signal in 9, and the N-alkyl signal in 8a–d (cf. Experimental Section).

Regioselective Opening of Epoxides. Among the reagents developed to increase regioselectivity[9–12] in the opening of epoxides by amines, diethylaluminum amides appeared to be highly regioselective with 1-hexene oxide leading to one regioisomer in 69% yield.[9] Because many adrenergic drugs have an *N*-isopropyl group (like propranolol or isoproterenol), we decided to study the reactivity of the above lithium aluminum amides 6b toward epoxides. Reagent 6b reacted smoothy with epoxides 12–14, leading in high yield (79% to 98%) of the desired β amino alcohols, Table II.



(equ 4)

In these cases THF appeared to be a better solvent; therefore, reagent 6b was prepared in the same way as above but in THF. The crude products of the reactions were analyzed by ^1H NMR spectroscopy prior to isolation.

The structures of the starting epoxides 12–14 and the two regioisomers of the corresponding amino alcohols were

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Table II. Opening of Epoxides by 6b

epox	solv	t (°C)	yield[a] (%)	epox/a/b	a/b	yield[b] (%)
12	Et_2O	25	~100	6/90/4	95/5	92
12	THF	0	~100	7/91/2	98/2	89
12	THF	25		8/86/6	93/7	
13	Et_2O	25	90	11/81/8	91/9	69
13	THF	0	92	8/90/2	97/3	79
14	THF	0	~100	0/100/0	100/0	98

[a] Yield in recovered compounds, starting epoxide being included. [b] Yield in isolated regioisomer a.

easily assigned, and their ratios were determined from their different ABX systems (cf. Experimental Section).

Conclusion

Lithium aluminum amides of the type **6a–6d** are less expensive and they are easier to prepare and to handle than the reagents generally used[2] such as alkali, magnesium, tin, titanium, aluminum, or trimethylsilyl amides. Furthermore, the lithium aluminum amides proved to be more efficient, resulting in near-quantitative yields of amides from esters and, in good yields (79–98%), to 2-[(*N*-substituted)amino]-1-arylethanols through highly regioselective opening of aryl epoxides (97–98% of the SN_2 regioisomer).

Experimental Section

General Aspects. Anhydrous Et_2O was distilled over $LiAlH_4$ and THF over Na/benzophenone. The amines (Lancaster or Fluka), ethyl lactate and trimethylsulfonium iodide (Fluka), δ-valerolactone (Janssen), epoxystyrene (Aldrich), and piperonal (Matheson Coleman & Bell) were used without further purification. Melting points were uncorrected and taken on a Reichert microscope. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 (^1H, 200 MHz; ^{13}C, 50 MHz). Flash chromatographies were carried out using silica gel (230–400 mesh) from Merck.

Synthesis of Reagents 6a–6d. A suspension of $LiAlH_4$ (1 g, 26 mmol) in anhydrous Et_2O or THF (20 mL) was refluxed for 90 min. After the mixture was cooled to 25 °C the amine (130 mmol) was added dropwise with stirring. After the addition was finished, stirring was maintained at 25 °C until precipitation was complete (15–30 min for $PrNH_2$, $iPrNH_2$, and $PhCH_2NH_2$, but overnight for $tBuNH_2$). After addition of anhydrous Et_2O or THF (about 15 mL) a ready-to-use-suspension is obtained.

Synthesis of Amides 8a–8d and 11. The ester **7**, or **10** (26 mmol), was added dropwise to the Et_2O suspension (obtained above) of the reagent and the new mixture stirred at 25 °C overnight (until the precipitate disappeared). The reaction was then carefully quenched by successive addition of 1 mL of H_2O, 1 mL of 10% NaOH, and 3 mL of H_2O. Stirring was maintained until the new precipitate became white and powdered. After filtration, the precipitate was carefully rinsed with CH_2Cl_2 (5 × 10 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give the crude products which were analyzed by ^1H NMR spectroscopy (200 MHz) before and after purification.

***N*-Propyl-2-hydroxypropanamide (8a)** was purified by distillation, bp 98 °C (0.01 mmHg). IR (neat), cm^{-1}: ν_{OH} and ν_{NH} = 3350; $\nu_{amide\ I}$ = 1650; $\nu_{amide\ II}$ = 1550. ^1H NMR ($CDCl_3$) δ ppm: 6.8 (1 H, broad s, NHCO); 4.17 (1 H, q, J = 6.5 Hz, CH); 3.22 (2 H, t, J = 6.5 Hz, CH_2N); 1.51 (2 H, sext, CH_2); 1.35 (3 H, d, CH_3); 0.91 (3 H, t, J = 6.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$), δ ppm: 175.7 (CO); 67.9 (CHO); 40.6 (CH_2N); 22.6 (CH_2); 20.9 (CH_3); 11.1 (CH_3).

Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.98; N, 10.67. Found: C, 55.16; H, 9.82; N, 10.67.

***N*-(1-Methylethyl)-2-hydroxypropanamide (8b)** was purified by distillation, bp 88–93 °C (0.01 mmHg). IR (neat), cm^{-1}: ν_{OH} and ν_{NH} = 3330; $\nu_{amide\ I}$ = 1645; $\nu_{amide\ II}$ = 1530. ^1H NMR ($CDCl_3$), δ ppm: 6.56 (1 H broad d, NHCO); 4.15 (1 H, q, J = 6.5 Hz, CH); 4.05 (1 H, sept d, J_{HCH} = 6.5 Hz, J_{HNH} = 7.5 Hz, CHN); 3.8 (1 H, broad s, OH); 1.42 (3 H, d, CH_3); 1.15 (6 H, d, J = 6.5 Hz, 2 CH_3). ^{13}C NMR ($CDCl_3$), δ ppm: 174 (CO); 67.4 (CHO); 40.4 (CHN); 22.0 ($2CH_3$); 20.5 (CH_3).

Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.98; N, 10.67. Found: C, 55.78; H, 9.23; N, 10.54.

***N*-(1,1-Dimethylethyl)-2-hydroxypropanamide (8c)** was purified by recrystallization from ether. White solid: mp 58 °C. IR (CCl_4), cm^{-1}: ν_{OH} and ν_{NH} = 3380; $\nu_{amide\ I}$ = 1660, 1680; $\nu_{amide\ II}$ = 1520. ^1H NMR ($CDCl_3$), δ ppm: 6.42 (1 H, broad s, NH); 4.07 (1 H, q, J = 6.5 Hz, CH); 1.40 (3 H, d, CH_3); 1.35 (9 H, s, tBu). ^{13}C NMR ($CDCl_3$), δ ppm: 174.8 (CO); 68.3 (CHO); 50.7 (C); 28.7 (CH_3, tBu); 21.1 (CH_3).

Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.67. Found: C, 58.16; H, 9.77; N, 9.79.

***N*-(Phenylmethyl)-2-hydroxypropanamide (8d)** was purified by distillation, bp 91–100 °C (0.01 mmHg). IR (neat), cm^{-1}: ν_{OH} and ν_{NH} = 3350; $\nu_{amide\ I}$ = 1650; $\nu_{amide\ II}$ = 1550. ^1H NMR ($CDCl_3$), δ ppm: 7.25 (5 H, m, H arom.); 7 (1 H, broad s, N H); 4.41 (2 H, d, J_{HNH} = 6 Hz, CH_2Ph); 4.22 (1 H, q, J = 6.5 Hz, CH); 3.5 (1 H, broad s, OH); 1.42 (3 H, d, CH_3). ^{13}C NMR ($CDCl_3$), δ ppm: 175.3 (CO); 137.0 (C); 128.2 (CH arom); 127 (CH arom); 67.7 (CHO); 42.4 (CH_2Ph); 20.6 (CH_3).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.18; H, 7.21; N, 8.08.

***N*-(1-Methylethyl)-5-hydroxypentanamide (11)** was obtained as a pale yellow viscous liquid. IR (neat), cm^{-1}: ν_{OH} and ν_{NH} = 3320; $\nu_{amide\ I}$ = 1650; $\nu_{amide\ II}$ = 1560. ^1H NMR ($CDCl_3$), δ ppm: 5.45 (1 H, broad s, NH); 4.05 (1 H, sept, J = 6.5 Hz, CHN); 3.63 (2 H, t, J = 6.5 Hz, CH_2O); 2.18 (2 H, t, J = 7 Hz, CH_2CO); 1.6 (4 H, m, CH_2CH_2); 1.13 (6 H, d, CH_3). ^{13}C NMR ($CDCl_3$), δ ppm: 172.4 (CO); 60.7 (CH_2O); 40.4 (CH); 35.3 (CH_2); 31.3 (CH_2); 31.7 (2 CH_3); 21.6 (CH_2).

Anal. Calcd for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.79. Found: C, 60.55; H, 10.53; N, 8.80.

Synthesis of Amino Alcohols 15–17. A suspension of **6b** (1.5 equiv) obtained as indicated above in THF was cooled to 0 °C, and a solution of the epoxide (1 equiv) in Et_2O or THF (5 mL) was added dropwise. The mixture was stirred at 0 °C for 4 h, and then the temperature was allowed to reach ambient. Workup and analysis of crude products by ^1H NMR were performed as above for the amides.

2-(*N*-Isopropylamino)-1-phenylethanol (15a). White solid: mp 75 °C (recryst. Et_2O). IR (CCl_4), cm^{-1}: ν_{OH} and ν_{NH} = 3450. ^1H NMR ($CDCl_3$), δ ppm: regioisomer **15a** major (90%), 7.2 (5 H, m, H arom); 4.68 (1 H, dd, X part of an ABX, $J_{AX} \approx 3.5$ Hz, $J_{BX} \approx 9$ Hz, CHO); 2.9 (1 H, A part of an ABX, J_{AB} = 12 Hz, $J_{AX} \approx 3.5$ Hz, CH_2N); 2.8 (1 H, sept, CH); 2.3 (1 H, B part of an ABX, J_{AB} = 12 Hz, $J_{BX} \approx 9$ Hz, CH_2N); 1.07 (6 H, d, J = 6.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$), δ ppm: 143.2 (C arom); 128.2 (2 CH arom); 127.3 (CH arom); 125.7 (2 CH arom); 71.6 (CHO); 54.7 (CH_2N); 48.7 (CH); 22.6 (CH_3); 22.4 (CH_3). ^1H NMR ($CDCl_3$), δ ppm: regioisomer **15b** (4%), 4.65 (1 H, dd, X part of an ABX, CHO); 3.65 (1 H, A part of an ABX, J_{AB} = 10 Hz, $J_{AX} \approx 4$ Hz); 3.45 (1 H, B part of an ABX, J_{AB} = 10 Hz, $J_{BX} \approx 8$ Hz).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.55; N, 7.81. Found: C, 73.98; H, 9.30; N, 7.56.

2-(*N*-Isopropylamino)-1-[3′,4′-(methylenedioxy)phenyl]-ethanol (16a). White solid: mp 91 °C (recryst. Et_2O). IR (CCl_4), cm^{-1}: ν_{OH} and ν_{NH} = 3450. ^1H NMR ($CDCl_3$), δ ppm: regioisomer **16a** major (91%), 6.85 (1 H, s, H arom); 6.77 (2 H, AB system, H arom); 5.95 (2 H, s, OCH_2O); 4.60 (1 H, dd, X part of an ABX, $J_{AX} \approx 3$ Hz, $J_{BX} \approx 8$ Hz, CHO); 2.85 (1 H, A part of an ABX, J_{AB} = 12 Hz, $J_{AX} \approx 3$ Hz, CH_2N); 2.75 (1 H, sept, CH); 2.60 (1 H, B part of an ABX, J_{AB} = 12 Hz, $J_{BX} \approx 8$ Hz, CH_2N); 1.05 (6 H, d, J = 6.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$), δ ppm: regioisomer **16a**, 147.6 (C arom); 146.7 (C arom); 137.3 (C arom); 119, 107.9, 106.3 (3 CH arom); 100.8 (OCH_2O); 71.7 (CHO); 54.8 (CH_2N); 48.6 (CHN); 22.8 (2 CH_3). ^1H NMR ($CDCl_3$) δ: regioisomer **16b** (2%),

3.6 (1 H, A part of an ABX, CH_2N).

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 65.01; H, 7.44; N, 7.21.

1-(*N*-Isopropylamino)-3-(1-naphthyloxy)-2-propanol (17a). Propranolol is usually isolated as its hydrochloride (see refs 18 and 19). White solid: mp 91-92 °C (recryst. Et_2O). IR (CCl_4), cm-1: ν_{OH} and ν_{NH} = 3620, 3440. ^1H NMR ($CDCl_3$), δ ppm: regioisomer **17a** (100%), 8.25 (1 H, m, H arom); 7.80 (1 H, m, H arom); 7.40 (4 H, m, H arom); 6.85 (1 H, dd, H arom); 4.15 (3 H, m, A^1B^1C part of an A^1B^1CXY, OCH_2CH-); 3.00 (1 H, X part of an A^1B^1CXY, J_{XY} = 12 Hz, $J_{CX} \approx 3$ Hz, CH_2N); 2.75 (1 H, sept CH); 2.70 (1 H, Y part of an A^1B^1CXY, J_{XY} = 12 Hz, $J_{CY} \approx 6.5$ Hz, CH_2N); 1.1 (6 H, d, J = 6.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$), δ ppm: 154.3 (C arom); 134.4 (C arom); 127.4, 126.3, 125.7, 125.1, 121.7, 120.5 104.8 (7 CH arom); 70.7 (CH_2O); 68.4 (CHO); 49.5 (CH_2N); 48.8 (CHN); 23 (2 CH_3).

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.09; H, 8.16; N, 5.39. Found: C, 74.28; H, 8.03; N, 5.25.

2-[3',4'-(Methylenedioxy)phenyl]oxirane (13). To a solution of trimethylsulfonium iodide (8 g, 40 mmol) in anhydrous THF (30 mL) was added NaH (0.95 g, 40 mmol), and the mixture was heated to 60 °C for 2 h. Then a solution of piperonal (4.5 g, 30 mmol) in THF (30 mL) was added dropwise. At the end of the addition, the mixture (pink) was stirred at 60 °C until no piperonal remained as shown by TLC (about 2 h). After addition of H_2O (15 mL) THF was evaporated under vacuum and the remaining aqueous phase was extracted with pentane (5 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give the epoxide (85%) which was used without further purification. The physical characteristics of 2-[3',4'-(methylenedioxy)phenyl]oxirane (13) corresponded to the known values.[17]

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Nitrones from Addition of Benzyl and Allyl Grignard Reagents to Alkyl Nitro Compounds: Chemo-, Regio-, and Stereoselectivity of the Reaction

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Received April 14, 1992

Reaction of allyl and benzyl Grignard reagents with functionalized nitroalkanes affords nitrones in good yield. This process shows considerable chemoselectivity; carbonyl groups and other highly reactive electrophilic functions are unaffected by the reaction conditions (THF, -70 °C). A mixture of regioisomers **4** and **5** is usually obtained, and the product distribution depends on the nature of the alkyl framework. An intermediate **3** is postulated, and the isomeric pair of nitrones arises, very likely through a selective syn elimination. α-Substituted alkyl chains give mostly conjugated products **4** while unbranched chains afford predominantly the nonconjugated nitrones **5**. The **4**/**5** ratio can be strongly modified by using a proton source of suitable strength; trichloroacetic acid produces **4** exclusively in the reaction of nitroethane with benzyl Grignard, while 2,6-dimethylphenol affords completely the nonconjugated nitrone **5**. The stereochemistry of the double bond is affected by the nature of the reagent used. Benzyl Grignard gives only *Z* nitrones **4** and **5**; 2-butenylmagnesium chloride gives nonconjugated *Z* nitrones and a predominance of *E* isomer in the conjugated nitrone **5**.

Recent years have witnessed a significant increase in the utilization of nitrones as highly valuable synthetic intermediates[1] and as useful spin trapping reagents.[2] In particular, nitrones can be considered versatile 1,3 dipoles for the construction of nitrogen heterocycles which constitute the backbone of various biologically active compounds.[3]

Addition of Grignard and lithium reagents to nitrones, although less explored, represents an alternative application of these compounds in synthesis.[4] This reaction was recently applied to the synthesis of enantiomerically pure amino and hydroxylamino derivatives, since it proceeds with high diastereoselectivity when an appropriate stereogenic group is placed close to the nitrogen atom of the parent nitrone.[5]

Several synthetic methods for nitrones have been reported, but very few of them show general applicability. Classical methods involve the condensation of N-monosubstituted hydroxylamines with carbonyl compounds[6] or direct oxidation of N,N-disubstituted hydroxylamines.[7]

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