Syntheses of α-Phenylneopentyl Chloride Enantiomers: (S)-(−)-1-Chloro-1-phenyl-2,2-dimethylpropane from (R)-(+)-1-Phenyl-2,2-dimethyl-1-propanol via the Reaction of Tri-n-butylphosphine in Carbon Tetrachloride and (R)-(+)-1-Chloro-1-phenyl-2,2-dimethylpropane from Anthranilic Acid

Herman E. Zieger,* Danielle Angrand Bright, and H. Haubenstock

The City University of New York, Department of Chemistry, Brooklyn College, Brooklyn, New York 11210, and The College of Staten Island, Staten Island, New York 10301

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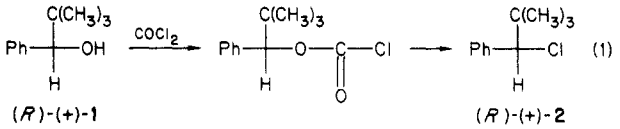
(*R*)-(+)-1-Phenyl-2,2-dimethyl-1-propanol ((*R*)-(+)-α-phenylneopentyl alcohol, **1**) was converted into (*S*)-(−)-1-chloro-1-phenyl-2,2-dimethylpropane ((*S*)-(−)-α-phenylneopentyl chloride, **2**) by means of the tri-*n*-butylphosphine–carbon tetrachloride reaction. The $[\alpha]^{25}_D$ −112° shows that the inversion stereospecificity in this process is 1.55 times higher than the S_Ni retention stereospecificity observed earlier upon treatment of (*R*)-(+)-**1** with phosgene to give (*R*)-(+)-**2**. Reaction of the (*S*)-(−)-**2** sample with (diphenylmethyl)lithium gave (*R*)-(−)-1,1,2-triphenyl-3,3-dimethylbutane with a minimum of 60% inversion of configuration in the coupling process. A five step synthesis of (*R*)-(+)-**2** from anthranilic acid involved resolution of a precursor to **2** and produced samples whose optical purity is 93% of that obtained in the R_3P/CCl_4 reaction.

(Diphenylmethyl)lithium reacts with neopentyl iodide (or bromide) with second-order kinetics to give 1,1-diphenyl-3,3-dimethylbutane in 89–95% yields.[1] The reaction of Ph_2CHLi with (*R*)-(+)-α-phenylneopentyl chloride (**2**) occurs with predominant inversion of configuration to give (*S*)-(+)-1,1,2-triphenyl-3,3-dimethylbutane.[2]

In order to determine the stereospecificity of this coupling process, we began work on the problem of determining the optical purity of (*R*)-(+)-**2**.

Previously, we were able to synthesize samples of (+)-**2** having $[\alpha]^{25}_D$ +72° by thermal decomposition of α-phenylneopentyl chlorocarbonate obtained from the reaction of α-phenylneopentyl alcohol (**1**) of high optical purity with phosgene;[2] see eq 1. The internal nucleophilic substitution



(1)

(S_Ni) reaction of chiral 2-butylchloroformate occurs with 100% retention of configuration to give (+)-2-chlorobutane.[3] In contrast, α-phenylethyl chloroformate rearranges with a predominant but not exclusive retention of configuration whose stereospecificity shows a solvent dependence indicative of a carbocation intermediate together with a large negative ρ value for several para-substituted α-phenylethyl chloroformate decompositions.[4]

The trialkyl- or triarylphosphine–tetrachloromethane–alcohol reaction[5] is reported to occur with high inversion stereospecificity with chiral alcohols.[6-9] Research on the mechanism of this three-component system was aided remarkably by Appel's analysis[10] of the reaction of triphenylphosphine with CCl_4 to give two phosphonium salt intermediates, $[Ph_3PCl]^+CCl_3^-$ and $[Ph_3PCCl_3]^+Cl^-$. The first of these intermediates reacts with an alcohol to produce an alkoxytriphenylphosphonium chloride salt together with a mole of $HCCl_3$. In the case of α-deuterioneopentyl alcohol, this intermediate alkoxytriphenylphosphonium chloride decomposes unimolecularly to form Ph_3PO and inverted α-deuterioneopentyl chloride.[7,11]

The second intermediate, $[Ph_3PCCl_3]^+Cl^-$, reacts rapidly with more Ph_3P to produce $Ph_3P{=}CCl_2$ and Ph_3PCl_2. The dichlorotriphenylphosphorane formed from this second intermediate also reacts with alcohols to give triphenylphosphine oxide and alkyl chlorides with inversion of configuration. It seemed reasonable to us to apply the trialkylphosphine–CCl_4 reaction to alcohol **1** in order to contrast the stereoselectivity of the S_Ni conversion of (+)-**1** to (+)-**2** by means of phosgene with the inversion stereoselectivity of the (+)-**1** to (−)-**2** conversion with $(n\text{-}C_4H_9)_3P/CCl_4$ reagent.

Second, we describe the synthesis of (+)-**2** from anthranilic acid via a precursor which contains a reactive functional group that is remote from the chiral center, is easily removable, and can be used to achieve resolution.

Table I. Specific Rotations of α-Phenylneopentyl Chloride: the *n*-Bu_3P–CCl_4 Experiments

run	$[\alpha]_D$, 1[a] deg	% ee 1[22c]	$[\alpha]^{25}_D$ 2,[b] deg	corrected $[\alpha]^{25}_D$
1	+31.6	100	−107.7	−107.7
2	+30.1	95	−106.5	−112.

[a] In acetone. [b] In THF.

Results

Application of the tri-*n*-butylphosphine–CCl_4 reaction to (*R*)-(+)-α-phenylneopentyl alcohol (**1**) of high optical

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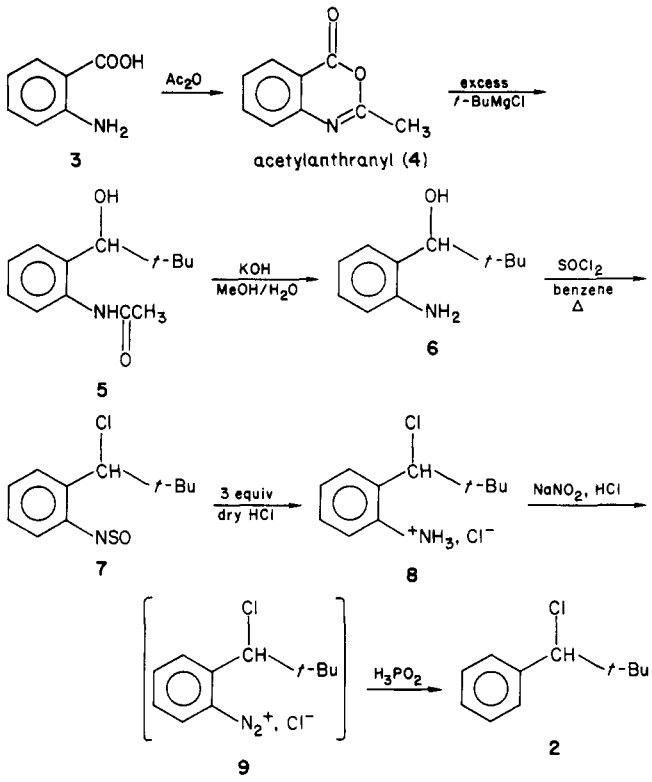
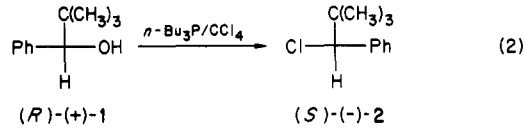
Scheme I



purity produced the chloride **2** of inverted configuration and specific rotation −112°; see eq 2 and Table I. This



(2)

is the highest specific rotation ever observed for α-phenylneopentyl chloride, and it shows the trialkylphosphine–CCl_4–alcohol reaction is of much higher stereospecificity than the alcohol → chlorocarbonate → retained configuration halide process.

Whether −112° is at or near the maximum value for optically pure (−)-**2** is difficult to assess. Some chiral benzylic alcohols have been shown to undergo partial racemization during reaction with Ph_3P–CCl_4.[13] Furthermore, an alternative attempt to determine the optical purity of **2** by application of an independent method such as NMR spectroscopy of chiral shift reagent complexes fails because halides are too weakly basic to form stable complexes (see below).

We chose the more rigorous approach to the question of optical purity by synthesizing a precursor to **2** which contains a reactive functional group that is remote from the chiral center, that is easily removable, and that can be used to achieve resolution. *o*-(1-Chloro-2,2-dimethylpropyl)-1-aminobenzene hydrochloride (**8** in Scheme I) was synthesized from anthranilic acid by the five-step synthesis shown in Scheme I in 43% overall yield. Further, the amino group could be removed from the aromatic ring by diazotization followed by H_3PO_2 reduction without loss of the benzylic chlorine to produce (±)-**2** in 83% yield.

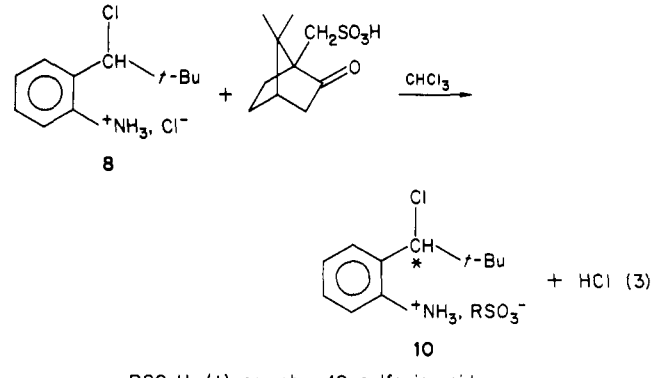
The addition of a benzene solution of acetylanthranyl (**4**, Scheme I) to an excess of *tert*-butylmagnesium chloride produced the secondary alcohol amide **5** [(1-hydroxy-2,2-dimethylpropyl-*o*-acetamidobenzene] in two steps following the literature precedent.[14] Addition of the first mole of *tert*-butylmagnesium chloride to the carbonyl group of **4** leads to the formation of *N*-acetyl-2-aminopivalophenone in situ. Grignard reduction by a second mole of *t*-C_4H_9MgCl reduces the keto group to the secondary alcohol in **5**, presumably because of steric hindrance in both the ketone and the Grignard reagent.

Hydrolysis of **5** in basic medium gave the alcohol amine **6** [*o*-(1-hydroxy-2,2-dimethylpropyl)-1-aminobenzene]. Conversion of **6** with thionyl chloride into α-[*o*-(*N*-sulfinylamino)phenyl]neopentyl chloride (**7**) occurred in 77% yield in an old, well-known reaction.[15] This sulfinyl amine exhibits a band in the IR at 1170 cm^{-1} characteristic of an aromatic N=S=O group.

Addition of 3 mol of dry gaseous HCl to the sulfinyl amine **7** regenerated the aromatic amine as the hydrochloride **8** in 94% yield. **8** is reasonably stable at room temperature, but the very reactive free amine could not be regenerated from it without polymerizing.

Resolution of *o*-(1-Chloro-2,2-dimethylpropyl)-1-aminobenzene Hydrochloride (8). Several different methods for resolving **8** were studied including anion exchange to form diastereoisomeric salts. Since **8** is the salt of a strong acid and a weak base, a resolving acid stronger than HCl was chosen in order to avoid acid–base equilibria problems. In addition, nonbasic solvents must be utilized to avoid solvolysis of the benzylic chlorine atom in **8** (1*S*)-(+)-Camphor-10-sulfonic acid was chosen as the resolving agent because of its high acid strength and its moderate solubility in $HCCl_3$. Upon mixing a chloroform solution of (±)-**8** with a chloroform solution of the resolving acid and chasing HCl with a gentle stream of argon, a slowly formed precipitate melting at 170–172 °C is obtained in 47% yield. Attempts to purify this salt by recrystallizations from methanol led to replacement of the benzylic chlorine atom with a methoxyl substituent.

Repetition of the resolution with 0.5 mol of (+)-camphor-10-sulfonic acid for each mole of racemic **8** gave a 13% yield of camphor sulfonate salt, **10**, whose mp was 177–180 °C; see eq 3. Diazotization of this sample of **10**



followed by treatment with H_3PO_2 gave (+)-α-phenylneopentyl chloride, $[\alpha]^{24°}_D$ +104.5 °C; see eq 4. Since (+)-α-phenylneopentyl chloride has the *R* configuration, the less soluble diastereoisomeric camphorsulfonate salt, from which (+)-**2** was obtained, also has the *R* configuration at the benzylic carbon. The camphorsulfonate salt

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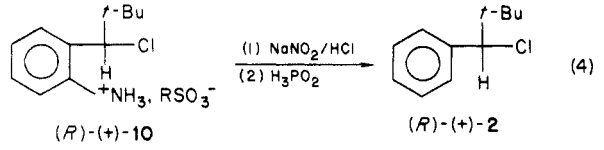
Table II. Proton NMR Spectral Parameters of $C_6H_5CHClC(CH_3)_3$ (2)[a]

entry	binuclear shift reagent (M)	chloride 2, M	CHCl mult	CHCl δ	CHCl relative area	CH_3 mult	CH_3 δ	CH_3 area
1		0.48	s	4.710	1.0 H[b]	s	1.016	9.0 H[b]
2[c]	$Eu(tfc)_3$ (0.3) + Ag(fod) (0.3)	0.2	s	4.686	0.61 H[d]	s	0.998	e
				4.676			0.994	
3[f]	$Eu(tfc)_3$ (0.3) + Ag(fod) (0.38)	0.17	s	4.680	0.94 H[d]	s	0.982	e
				4.668				
4	$Yb(tfc)_3$ (0.07) + Ag(fod) (0.38)	0.07	s	4.620	0.91 H[d]	s	0.9911	8.9 H[d]
				4.605			0.9769	
5	$Yb(tfc)_3$ (0.09) + Ag(fod) (0.10)	0.04	s	4.600	0.92 H[d]	s	0.9823	8.7 H[d]
				4.587			0.9699	

[a] Spectra were run in $CDCl_3$ solvent containing tetramethylsilane at ambient temperature unless indicated otherwise. [b] Methyl area normalized to 9.0 H. Aromatic signal = 5.3 H. [c] Spectral parameters after 94 pulses. [d] Combined area for overlapping singlets. Aromatic peak area defined as 5.0 H. [e] Area measurement not possible due to interference from shift reagent signals. [f] Spectrum obtained at 263 K.



(R)-(+)-10 (R)-(+)-2

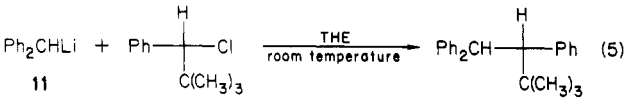
10 is not optically pure because recrystallization from $HCCl_3$ improved its mp to 181–184 °C.

It became clear from these results that an independent method for determining the optical purity of the halide was needed. The application of chiral lanthanide shift reagents was investigated as an alternative method for distinguishing the enantiomers of 2.

While tris[3-(trifluoroacetyl)-*d*-camphorato]europium (III) [$Eu(tfc)_3$] and tris[3-(heptafluorobutyryl)-*d*-camphorato]europium (III) [$Eu(hfbc)_3$] have been generally used with many classes of compounds,[16,17] these reagents do not produce useful shifts with weakly nucleophilic substrates such as aromatic or halogen compounds. Therefore, a variety of silver β-diketonate–lanthanide complexes[18–21] were explored. Chiral binuclear complexes have been applied to terpenes, although these reagents have not been used with benzylic halides. An obvious potential drawback is the reactivity of halides toward the silver-containing reagents.

The results of several experiments are summarized in Table II. At ambient temperature separation of the methine proton signal into two singlets was observed in the presence of $Eu(tfc)_3$–Ag(fod) and $Yb(tfc)_3$–Ag(fod) ($\Delta\Delta\delta$ 0.01 and 0.015, respectively; entries 2 and 4, Table II). Small separations of the methyl signal were also observed. With the former shift reagent some reaction of the chloride occurred at ambient temperature. This was evident from the reduced relative area of the methine proton signal and the appearance of impurity peaks. When the spectrum was run at 263 K the unwanted reaction was suppressed (entry 3). Satisfactory spectra were obtained with $Yb(tfc)_3$–Ag(fod) at ambient temperature without the complication of side reactions (entries 4 and 5). Increasing the molar ratio of shift reagent to substrate did not result in improved separation of the methine proton singlets. Because of the very small separations found at 250 MHz on racemic 2, no attempts were made on (+)-2 or (−)-2 to determine optical purity by this method.

Since the question of the optical purity of α-phenylneopentyl chloride originated in a study of the stereochemistry of its coupling reaction with (diphenylmethyl)lithium (11) a sample of 2 having a specific rotation of −106.5° was treated with 11; see eq 5. It produced



(S)-(−)-2 (R)-(−)-12

(R)-(−)-3,3-dimethyl-1,1,2-triphenylbutane (12) of specific rotation −113° at 25 °C. Since optically pure (R)-(−)-12 exhibits $[\alpha]^{22}_D$ −188.6°, the % enantiomeric excess of the sample of hydrocarbon 12 obtained in the coupling process of eq 5 is 60%. The significance of this result is that the combination of the optical purity of (S)-(−)2 and the stereospecificity of the coupling reaction is not less than 60%. If coupling occurs with 100% inversion of configuration, then halide (−)-2 is 60% optically pure. Some time ago, however, we showed that 3 reacted with (−)-α-phenylethyl chloride to produce (+)-1,1,2-triphenylpropane with 70% inversion of configuration.[2b] It seems unreasonable to assume that the sterically more hindered (−)-2 reacts with 11 with higher stereospecificity than (−)-α-phenylethyl chloride. Consequently, we expect future research to show that the resolution has produced material which is at least 85% optically pure.

Experimental Section

Routine NMR spectra were obtained on a Varian T-60 spectrometer. Infrared spectra were obtained on a Perkin-Elmer Model 1320 spectrometer. Optical rotations were observed with an O.C. Rudolph & Sons Model No. 70 polarimeter. The lanthanide shift reagents were obtained from the Aldrich Chemical Co. Silver β-diketonates were prepared as described by Sievers.[18–21] Spectra were recorded with a WM 250-MHz Bruker NMR spectrometer. Pulse angles of approximately 9–18° were employed. The general procedure was as follows: a solution of the lanthanide shift reagent in $CDCl_3$ containing 99.8 atom % D and Me_4Si were added to the silver β-diketonate, and the mixture was vigorously shaken for 2–2.5 min and centrifuged. The supernatant was then transferred to an NMR tube. During this procedure care was taken to protect the silver-containing reagents from light. Immediately before placing the sample into the probe of the spectrometer a solution of the chloride in $CDCl_3$ was added to the NMR tube, and the contents were shaken. The reported molarities (Table II) are not exact because a small amount of

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insoluble residue usually remained after centrifugation of the binuclear complex.

Resolution and Optical Purity of (*R*)-(+)-α-Phenylneopentyl Alcohol. Resolution of α-phenylneopentyl alcohol was accomplished with *l*-cinchonidine [Aldrich Chemical Co., $[\alpha]^{23}_D$ −109.2° (*c* 1.5, C_2H_5OH), mp 200–203 °C] following the procedure of Winstein and Morse.[22c] The observed $[\alpha]^{21}_D$ +31.2 ± 0.4° was consistently higher than the literature value ($[\alpha]^{23}_D$ +30.6 (in acetone)) probably because our concentrations were lower. Our mp for (*R*)-(+)-1 was 55.5–56.0 °C, in good agreement with the literature (mp 56.1–56.5 °C).

(*S*)-(−)-α-Phenylneopentyl Chloride from (*R*)-(+)-α-Phenylneopentyl Alcohol: *n*-Bu_3P–CCl_4 Experiments. Run 1. To a stirred solution of (*R*)-(+)-α-phenylneopentyl alcohol[22c] [762.4 mg, 4.65 mmol, mp 55–56 °C, $[\alpha]^{21}_D$ +31.6° (0.03757 g/mL acetone)] in 9.3 mL of CCl_4 was added tri-*n*-butylphosphine (8.7 mmol, 2.2 mL) under an argon atmosphere. The reaction mixture was refluxed for 14 h. The solvent was evaporated and the residual oil passed through alumina with 80:20 petroleum ether/benzene as the eluent. There was obtained 416.9 mg (49%) of (*S*)-(−)-α-phenylneopentyl chloride,[2] $[\alpha]^{25}_D$ −107.7° (0.03565 g/mL, THF).

Run 2. (*R*)-(+)-α-Phenylneopentyl alcohol [5.0 g, 30.5 mmol, mp 54–55 °C, $[\alpha]^{26}_D$ +30.1° (0.044 g/mL acetone)] in 61 mL of CCl_4 was refluxed with *n*-Bu_3P (12.4 mL 10.0 g, 49.3 mmole for 48 h. Removal of the excess CCl_4, followed by chromatography over alumina (eluent, 80:20 petroluem ether/benzene) of the residual oil and distillation in vacuo yielded 3.02 g of (*S*)-(−)-α-phenylneopentyl chloride (54%), bp 84–85 °C (7 mm), $[\alpha]^{25}_D$ −106.8° (0.1190 g/mL, THF).

Synthesis and Thermal Decomposition of Chiral α-Phenylneopentyl Chlorocarbonate. Run 1. An ether solution of lithium α-phenylneopentyl alkoxide obtained by treating (*S*)-(−)-α-phenylneopentyl alcohol [10.0 g, 0.0609 mol, $[\alpha]^{23}_D$ −20.1° (0.0409 g/mL, acetone), 66% ee] in 100 mL of dry ether with an equimolar amount of *n*-butyllithium was reacted with phosgene at −60 °C. Filtration of LiCl at room temperature followed by evaporation of the ether produced 12.9 g of (*S*)-(−)-α-Phenylneopentyl chlorocarbonate [93% yield, $[\alpha]^{24}_D$ −24.0° (0.05079 g/mL, CCl_4), $\gamma_{C=O}$ = 1780 cm^{-1}]. Decomposition in boiling dioxane (100 mL, 1 h) followed by removal of the solvent and distillation in vacuo produced 7.0 g of (*S*)-(−)-α-phenylneopentyl chloride[23] [63% yield, $[\alpha]^{25}_D$ −51.1° (0.11925 g/mL THF)], bp 70–75 °C (3 mm).

Run 2. (−)-α-Phenylneopentyl chlorocarbonate was prepared as described in run 1. The reaction mixture was cooled to −60 °C before filtration to separate LiCl. The cooling should minimize the amount of LiCl dissolved in the ether solution of the chlorocarbonate. (−)-2-Phenylneopentyl chlorocarbonate [6.0 g, 0.0265 mol, $[\alpha]^{24}_D$ −24.2° (0.06482 g/mL, CCl_4), 66% ee] was dissolved in 50 mL of dry dioxane and heated under reflux for 1 h. Removal of the dioxane followed by distillation in vacuo of the residue gave 3.1 g of (*S*)-(−)-α-phenylneopentyl chloride, bp 83–84 °C (6 mm), 64% yield, $[\alpha]^{24}_D$ −52.4° (0.12432 g/mL, THF).

Run 3. (−)-α-Phenylneopentyl chlorocarbonate [6.5 g, 0.0287 mol, $[\alpha]^{24}_D$ −24.2° (0.06482 g/mL, CCl_4), 66% ee] prepared as in run 2 were dissolved in 50 mL of dry toluene and boiled for 1 h. Distillation of the toluene at atmospheric pressure followed by distillation in vacuo of the residue afforded 3.3 g of (−)-α-phenylneopentyl chloride, bp 80–85 °C (7 mm), 63% yield, $[\alpha]^{24}_D$ −35.7° (0.08478 g/mL, THF).

The Reaction of (Diphenylmethyl)lithium with (*S*)-(−)-α-Phenylneopentyl Chloride. (*S*)-(−)-α-Phenylneopentyl chloride [2.057 g, 0.0113 mol, $[\alpha]^{25}_D$ −106.8° (THF, 0.1119 g/mL)] in 25 mL of THF was added dropwise over a period of 15 min to (diphenylmethyl)lithium (0.0113 mol) in 20 mL of the THF at room temperature. The mixture was allowed to stir overnight. After workup with aqueous NH_4Cl and ether removal, 3.78 g of an oil was obtained. Column chromatography of the mixture on alumina gave 884 mg of (*R*)-(−)-1,1,2-triphenyl-3,3-dimethylbutane, which was recrystallized from methanol, mp 135–139 °C, $[\alpha]^{26}_D$ −113.3° (0.0128 g/mL CCl_4). The IR and NMR spectra of this sample were identical with those of an authentic sample of the hydrocarbon.[2]

Synthesis of Acetylanthranyl (4). Acetylanthranyl [244 g, bp 144–145 °C (12 mm), mp 78–80 °C, 75.7%) was prepared from 2 mol of anthranilic acid (274 g) and 6 mol of acetic anhydride (618 g, 580 mL) according to the literature directions.[24,25]

Synthesis of α-(*o*-Acetamidophenyl)neopentyl Alcohol.[5] To the Grignard reagent formed by the reaction of 1.65 mol of *tert*-butyl chloride (152.5 g, 180 mL) and 2.0 mol of magnesium (48 g) in 300 mL of dry ether was added dropwise a solution of 86.2 g (0.53 mole of acetylanthranyl in 350 mL of dry benzene. Stirring was continued for 36 h. At the end of this time, the reaction mixture was hydrolyzed with ice/concentrated hydrochloric acid and extracted with 2 × 250 mL of ether. The ether layer was washed once with 250 mL of water followed by 3 × 250 mL of 1 N NaOH and 500 mL of water and dried over magnesium sulfate. Evaporation of the solvent gave 82.4 g of crystals, mp 120–122 °C, 70% yield. Recrystallization from benzene–petroleum ether brought the melting point to 121–123 °C: IR (cm^{-1}) 3400, 3300, 1600; NMR δ 0.86 (s, 9 H), 1.91 (s, 3 H), 4.40 (1 H, s), 4.73 (1 H, s), 6.90–7.25 (m, 3 H), 8.01 (1 H, d, *J* = 7 Hz), 9.91 (s, 1 H). Anal. Calcd for C, H: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.44; H, 8.52; N, 6.26.

Synthesis of α-(*o*-Aminophenyl)neopentyl Alcohol (6). A mixture of 94.7 g of amide **5** (0.43 mol) and 150 mL of Claisen's alkali (50.7 g, 0.903 mol of KOH in 37 mL of H_2O completed to 150 mL with methanol) was refluxed for 23 h. At the end of this time, the reaction mixture was cooled, and extracted twice with ether. The ether extracts were washed with water and brine and dried over potassium carbonate. Removal of the solvent followed by recrystallization of the solid from benzene/petroleum ether gave 70.6 g of crystals: mp 74–75 °C; 92% yield; IR (cm^{-1}) 3434, 3421, 3270 (OH and NH_2); NMR δ 0.93 (s, 9 H), 3.53 (br, 3 H), 4.38 (s, 1 H), 6.50–7.33 (m, 4 H). Anal. Calcd for C, H: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.55; H, 9.45; N, 7.56.

Synthesis of α-[*o*-(*N*-Sulfinylamino)phenyl]neopentyl Chloride (7). To a solution of 61 g (0.34 mol) of **6** in 500 mL of benzene was added dropwise 150 mL of thionyl chloride. A solid was formed. After the addition was completed, the mixture was refluxed for 23 h. Benzene and excess thionyl chloride were distilled. Distillation in vacuo of the residue gave 640 g of an orange liquid: bp 126–128 °C (3 mm); 77% yield; IR (cm^{-1}) 1170 (NSO band); NMR δ 1.05 (s, 9 H), 5.90 (s, 1 H), 7.43–8.17 (m, 3 H), 8.77–8.97 (m, 1 H).

Synthesis of the Hydrochloride Salt of α-(*o*-Aminophenyl)neopentyl Chloride from Sulfinyl Amine 8. Dry HCL was passed for 4 h through a solution of chloro sulfinyl amine **7** (48.1 g, 0.197 mol) in 250 mL of dry ether. The precipitate was washed with dry ether, and 43.5 g of solid (mp 158–160 °C, 94% yield) was collected: IR (cm^{-1}), 2900 (br NH_3^+); NMR δ 1.13 (s, 9 H), 5.48 (s, 1 H), 7.27–7.87 (m, 4 H), 10.8 (br, 3 H). Anal. Calcd: C, 56.42; H, 7.32; N, 5.98; Cl, 30.28. Found: C, 56.16; H, 7.32; N, 5.85; Cl, 30.29.

Resolution of the Ammonium Hydrochloride Salt of α-(*o*-Aminophenyl)neopentyl Chloride. A solution of 12.2 g of the ammonium hydrochloride salt of α-(*o*-aminophenyl)neopentyl chloride (0.0521 mol of **8**) in 100 mL of $CHCl_3$ was mixed with a solution of 6.10 g (0.0261 mol) of (1*S*)-(+)-10-camphorsulfonic acid in 50 mL of $CHCl_3$. Argon was bubbled through the solution to eliminate HCl. After 22 h, 2.8 g of the ammonium hydrochloride (+)-10-camphorsulfonate salt of α-(*o*-aminophenyl)neopentyl chloride (13%, **10**), mp 177–180 °C, was obtained: IR (cm^{-1}) 1745 (C=O), 1620 (C=C); NMR (Me_2SO-d_6) δ 0.80 (3 H, s), 0.92 (3 H, s), 1.07 (9 H, s). Anal. Calcd: C, 58.66; H, 7.50; N, 3.26; Cl, 8.24; S, 7.46. Found: C, 58.80; H, 7.66; N, 3.14; Cl, 8.52; S, 7.61.

Synthesis of (*R*)-(+)-α-Phenylneopentyl Chloride from 10. **10** (1.2 g, 2.79 mmol) was added to 15 mL of concentrated HCl and 10 mL of H_2O at 0 °C. Excess $NaNO_2$ (1.5 g, 21.7 mmol) dissolved in 10 mL of H_2O at 0 °C. Excess $NaNO_2$ (1.5 g, 21.7 mmol) dissolved in 10 mL of H_2O was added to the suspension resulting in the formation of an orange diazonium salt. After the mixture was stirred for 5 min at 0 °C, 30 mL of a precooled 50% solution of H_3PO_2 was added to the diazonium ion solution. After being stirred for 2 h at 0 °C, the reaction mixture was extracted with 3 × 50 mL of ether. The combined organic layers were

(23) The IR and NMR spectra of this sample were identical with those of an authentic sample of racemic α-phenylneopentyl chloride.[2]

(24) Bogert, M. T.; Seil, H. A., *J. Am. Chem. Soc.* **1907**, *29*, 529.

(25) Bogert, M. T.; Gortner, R. A.; Amend, C. G. *J. Am. Chem. Soc.* **1911**, *33* 949.

washed with 3 × 50 mL of saturated $NaHCO_3$ and 50 mL of water, dried over $MgSO_4$, and concentrated in the rotary evaporator to give a brown oil, 784 mg. Chromatography of this oil over 30 g of silica gel with petroleum ether removed the resolving agent and produced two fractions of an oil whose IR and NMR spectra exactly match those obtained earlier in this laboratory[2] for (*R*)-(+)-α-phenylneopentyl chloride, $[\alpha]^{24}_D$ +104.5° (0.0440 g/mL, THF) on fraction 1 (0.440 g, 86.4%): NMR ($CDCl_3$) δ 1.0 (9 H, s, 4.7 (1 H, s), 7.4 (5 H, m).

Run 2. **10** (1.553 g, 3.616 mmol) produced 531 mg (80%) of (+)-**2**, $[\alpha]^{26}_D$ +102°. Bulb-to-bulb short-path distillation at 0.04 torr with warm water heating at 52–55 °C and dry ice/acetone chilling at −50 °C gave an analytical sample whose specific rotation was unchanged, $[\alpha]^{24}_D$ 101° (0.2335 g/15.5 mL, THF). Anal. Calcd for $C_{11}H_{15}Cl$: C, 72.32; H, 8.28; Cl, 19.41. Found: C, 71.41, 71.40; H, 8.18, 8.17; Cl, 18.72, 18.86. Gas chromatographic analysis of this sample (8ft, 3% OV 101) in a H-P 5880 A instrument showed two trace impurities in addition to (+)-**2**. The ^1H NMR integrated correctly and redistillation failed to remove the impurities. The $[\alpha]^{26}_D$ of +113° (68.9 mg/20 mL acetone) suggests that rotations in acetone are greater than in THF.

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Registry No. (±)-**1**, 57377-60-3; (+)-(*R*)-**1**, 23439-91-0; (*S*)-**1** (lithium alkoxide), 100702-90-7; (*S*)-**1** (chloro carbonate), 100837-35-2; (+)-(*S*)-**2**, 100895-65-6; (*R*)-**2**, 82323-56-6; **3**, 118-92-3; **4**, 525-76-8; (±)-**5**, 100702-92-9; (±)-**6**, 100702-93-0; (±)-**7**, 100702-94-1; (±)-**8**, 100702-95-2; (*R*)-**10**, 100702-97-4; Bu_3P, 998-40-3; CCl_4, 56-23-5; (*R*)-$(C_6H_5)_2CHCH(C_6H_5)C(CH_3)_3$, 100702-91-8; $(C_6H_5)_2CHLi$, 881-42-5; *t*-BuCl, 507-20-0.

Reactions of 2-Halothiazoles with Ketone Enolates and Nitrile Carbanions[1a]

Samuel C. Dillender, Jr.,[1b] Thomas D. Greenwood, Mukta S. Hendi, and James F. Wolfe*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

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Photostimulated reactions of 2-chlorothiazole (**1a**), 2-chloro-4-methylthiazole (**1b**), and 2-chloro-5-methylthiazole (**1c**) with pinacolone potassium enolate (**2a**) in liquid NH_3 lead to formation of mono- and bis-2-thiazolyl ketones **3a–c** and **4a–c** via the $S_{RN}1$ mechanism. A similar reaction with 2-bromothiazole (**1d**) gave **3a** but no **4a**. Reaction of **1a** with **2a** in the dark, or with the potassium enolate of diisopropyl ketone (**2b**) under near-UV irradiation or in the dark, does not result in chloride displacement. Instead, carbinols **5a–b**, derived from initial ionization of H_5 of **1a** followed by aldol-type condensation of the resulting carbanion (**11**) with neutral ketone, are produced in good yields. Carbanion **11** can also be produced in synthetically useful concentrations by metalation of **1a** with KNH_2, *n*-BuLi, and LDA, with the latter base being most effective. Carbanions derived from acetonitrile, propionitrile, and phenylacetonitrile react smoothly with **1a** in liquid NH_3 to give the corresponding monosubstitution products resulting from chloride displacement. However, these reactions appear to proceed by an addition–elimination (S_NAr) mechanism rather than an $S_{RN}1$ process.

In a continuing study[2] of heteroaromatic nucleophilic substitution reactions which take place via a radical chain ($S_{RN}1$)[3] process, we have begun to investigate the suitability of halogenated π-excessive heterocycles as substrates in such reactions. Although the participation of various classes of π-deficient heterocycles in $S_{RN}1$ reactions has now been demonstrated,[2] the only π-excessive substrates studied thus far are the 2- and 3-halothiophenes.[4] We now wish to describe the results of an investigation in which 2-halothiazoles **1a–d** were employed as π-excessive substrates in reactions with ketone enolate and nitrile carbanion nucleophiles.

Results

Reactions with Ketone Enolates. Photostimulated reaction of 2-chlorothiazole (**1a**) with 4 equiv of the potassium enolate of pinacolone (**2a**), generated by means of KNH_2 in liquid NH_3, afforded a 53% yield of monosubstitution product **3a** along with 25% of disubstitution product **4a** (exp 1, Table I). 2-Bromothiazole (**1d**) reacted similarly to give a 44% yield of **3a**, but no **4a** was found to be present by TLC or ^1H NMR analysis (expt 2).

When denied the catalytic effect of near-UV illumination, reactions of **1a** with enolate **2a** and with the potassium enolate of diisopropyl ketone (**2b**) took a decidedly different course. Thus, exposure of **1a** to excess **2a** in the dark gave carbinol **5a** in 70% isolated yield (expt 3). Addition of 10 mol % of the radical scavenger, di-*tert*-butyl nitroxide (DTBN)[5] to an illuminated reaction of **1a** with

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