($CDCl_3/Me_4Si$) δ 7.27 (s, C_6H_5), 5.38 (s, OCH); mass spectrum, *m/e* 349.1570 (calcd for deprotonated parent $C_{26}H_{20}O$ 349.1591), 272.1179 (calcd for $C_{20}H_{16}O$ fragment 272.1200), 183.0794 (calcd for $C_{13}H_{11}O$ fragment 183.0809), 167.0849 (calcd for $C_{13}H_{11}$ fragment 167.0861). Anal. Calcd for $C_{26}H_{27}O$: C, 89.11; H, 6.33. Found: C, 88.98; H, 6.36.

The hexane mother liquors were filtered and evaporated, and the residue was distilled in a Kugelrohr apparatus at 75 °C (0.1 mm) to give colorless liquid product **3d**. Fluorodiphenylmethane has the following: bp 75 °C (0.1 mm) [lit. bp 105–108 °C (2 mm),[8a] 110–113 °C (1 mm[8b])]; IR ($CHCl_3$) ν_{max} 3040, 3000, 2870, 1650, 1590, 1505 cm^{-1}; UV (isooctane) λ_{max} 252 nm (ε 465), 258 (515), 264 (395); ^1H NMR ($CDCl_3/Me_4Si$) δ 7.20 (m, C_6H_5), 6.35 (d, *J* = 48 Hz, CHF) [lit.[8b] δ 7.3, 6.4 (d, *J* = 48 Hz)]; ^{19}F NMR ($CDCl_3/CFCl_3$) δ −167.34 (d, *J* = 48 Hz, CHF). Anal. Calcd for $C_{13}H_{11}F$: C, 83.84; H, 5.95. Found: C, 83.54; H, 6.40.

Fluorotriphenylmethane. Similar treatment of triphenylcarbinol (6.5 g, 25 mmol) with DAST (25 mmol) gave 6.5 g of crude fluoride; no trace of bis(triphenylmethyl) ether[9] was detected by ^1H NMR. The crude product was recrystallized from 50 mL of hexane; yield 5.57 g (21.2 mmol, 85%). The analytical sample was recrystallized again and dried at 25 °C (0.1 mm). Pure fluorotriphenylmethane has the following: mp 102–103 °C (lit. mp 103–104,[10a] 105–106 °C[10b]); IR ($CHCl_3$) ν_{max} 3040, 1590, 1570, 1480, 1440 cm^{-1}; UV (EtOH) λ_{max} 252 nm (ε 560), 258 (710), 264 570); ^1H NMR ($CDCl_3/Me_4Si$) δ 7.25 (s) C_6H_5; ^{19}F NMR ($CDCl_3/CFCl_3$) δ −126.67 (s, C–F; lit.[10b] δ 49.6 from CF_3CO_2H); mass spectrum, *m/e* 262.1150 (calcd for $C_{19}H_{15}F$ parent 262.1157), 185.0759 (calcd for $C_{13}H_{10}F$ fragment 185.0766), 165.0695 (calcd for $C_{13}H_9$ fragment 165.0704). Anal. Calcd for $C_{19}H_{15}F$: C, 86.99; H, 5.76. Found: C, 86.92; H, 5.81.

Registry No. **1a**, 1210-34-0; **1b**, 10354-00-4; **1c**, 1689-64-1; **1d**, 91-01-0; **2a**, 83693-20-3; **2b**, 35066-77-4; **2c**, 31859-93-5; **2d**, 574-42-5; **3c**, 20825-90-5; **3d**, 579-55-5; DAST, 38078-09-0; fluorotriphenylmethane, 427-36-1; triphenylcarbinol, 76-84-6.

(8) (a) Mindl, J.; Pivoňka, P.; Večeřa, M. *Collect. Czech. Chem. Commun.* **1972**, *37*, 2568. (b) Zieger, H. E.; Angres, I.; Mathisen, D. *J. Am. Chem. Soc.* **1976**, *98*, 2580.

(9) (a) Gomberg, M. *J. Am. Chem. Soc.* **1913**, *35*, 205. (b) Halford, J. O. *Ibid.* **1929**, *51*, 2159.

(10) (a) Commercially available from Cationics Inc. (b) Rozhkov, I. N.; Knunyants, I. L. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1972**, 1223. (c) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 786.

(11) Correspondence should be addressed to the Biochemicals Department, Pharmaceuticals Division, Building 353, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, DE 19898.

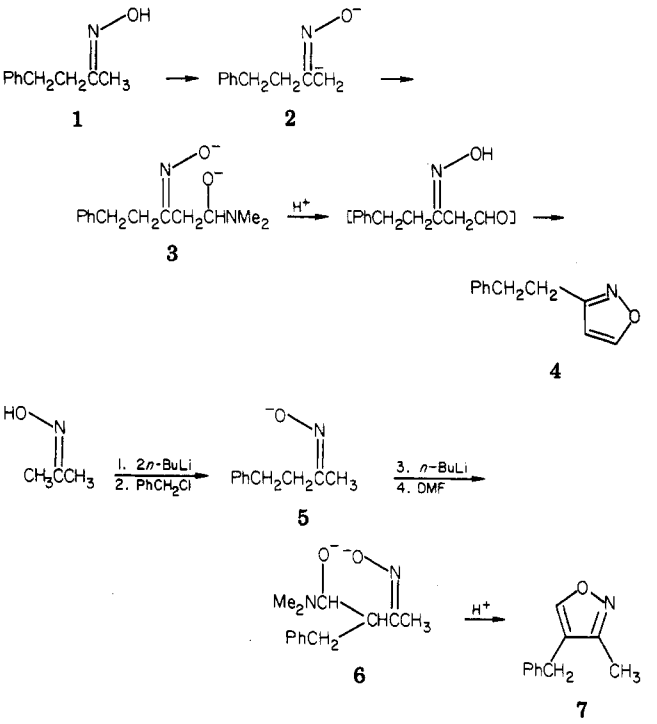
Regiospecific Synthesis of 3-Substituted 5-Alkylisoxazoles by Modification of the Dilithio Oxime Route to Isoxazoles

Dennis H. Hoskin and R. A. Olofson*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received June 7, 1982

A useful regiospecific synthesis of unsymmetrical[1] isoxazoles from oximes is described in a recent publication from this laboratory.[2] The method is illustrated by the conversion of benzylacetone oxime (**1**) to the isoxazole (**4**, 91% overall yield distilled) by deprotonation of **1** with *n*-BuLi to form the *syn*-dilithio salt (**2**), which is acylated by DMF to give **3**. The latter subsequently is cyclized to **4** with hot aqueous acid. In a variant of the above route, the isomeric isoxazole (**7**) has been obtained in 82% pure



yield by successive treatment of acetone oxime with (1) 2*n*-BuLi, (2) $PhCH_2Cl$, (3) *n*-BuLi, (4) DMF, and (5) H^+.

Crucial to the utility and success of these processes are the following facts: (A) Of the two possible oxime geometrical isomers, only the less hindered (e.g., **1**) usually is obtained on reaction of ketones with hydroxylamine.[3] However, products from the more hindered isomer are available by the second scheme depicted (i.e., via **5**). (B) Oxime anions and dianions retain their stereochemical integrity, and deprotonation affords syn products exclusively (e.g., **2**, **3**, and **6**).[4] (C) Adducts such as **3** (**6**) do not split off Me_2NH until acid treatment.[5]

The methodology above is especially valuable for the synthesis of many kinds of historically difficult to obtain unsymmetrical isoxazoles (e.g., 3-substituted, 4-substituted/unsubstituted, 5-unsubstituted or -aryl[6]). Thus, its availability substantially extends the utility of isoxazoles as precursors, intermediates, and reagents in preparative organic chemistry, an area in which this ring system already is preeminent vs. other heteroaromatic systems.[7]

5-Alkylisoxazoles with 3-substituents (4-substituted/unsubstituted) are the most important class of unsymmetrical isoxazoles not accessible by the processes of Barber and Olofson and which cannot be made easily by older routes. Here, the oxime schemes fail because the dianion preferentially abstracts a proton from the amide reactant to yield an enolate instead of adding to the amide carbonyl (→ **3**). In this paper, we report variants of the Barber–Olofson methods that largely avoid this problem and afford 5-alkylisoxazoles in moderate yield.

Success requires reversing the selectivity of the dianion to favor carbonyl addition (b in **8**) instead of deprotonation (a in **8**). We thought this could be achieved by significantly increasing the electrophilicity of the carbonyl carbon of the acylating agent. Then attack at that carbon should

(1) Defined as when the substituents on C_3 and C_5 are different. Classical isoxazole syntheses from $RCOCH_2COR^1$ usually yield isomer mixtures.

(2) Barber, G. N.; Olofson, R. A. *J. Org. Chem.* **1978**, *43*, 3015.

(3) Without stereospecificity, oximes would be poor derivatives in classical qualitative organic analysis; see ref 2.

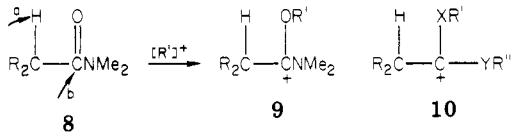
(4) For rationalizations and evidence, see ref 2.

(5) Otherwise an equivalent of **2** would be destroyed by reaction with the more acidic β-dicarbonyl-type species thus formed.

(6) For recent review and references to earlier reviews, see Wakefield, B. J.; Wright, D. J. *Adv. Heterocycl. Chem.* **1979**, *25*, 147.

(7) For highlights, see ref 6 and footnote 2 in ref 2.

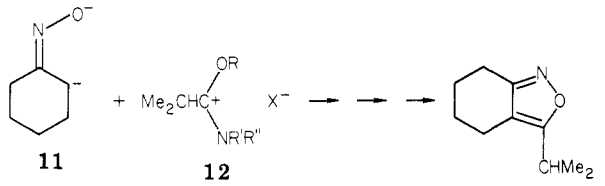
0022-3263/82/1947-5222$01.25/0



8 9 10

be more likely because the reaction would be more exothermic and thus more sensitive to ground-state charge distribution (vs. relative reaction thermodynamics, Hammond postulate). However, any change in acylating agent (vs. **8**) to enhance C electrophilicity must not also facilitate elimination of a leaving group from the adduct (e.g., **3**).[5] Within this restriction, it was concluded that the most promising acylating agent for testing would be the cation **9** or the more general species **10**.

In the first model experiments, the reaction of dilithiocyclohexanone oxime (**11**) with excess O-methyl salt



11 12 13

a, R = R′ = R″ = Me; $X^- = FSO_3^-$
b, R = R′ = R″ = Me; $X^- = CF_3SO_3^-$
c, R = Me; R′ = R″ = Et; $X^- = FSO_3^-$
d, R = Me; R′ = Et; R″ = Ph; $X^- = FSO_3^-$
e, R = Me; R′ = R″ = *n*-Bu; $X^- = FSO_3^-$
f, R = Et; R′ = R″ = *n*-Bu; $X^- = BF_4^-$

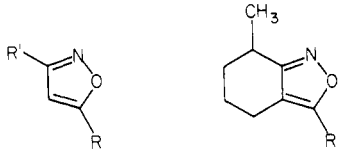
(**12a**) was studied. We obtained the latter as a solid by mixing *N,N*-dimethylisobutyramide (**14**) with commercial $MeOSO_2F$. In this test, the yield of isoxazole (**13**) after an otherwise standard Barber–Olofson reaction and workup was only 28%, and the distilled product was contaminated with much amide (**14**). Still, this was a major improvement over the control experiment wherein no isoxazole was found using the amide (**14**) as the acylating reagent. Several experiments varying reactant ratio, concentration, time and direction of addition, solvent, and other factors failed to improve the situation: inverse addition (add **11** to **12a**) was particularly bad (11% yield), and the presence of some amide (**14**) in the salt (**12a**) only reduced the yield slightly.

The main problem was the insolubility of **12a** in the preferred nonpolar reaction solvents (DME or THF) and the reduced efficiency of the process when dipolar aprotic cosolvents (e.g., HMPT) were included in the mixture. The limitations on solvent choice led to efforts to structurally modify **12a** to reduce its polarity and thus increase its solubility in the reaction medium. An optimum site for such modification would be the Me_2N moiety, a group destined for discard in the reaction sequence and which ordinarily would not be present in the commercial precursor to **12**. No improvement was realized with **12b–d**. However, the economical and lipophilic di-*n*-butylamino salt (**12e**) dissolved in ethers, and the yield of **13** increased to 41% in THF and 53% in DME.

O-Demethylation of **12a–e** seemed to be a significant side reaction. To inhibit this S_N2 displacement, we tested *O*-ethyl salt (**12f**), and with this reactant, the yield of **13** rose to 65%. In the early studies, $Et_3O^+BF_4^-$ was utilized as the reagent for introduction of the *O*-ethyl substituent. In later work, commercial $EtOSO_2CF_3$ was employed with similar success, but $EtOSO_2F$ gave inferior results. The O-dealkylation side reaction has a special disadvantage when N-*n*-Bu_2 salts are used as the acylating reagents because the side product, *N,N*-dibutyl amide, often co-distills with the desired isoxazole. To eliminate this complication, we devised a special workup in which the product mixture was treated with $LiAlH_4$ to reduce the amide to the tertiary amine, which then was separated from the desired isoxazole by acid extraction (no amide left).[8] (The only other occasional product contaminant was the starting oxime. When this codistilled with the isoxazole, we could readily remove it by passing the mixture through a short basic alumina plug.)

In the hope that varying the ground-state charge distribution and heteroatom stabilization of the cation would reduce side reactions, we prepared other potential acylating salts and tested them in the isoxazole-forming reaction. With $Me_2CHC(SR)NR_2^+$, the yields of **13** were inferior, and with the analogous 4,4,5,5-tetramethyl-1,3-dioxolenium, 1,3-dimethylimidazolinium, and 3,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazinium cations, no isoxazole was found.[9]

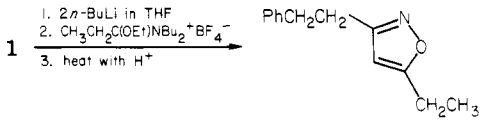
In tests of the scope and limitations of the new isoxazole synthesis, the 3-arylisoxazole (**15a**) was isolated in 41%



15a, R = $CH(CH_3)CH_2CH_3$; R′ = C_6H_5
b, R = $CH(CH_2CH_3)_2$; R′ = CH_3

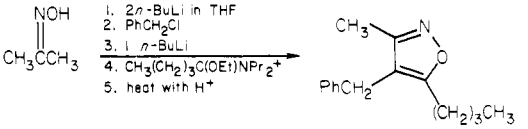
16a, R = $CH(CH_3)_2$
b, R = CH_3

yield, **15b** in 47% yield, and **16a** in 27% yield from the requisite $RC^+(OEt)NBu_2$ salts. The reduced yields vs. **13** derived, at least in part, from the need to use THF instead of the preferred DME to achieve dilithiation of the oxime precursors. In DME, the solubilities of the lithio oximes were too poor to permit dilithiation to proceed to completion. To demonstrate the regiospecificity of the new process, we prepared the phenethylisoxazole (**17**) in 17%



17

overall yield from benzylacetone oxime by the indicated series of steps. None of the isomeric 4-benzyl-5-ethyl-3-methylisoxazole was found. In another test of regiospecificity combined with introduction of an extra substituent (vide supra), the isoxazole (**18**) was obtained in 18% overall



18

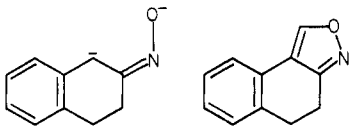
yield from acetone oxime by the five-step reaction sequence depicted. Again the product was not contaminated with any isomeric isoxazole. The lower yields of **17** and **18** vs. **15a,b** and **16a** are probably a consequence of an enhanced deprotonation side reaction (type a in **9**) in primary alkyl

(8) Isoxazoles do not react with $LiAlH_4$ and also are only very weakly basic.

(9) For a complete discussion of this work along with additional experimental data, see Hoskin, D. H. Ph.D. Thesis, The Pennsylvania State University, University Park, PA, 1981.

salts vs. the secondary alkyl salts used in the earlier syntheses. Failure to obtain any 5-methylisoxazole (**16b**) from $CH_3C(OEt)NBu_2^+$ is in accord with this rationalization.

Another useful application was found for the methodology introduced here. The Barber–Olofson process does not work (unpublished results) for delocalized dilithio oximes such as **19** because these species are too stable and



19

20

unreactive to be attacked by DMF (or benzamides). When the reaction was performed with the more electrophilic $HC(OMe)NMe_2^+FSO_3^-$ or $HC(OEt)NMe_2^+BF_4^-$, the 5-unsubstituted isoxazole (**20**) was regiospecifically formed in 41–62% overall yield from β-tetralone oxime.

The overall yields in the above reaction sequences sometimes are only modest. However, the reactants are readily available, and, in summary, it should be noted that the new process reported here is among the first known regiospecific routes to isoxazoles with the substitution patterns exemplified by **13**, **15a,b**, **16–18**, and **20**.[6,10] In the past, it has usually proved impossible to isolate such isoxazoles pure.[6]

Experimental Section[9,11]

All ground glassware utilized in the preparation and subsequent acylations of the dilithio oximes was dried in an oven at 150 °C, assembled while warm, and allowed to cool under a stream of dry N_2. The apparatus was designed to ensure that all subsequent reactions were performed under a slight N_2 pressure. When used as reaction solvents, the THF and 1,2-dimethoxyethane (DME) were refluxed over and distilled from $LiAlH_4$ just before use. Commercial *n*-butyllithium in hexane (ca. 2 M) and MeLi in ether (1–2 M) were analyzed as in ref 2. Oxime and amide precursors either were obtained commercially or made by standard methods.[12] Only optimum processes are included here. Other experimental variations outlined under Discussion are given in ref 9.

5-Isopropyl-3,4-tetramethyleneisoxazole (13). General Process. A solution of $Et_3O^+BF_4^-$ (9.0 g, 0.05 mol) and *N,N*-di-*n*-butylisobutyramide (11 g, 0.054 mol) in CH_2Cl_2 (10 mL) was left overnight and then evaporated at reduced pressure, and the residue was triturated 3 times with hexanes. Residual solvent was evaporated, and the salt (**12f**) thus obtained as a hygroscopic oil (15 g, 95% yield) was used without further purification: ^1H NMR (CD_3CN) δ 4.80 (q, 2 H, J = 7 Hz), 3.9–3.3 (m, 5 H), 1.8–1.2 (m, 17 H), 1.2–0.8 (m, 6 H).

n-BuLi (20 mL, 0.047 mol) was added over 25 min to a stirred, cooled (0 °C) solution of cyclohexanone oxime (2.40 g, 0.021 mol) in DME (40 mL). As the first *n*-BuLi equivalent was added, a white solid precipitated, but this almost all dissolved as addition was completed. Stirring was continued for 1 h, and then **12f** (10 g, 0.03 mol) in DME (20 mL) was added (75 min) to the reaction mixture. This was allowed to warm to room temperature and stirred overnight. Next, the mixture was poured into a rapidly stirred solution of concentrated H_2SO_4 (9 g), diluted with 4:1 THF/H_2O (62 mL total, 1.5 M in H_2SO_4). Hydrolysis, cyclization, and dehydration to **13** was completed by refluxing the mixture 1.5 h. Separation of the aqueous from the organic phase of the cooled mixture was followed by careful addition of solid $NaHCO_3$ (along with enough water to dissolve precipitated salts) to the aqueous extract until the solution was ca. pH 8. The aqueous solution then was extracted with hexanes (3 × 30 mL) (without delay since a flocculent solid slowly forms and causes emulsification during extraction). We continued the workup by combining the hexane extracts with the initial organic phase and washing successively with 5% aqueous $NaHCO_3$ (2 × 25 mL), 2% aqueous HCl (20 mL), water (2 × 20 mL), and brine (20 mL). The dried ($MgSO_4$) solution was fractionally distilled to give a fraction [bp 75–79 °C (0.6 mm), 4.2 g] that analyzed (GC) as a 55:45 mixture of **13** and dibutylisobutyramide.

Removal of the amide contaminant was effected by dripping (30 min) the isoxazole/amide mixture in THF (17 mL) into a stirred slurry of $LiAlH_4$ (0.4 g, 0.01 mol) in THF (17 mL). Stirring was continued for 3 h and then the mixture was refluxed for 1 h and finally left at room temperature overnight before the slow addition of water to destroy the excess $LiAlH_4$. Then, acidification to pH 3 with 10% aqueous HCl and dilution with hexanes (80 mL) was followed by separation. The organic layer was washed with 5% aqueous HCl (17 mL), water (8 mL), 10% aqueous K_2CO_3 (8 mL), water (8 mL), and brine (17 mL), dried ($MgSO_4$), rotoevaporated, and vacuum distilled to give 2.3 g (64% yield) of pure **13** (clear oil): bp 73.5–74.5 °C (0.6 mm) (before the final distillation the oil already was 96% pure, GC); ^1H NMR (CCl_4) δ 1.23 (d, 6 H, J = 7 Hz), 1.4–1.9 (m, 4 H), 2.2–2.7 (m, 4 H), 2.96 (septet, 1 H, J = 7 Hz); mass spectrum (70 eV), m/e (relative intensity) 165 (100, M^+), 150 (20), 136 (10), 122 (67), 94 (12), 80 (24), 71 (24); high-resolution mass spectrum, m/e 165.1146 ($C_{10}H_{15}NO$ requires 165.1154).

3-Isopropyl-7-methyl-4,5,6,7-tetrahydro-2,1-benzisoxazole (16a). Compound **12f** (0.087 mol) in DME (55 mL) was added (40 min) to a stirred THF (110 mL) solution of the dilithio oxime from 2-methylcyclohexanone oxime (0.06 mol) and *n*-BuLi (0.12 mol) at 0 °C. Reaction and workup as above (including the $LiAlH_4$ step) afforded pure **16a** (27% yield, clear oil): bp 74–81 °C (0.6 mm); ^1H NMR (CCl_4) δ 0.8–2.1 (m, 13 H with ca. 6 H d at 1.23, J = 7 Hz, and ca. 3 H d at 1.26, J = 7 Hz), 2.1–2.7 (m, 3 H), 2.98 (septet, 1 H, J = 7 Hz); mass spectrum (70 eV), m/e (relative intensity), 179 (65, M^+), 164 (12), 124 (100); high-resolution mass spectrum, m/e 179.1302 ($C_{11}H_{17}NO$ requires 179.1310).

3-Phenyl-5-(1-methylpropyl)isoxazole (15a). Reaction of CF_3SO_3Et with $EtCH(Me)C(O)N(n\text{-}Bu)_2$ in CH_2Cl_2 overnight afforded crude $EtCH(Me)C(OEt)NBu_2^+CF_3SO_3^-$ in quantitative yield after workup as in the synthesis of **12f**. Standard reaction of the new salt in DME with dilithioacetophenone oxime in THF and workup (including $LiAlH_4$ step and passing the $LiAlH_4$ product through a short basic alumina plug to remove an oxime contaminant) gave pure **15a** in 41% yield (clear oil): bp 120–124 °C (1.1 mm); ^1H NMR (CD_3CN) δ 0.84 (t, 3 H, J = 7 Hz), 1.21 (d, 3 H, J = 7 Hz), 1.2–1.9 (m, 2 H), 2.78 (sextet, 1 H, J = 7 Hz), 6.16 (s, 1 H), 7.1–7.4 (m, 3 H), 7.6–7.9 (m, 2 H); mass spectrum (70 eV), m/e (relative intensity) 201 (32, M^+), 173 (6), 144 (100); high-resolution mass spectrum m/e 201.1151 ($C_{13}H_{15}NO$ requires 201.1153).

3-Methyl-5-(1-ethylpropyl)isoxazole (15b). Standard reaction of $Et_2CHC(OEt)NBu_2^+CF_3SO_3^-$ with dilithioacetone oxime ($LiAlH_4$ step and alumina filtration unnecessary) in THF afforded **15b** in 47% yield (clear oil): bp 78 °C (10 mm); ^1H NMR (CCl_4) δ 0.83 (t, 6 H, J = 7 Hz), 1.3–1.9 (m, 4 H), 2.17 (s, 3 H), 2.62 (pentet, 1 H, J = 7 Hz), 5.72 (s, 1 H); mass spectrum (70 eV), m/e (relative intensity) 153 (58, M^+), 125 (100), 124 (80); high-resolution mass spectrum, m/e 153.1167 ($C_9H_{15}NO$ requires 153.1153).

3-(2-Phenylethyl)-5-ethylisoxazole (17). Standard reaction of $EtC(OEt)NBu_2^+BF_4^-$ with the dilithio salt of 1[2] (including the $LiAlH_4$ and alumina steps) gave pure **17** (clear oil) in 17% yield, bp 104–107 °C (0.5 mm) (another 3% in a second alumina fraction); ^1H NMR ($CDCl_3$) δ 1.12 (t, 3 H, J = 7.5 Hz), 2.54 (q, 2 H, J = 7.5 Hz), 2.83 (s, 4 H), 5.63 (s, 1 H), 7.08 (s, 5 H); mass spectrum (70 eV), m/e (relative intensity) 201 (43, M^+), 104 (45), 91 (100); high-resolution mass spectrum, m/e 201.1164 ($C_{13}H_{15}NO$ requires 201.1153).

4-Benzyl-5-butyl-3-methylisoxazole (18). Acetone oxime in THF was reacted successively with BuLi (2 equiv), benzyl chloride (1 equiv), and BuLi (1 equiv) as in ref 2 and then treated with $BuC(OEt)NPr_2^+BF_4^-$ in DME in the standard reaction

(10) For a complementary new route, see Brunelle, D. J. *Tetrahedron Lett.* **1981**, *22*, 3699.

(11) For list of apparatus used in physical and spectral measurements, see Olofson, R. A.; Cuomo, J. *J. Org. Chem.* **1980**, *45*, 2538.

(12) New amides (spectral and analytical data in ref 9): $Me_2CHC(O)NBu_2$, bp 90–91 °C (1.1 mm); $Me_2CHC(O)N(Et)Ph$, bp 77.5–78.5 °C (0.5 mm); $EtCHMeC(O)NBu_2$, bp 86–88 °C (0.6 mm); $Et_2CHC(O)NBu_2$, bp 95–97.5 °C (0.2 mm); $EtC(O)NBu_2$, bp 78 °C (0.6 mm); $BuC(O)NPr_2$, bp 81–82 °C (0.5 mm).

($LiAlH_4$ and alumina steps). Compound **18** was obtained in 18% overall yield: bp 120–123 °C (0.6 mm); ^1H NMR (CCl_4) δ 0.7–1.9 (m), 1.92 (s, 3 H), 2.4–2.8 (m, 2 H), 3.57 (s, 2 H), 6.6–7.3 (m, 5 H); high-resolution mass spectrum, *m/e* (relative intensity) 229.1458 (100, M^+) ($C_{15}H_{19}NO$ requires 229.1467).

4,5-Dihydronapth[2,1-*c*]isoxazole (20). Crude **20** was made by standard formation[2] of a THF solution of the dilithio salt of β-tetralone oxime and then reaction with a solution of $Me_2NCHOMe^+FSO_3^-$, which we made by stirring FSO_3Me with DMF (2 equiv) and then diluting with 0.5 volume of DME. Hydrolysis, cyclization, dehydration, and workup (no $LiAlH_4$ or alumina) yielded a distillation fraction that analyzed (NMR) as 80% pure. An ether solution of this was titrated with CF_3SO_3H, yielding a solid which was triturated with more ether. The solid was partitioned between water and ether, the layers were separated, and the aqueous solution was extracted with more ether. The combined ether extracts were washed with water, dried (Na_2SO_4), and evaporated to give pure **20** in 62% yield (clear oil): bp 112–117 °C (0.3 mm); ^1H NMR (CCl_4) δ 2.79 (s, 4 H), 6.9–7.6 (m, 4 H), 8.38 (s, 1 H); high-resolution mass spectrum, *m/e* (relative intensity) 171.0683 (100, M^+) ($C_{11}H_9NO$ requires 171.0684). When $Me_2NCHOEt^+BF_4^-$ was used as the acylating agent, the crude **20** was obtained in 41% estimated yield (61% pure).

Acknowledgment. We thank the National Institutes of Health for the grant (GM 13980) that supported this research.

Registry No. **1**, 6944-54-3; **11**·2Li$^+$, 83665-90-1; **12a**, 83665-93-4; **12b**, 83665-94-5; **12c**, 83665-96-7; **12d**, 83665-98-9; **12e**, 83666-00-6; **12f**, 83681-31-6; **13**, 83666-01-7; **15a**, 83666-02-8; **15b**, 83666-03-9; **16a**, 83666-04-0; **17**, 83666-05-1; **18**, 83666-06-2; **19**·2Li$^+$, 83681-29-2; **20**, 83666-07-3; $EtCH(Me)C(OEt)NBu_2^+CF_3SO_3^-$, 83666-09-5; $Et_2CHC(OEt)NBu_2^+CF_3SO_3^-$, 83666-11-9; $EtC(OEt)NBu_2^+BF_4^-$, 83666-13-1; $BuC(OEt)NPr_2^+BF_4^-$, 83666-15-3; $Me_2NCHOMe^+FSO_3^-$, 83666-16-4; dilithio-2-methylcyclohexanone oxime, 83666-17-5; dilithioacetophenone oxime, 79043-01-9; dilithioacetone oxime, 83665-91-2.

Following the Course of Resolution of Carboxylic Acids by ^{13}C NMR Spectrometry of Amine Salts

Francis X. Webster, Xiao-nong Zeng, and Robert M. Silverstein*

Department of Chemistry, College of Environmental Science & Forestry, Syracuse, New York 13210

Received March 15, 1982

Resolution of a racemic carboxylic acid by recrystallization of its salt with an amine enantiomer, such as (−)-quinine, is frequently the method of choice, especially on a large scale.[1] Resolution is followed by decomposition of the salt and determination of the optical rotation on a weighed sample of the regenerated carboxylic acid; the steps are repeated to constant optical rotation. The procedure is tedious, and assignment of enantiomeric purity by optical rotation requires confirmation, usually by HPLC or GC separation of diastereomeric derivatives or by means of NMR spectrometry with chiral shift reagents.[2]

Although ^{13}C NMR spectrometry has been used to measure diastereomeric ratios of covalent compounds,[3,4] we now report that ^{13}C NMR spectrometry of solutions of amine salts affords a direct, facile procedure for determining enantiomeric composition throughout the resolution procedure. Obviously, this procedure is also applicable to the resolution of racemic amines and of racemic alcohols through the half-ester with phthalic anhydride. However, the procedure is not necessarily applicable to all combinations of carboxylic acids and amines; our studies were limited to quinine salts, but the procedure was successful in every case.

Table I. Chemical Shifts for a Pair of Peaks Representing Corresponding Carbon Atoms in Diastereomeric Quinine Salts

compound	no.	chem shifts, Hz
2-ethylhexanoic acid	1	2448.7, 2431.9[a]
2-methylbutanoic acid	2	353.3, 350.4[b]
2-phenylpropanoic acid	3	1807.1, 1767.8[a,d]
trans-phenylcyclopropanecarboxylic acid	4	1582.7, 1525.4[a,d]
2-phenylbutanoic acid	5	366.5, 361.0[b]
3-phenylbutanoic acid	6	754.9, 752.5[b]
2-cyclopenteneacetic acid	7	867.4, 859.0[b]
3-methyl-5-oxo-3-cyclohexene-1-carboxylic acid	8	4071.1, 4065.3[c,d]
tetrahydro-5-oxo-2-furancarboxylic acid	9	2448.7, 2431.9[a]

[a] Bruker widebore WM-360. [b] Varian CFT-20. [c] Varian XL-100. [d] We confirmed that this pair of peaks represented corresponding carbon atoms of the diastereomeric salts by following the change in ratio of peak intensities during the course of resolution.

Table II. Comparison of Enantiomeric Ratios of 2-Phenylpropanoic Acid (3) to Diastereomeric Ratios of Its Quinine Salt

recrystn no.	$[\alpha]^{22}_D$, deg, for acid[a]	ratio of acid enantiomers	ratio of diastereomeric salts
1	−15.5 (*c* 1.188, EtOH)	59.8/40.2	59.0/41.0
2	−44.3 (*c* 1.394, EtOH)	78.0/22.0	79.0/21.0
3	−58.7 (*c* 1.002, EtOH)	87.0/13.0	88.1/11.9
4	−70.8 (*c* 1.340, EtOH)	94.8/5.2	96.5/3.5

[a] The pure (−) acid has a specific rotation of −79.1° (*c* 1.567, EtOH).

Results and Discussion

We obtained NMR spectra of the quinine salts of nine carboxylic acids (Table I) on a Varian CFT-20, a Varian XL-100, and a Bruker Widebore WM-360. Compounds **1–7** were chosen because they were commercially available and had previously been resolved.[5-11] Compounds **8** and **9** were chosen because we were interested in obtaining the enantiomers for another study. In each case, at least one pair of peaks was found for the corresponding carbon atoms in each diastereomer. We followed the course of resolution of compounds **3** and **4** by determining the ratio of the diastereomeric salts, after each recrystallization,

(1) Wilen, S. H. "Tables of Resolving Agents and Optical Resolutions"; University of Notre Dame Press: Notre Dame, IN, 1972.
(2) Wilen, S. H.; Collet, A.; Jaques, J. *Tetrahedron* **1977**, *33*, 2725.
(3) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081.
(4) Heimstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183.
(5) Shecter, H.; Brain, D. K. *J. Am. Chem. Soc.* **1963**, *85*, 1806.
(6) Odham, G. *Ark. Kemi* **1963**, *20*, 507.
(7) Fredga, A. *Ark. Kemi* **1954**, *7*, 241.
(8) Inouye, Y.; Sugita, T.; Walborsky, H. M. *Tetrahedron* **1964**, *20*, 1695.
(9) Pettersson, K. *Ark. Kemi* **1956**, *10*, 283.
(10) Weidler, A. M.; Bergson, G. *Acta Chem. Scand.* **1964**, *18*, 1483.
(11) Mislow, K.; Steinberg, I. V. *J. Am. Chem. Soc.* **1955**, *77*, 3807.

0022-3263/82/1947-5225$01.25/0