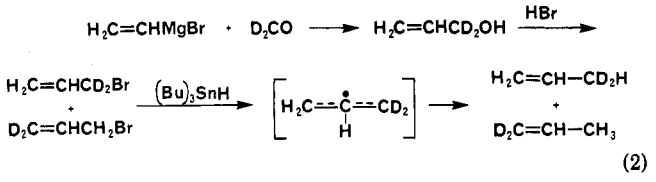
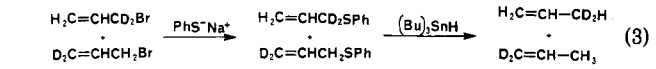
Dideuterioallyl bromide was prepared as shown in eq 2 and was reduced at 50 °C by tributyltin hydride in a radical-chain process. The propene was trapped at low



(2)

temperature in toluene-d_8 and the ratio of 1,1- to 3,3-dideuteriopropene was determined by NMR. Hydrogen atom abstraction is favored at the CH_2 terminus of the 1,1-dideuterioallyl radical by a factor of 1.056 ± 0.002.

Dideuterioallyl phenyl sulfide was prepared from the bromide and was reduced by tributyltin hydride at 78 °C.[4] The deuterium distribution in the resulting propene indicated a preference for hydrogen atom abstraction at the CH_2 terminus of the 1,1-dideuterioallyl radical of 1.080 ± 0.002.



(3)

The secondary H–D isotope effects are much smaller than the apparent isotope effects observed in the reactions of ethylallene and are within a reasonable range for secondary H–D IE's. Even though this reaction involves an *increase* in bonding at the reaction center which might be expected to give rise to an *inverse* secondary effect, the observed value is normal. This suggests that the reaction coordinate involves some motion of the "secondary" hydrogens. Further studies are therefore required in order to derive experimental data which will provide for an understanding of the anomolously high IE's observed in the reactions of ethylallene.

Experimental Section

Preparation of Dideuterioallyl Bromide. An experimental apparatus was constructed as illustrated for the synthesis of 2-(hydroxymethyl)cyclopentanone.[5] Paraformaldehyde-d_2 (1.7 g, 53 mmol) was placed in a two-necked, round-bottomed flask immersed in an oil bath. The outlet side of the flask was attached by glass tubing to an inlet bubbler tube to a two-necked, round-bottomed flask containing a twofold excess of vinylmagnesium bromide in THF (Aldrich Chemical Co.). An argon stream was passed over the paraformaldehyde-d_2 and through the bubbler tube into the vinylmagnesium bromide solution. The flask containing the paraformaldehyde-d_2 was heated to 180–190 °C. After the disappearance of the paraformaldehyde-d_2 the vinylmagnesium bromide solution was refluxed for 1 h. The reaction mixture was cooled and was slowly poured into 25 mL of cold 10% aqueous $MgSO_4$. Aqueous sulfuric acid (30%) was then slowly added. The top organic layer was decanted, and the aqueous layer was extracted twice with 30-mL portions of diethyl ether. The combined organic fractions were dried ($MgSO_4$), and the diethyl ether and THF were carefully removed by fractional distillation, giving 2.5 g (79%) of 1,1-dideuterio-2-propen-1-ol. The NMR spectrum of the product contained only vinyl hydrogen resonances at δ 4.99, 5.11, and 5.85.

Dideuterioallyl bromide was prepared with the reported procedure for the preparation of allyl bromide from allyl alcohol.[6] The NMR spectrum of product showed peaks at δ 3.9, 5.1, 5.3, and 6.0. Integration of the resonances indicated the product to be a 3.3:1 mixture of 3,3- and 1,1-dideuterioallyl bromide.

Preparation of Dideuterioallyl Phenyl Sulfide. Dideuterioallyl phenyl sulfide was prepared according to the procedure used for the preparation of crotyl phenyl sulfide[7] by reacting sodium thiophenoxide with the dideuterioallyl bromide in methanol. The NMR of the product showed resonances at δ 3.36, 4.98, 5.07, 5.78, and 7.27. Integration of the NMR spectrum indicated the product to be a 55:45 mixture of 1,1- and 3,3-dideuterioallyl phenyl sulfide.

Reduction of Dideuterioallyl Bromide with Tributyltin Hydride. The reduction of the dideuterioallyl bromide with tributyltin hydride was carried out in a manner similar to that used for the reduction of propargyl bromide.[8] In a 10-mL flask equipped with a condensor were placed 0.18 g (1.45 mmol) of the dideuterioallyl bromide, 0.42 g (1.45 mmol) of tributyltin hydride, and 12 mg of 2,2-azobis(isobutyronitrile) (AIBN). A T-tube was placed in the top of the condensor, one side of which was connected by a short piece of tubing to a long syringe needle which was directed below the surface of toluene-d_8 in an NMR tube maintained at <-40 °C. A slow stream of argon was passed through the T-tube and the syringe needle. The contents of the flask were heated at 50 °C for 3 h. The NMR tube was capped, and the NMR spectrum was recorded and integrated. The ratio of 1,1- to 3,3-dideuteriopropene was calculated from the relative intensities of the CH= and $=CH_2$ resonances, giving a value of 1.057. A second run gave a value of 1.054.

Reduction of Dideuterioallyl Phenyl Sulfide with Tributyltin Hydride. The general procedure for the reduction of dialkyl sulfides with tributyltin hydride[4] was employed. 1,1-Dideuterioallyl phenyl sulfide (0.30 g, 2 mm) was reduced with 0.64 g (2.2 mm) of tributyltin hydride and 5 mol % AIBN in 2 mL of refluxing benzene by using the experimental setup described above. The ratio of 1,1- to 3,3-dideuteriopropene was determined by NMR to be 1.081. The results of a second run gave a value of 1.080.

Acknowledgment. We acknowledge grants from the National Institutes of Health and the University of Notre Dame for the purchase of a Nicolet NB-300 NMR system used in these studies.

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α-Hydroxy Thioamides: Useful Intermediates for the Synthesis of Functionalized Thiazoles

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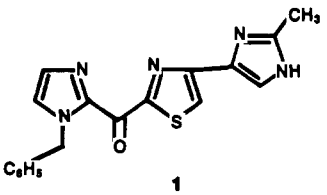
In connection with work designed to discover novel therapeutic agents, a practical synthesis of **1** was sought. A variety of approaches to this compound can be envisioned, and indeed, a number of these were investigated. However, the one that ultimately proved successful hinged on the availability of a key α-hydroxy thioamide. This note describes a novel approach to these compounds which not only allows for the synthesis of **1** but also appears to be quite general.



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A convergent synthesis of **1** was eventually decided upon in which the α-bromo ketone **2** would be condensed with a properly functionalized thioamide. Surprisingly, at this

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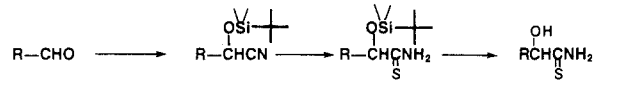
Table I. Conversion of Aldehydes to α-Hydroxy Thioamides

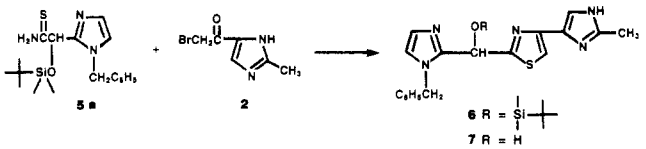


4 a-d 5 a-d 8 b, c

	R	% yield 4	5	8
a		94	52	
b	C_6H_5	74	63	98
c	$CH_3(CH_2)_4$	68	37	54
d		84	32	

time no general syntheses of thioamides with α-hydroxy groups had appeared in the literature.[1] A reasonable approach involved conversion of an aldehyde to a protected cyanohydrin species. Conversion of the nitrile to a thioamide using mild conditions would then give the key α-hydroxy thioamide in a protected form. In the event, reaction of 1-benzylimidazole-2-carboxaldehyde (**3**) with trimethylsilyl cyanide using zinc iodide as catalyst proved to be both slow and incomplete. However, by employing Greenlee's method[2] of a potassium cyanide/18-crown-6 complex and *tert*-butyldimethylsilyl cyanide, the desired adduct **4a** was smoothly obtained in 94% yield. Treatment of **4a** with diphenylphosphinodithioic acid (Ph_2PS_2H)[3] gave thioamide **5a** in 52% yield (see Table I). These mild conditions for thioamide formation are noteworthy in that the silyl protecting group remains intact.

Deprotection of **5a** with $(n\text{-}Bu)_4NF$ gave a mixture of the desired α-hydroxy thioamide along with the corresponding 2-keto thioamide, attesting to the ease of oxidation of this species *in this substrate*. Although the α-keto derivative was the ultimate product, generation of this moiety at this stage was unattractive since it was our experience that electron-withdrawing groups α to the thioamide tended to reduce the reactivity of the thioamide in the subsequent condensations. Thus, **5a** was allowed to react directly with **2** to give 85% of the desired thiazole **6**. Deprotection of the hydroxy function with $(n\text{-}Bu)_4NF$ gave the α-hydroxythiazole **7** in 54% yield. Oxidation of **7** with MnO_2 afforded 51% of the target **1**.



In order to explore the generality of this procedure, three other aldehydes (benzaldehyde, hexanal, and pyridine-2-carboxaldehyde) were chosen as substrates, and the results obtained are also summarized in Table I. As can be seen, both benzaldehyde and hexanal can be readily carried through the three steps in moderate yields to afford the desired α-hydroxy thioamides. Unlike the heterocyclic α-hydroxy thioamides, **8b** and **8c** can be isolated and purified without concomitant oxidation of the hydroxyl group. The pyridyl case, however, mimics that of the imidazole. Nevertheless, this synthesis appears to be general. Furthermore, as was demonstrated in the synthesis of **1**, the protected intermediates, **5a–d**, can be manipulated readily, thus allowing for deprotection at a later stage if necessary.

In summary, this synthetic sequence is suitable for the synthesis of α-hydroxy thioamides particularly those with heterocyclic appendages. These materials are of great utility in the synthesis of α-hydroxy- and α-ketothiazoles not available by traditional routes. Furthermore, these intermediates should also prove to be of value in the synthesis of other heterocycles that employ thioamides.

Experimental Section

^1H NMR spectra were obtained on a Varian T-60 spectrometer. Chemical shifts from tetramethylsilane are reported on the δ scale. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Melting points are uncorrected and were obtained in open capillaries on a Thomas-Hoover melting point apparatus. Solvents and reagents were commercially available and, unless otherwise noted, were used directly.

2-(*tert*-Butyldimethylsiloxy)-2-(1-benzyl-2-imidazolyl)-acetonitrile (4a). A mixture of 54.3 g (0.38 mol) of *tert*-butyldimethylsilyl cyanide, 4.1 g (0.063 mol) of potassium cyanide, and 4.1 g (0.15 mol) of 18-crown-6 was placed in a 2-L round-bottomed three-necked flask fitted with a dropping funnel and overhead stirrer. To this mixture of solids was added dropwise a solution of 70.8 g (0.38 mol) of 1-benzylimidazole-3-carboxaldehyde (**3**)[4] in 750 mL of methylene chloride at room temperature under nitrogen over 30 min. After addition was complete, the mixture was stirred at room temperature for 20 h. The mixture was placed on a silica gel flash chromatography column using 4:1 ether/hexane as eluent, thereby affording 116.7 g (94%) of **4a** as a white solid: mp 86.5–88 °C; NMR ($CDCl_3$) 7.5–7.1 (m, 5 H), 6.90 (d, 1 H), 6.73 (d, 1 H), 5.77 (s, 1 H), 5.33 (s, 2 H), 0.82 (s, 9 H), 0.20 (s, 3 H), 0.08 (s, 3 H). Anal. Calcd for $C_{18}H_{25}N_3OSi$: C, 66.01; H, 7.69; N, 12.83. Found: C, 65.99; H, 7.69; N, 12.77.

2-(*tert*-Butyldimethylsiloxy)-2-phenylacetonitrile (4b). With the same procedure outlined for the synthesis of **4a**, benzaldehyde was converted into **4b**, bp 72–74 °C (0.1 mmHg) in 74% yield: NMR ($CDCl_3$) 7.47 (s, 5 H), 5.52 (s, 1 H), 0.99 (s, 9 H), 0.23 (s, 3 H), 0.18 (s, 3 H). Anal. Calcd for $C_{14}H_{21}NOSi$: C, 67.97; H, 8.55; N, 5.66. Found: C, 67.91; H, 8.48; N, 5.56.

1-(*tert*-Butyldimethylsiloxy)-1-cyanohexane (4c). With the same procedure outlined for the synthesis of **4a**, hexanal was converted into **4c**, bp 56 °C (0.01 mmHg) in 68% yield: NMR ($CDCl_3$) 4.23 (t, 1 H), 2.0–1.1 (m, 8 H), 0.98 (s + t, 12 H), 0.20 (s, 3 H), 0.13 (s, 3 H). Anal. Calcd for $C_{13}H_{27}NOSi$: C, 64.67; H, 11.27; N, 5.80. Found: C, 64.26; H, 11.01; N, 6.17.

2-(*tert*-Butyldimethylsiloxy)-2-(2-pyridyl)acetonitrile (4d). With the same procedure outlined for the synthesis of **4a**, pyridine-2-carboxaldehyde was converted into **4d**, bp 85–86 °C (0.02 mmHg), in 84% yield; NMR ($CDCl_3$) 8.62 (m, 1 H), 7.98 (m, 1 H), 7.6–7.4 (m, 2 H), 6.10 (s, 1 H), 0.90 (s, 9 H), 0.22 (s, 3 H), 0.14 (s, 3 H). Anal. Calcd for $C_{13}H_{20}N_2OSi$: C, 62.86; H, 8.12; N, 11.28. Found: C, 62.98; H, 7.98; N, 11.49.

2-(*tert*-Butyldimethylsiloxy)-2-(1-benzyl-2-imidazolyl)-thioacetamide (5a). A mixture of 68.8 g (0.21 mol) of 2-(*tert*-butyldimethylsiloxy)-2-(1-benzyl-2-imidazolyl)acetonitrile (**4a**), 105.4 g (0.42 mol) of diphenylphosphinodithioic acid,[3] and 2 L of isopropyl alcohol was heated at 60 °C for 8 h. The resulting precipitate was collected and then dissolved in 1.25 L of ethyl acetate. The ethyl acetate solution was washed with a 1 N NaOH solution (5 × 250 mL), and with a saturated NaCl solution (1 × 250 mL), then dried over Na_2SO_4, filtered, and evaporated, leaving a brown gum. This was purified by silica gel chromatography (to remove a less polar impurity from the product) using 20:10:1 hexane/methylene chloride/methanol as eluent to give 44 g of a yellow solid. This material was further purified by dissolving in 200 mL of boiling toluene/cyclohexane (1:1), decolorizing with DARCO, and, after filtration, allowing the filtrate to sit in a refrigerator overnight. In this way, 39.6 g (52%) of the product

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was isolated as a white crystalline solid: mp 173.5–174.5 °C; NMR ($CDCl_3$) 8.65 (br, 2 H), 7.47 (s, 5 H), 7.17 (d, 1 H), 6.90 (d, 1 H), 5.91 (s, 1 H), 5.50 (d, 1 H), 5.42 (d, 1 H), 1.02 (s, 9 H), 0.22 (s, 3 H), 0.10 (s, 3 H). Anal. Calcd for $C_{18}H_{27}N_3OSSi$: C, 59.79; H, 7.53; N, 11.62. Found: C, 59.71; H, 7.29; N, 11.44.

2-(*tert*-Butyldimethylsiloxy)-2-phenylthioacetamide (5b). A mixture of 5.0 g (20 mmol) of 2-(*tert*-butyldimethylsiloxy)-2-phenylacetonitrile (**4b**), 10.4 g (42 mmol) of diphenylphosphinodithioic acid,[3] and 400 mL of isopropyl alcohol was heated at 60 °C for 24 h. The mixture was cooled to room temperature, and the precipitate was removed by filtration, washed with isopropyl alcohol and then ether. The combined filtrate and washings were concentrated and the residue chromatographed over silica gel with 29:1 hexane/ethanol as eluent. After removal of less polar impurities, the product was collected as a solid. Recrystallization from low boiling petroleum ether (4.5 g/7.5 mL of solvent and then cooling in dry ice/acetone) afforded 3.6 g (63%) of **5b** as a white crystalline solid: mp 52–54 °C; NMR ($CDCl_3$) 8.4 (br, 2 H), 7.7–7.2 (m, 5 H), 5.53 (s, 1 H), 0.98 (s, 9 H); 0.17 (s, 3 H), 0.08 (s, 3 H). Anal. Calcd for $C_{14}H_{23}NOSSi$: C, 59.74; H, 8.24; N, 4.98; S, 11.39. Found: C, 59.77; H, 8.10; N, 4.67; S, 11.74.

2-(*tert*-Butyldimethylsiloxy)thioheptanamide (5c). With the same procedure outlined for the synthesis of **5b**, 1-(*tert*-butyldimethylsiloxy)-1-cyanohexane (**4c**) was converted to **5c**, mp 40–41 °C, in 37% yield: NMR ($CDCl_3$) 8.0–7.6 (br, 2 H) 4.59 (t, 1 H), 2.0–1.2 (m, 8 H), 0.96 (s + t, 12 H), 0.13 (s, 3 H), 0.10 (s, 3 H). Anal. Calcd for $C_{13}H_{29}NOSSi$: C, 56.67; H, 10.61; N, 5.08. Found: C, 56.79; H, 10.86; N, 4.79.

2-(*tert*-Butyldimethylsiloxy)-2-(2-pyridyl)thioacetamide (5d). With the same procedure outlined for the synthesis of **5b**, 2-(*tert*-butyldimethylsiloxy)-2-(2-pyridyl)acetonitrile (**4d**) was converted to **5d**, mp 106.5–107.5 °C, in 42% yield: NMR ($CDCl_3$) 8.70 (m, 1 H), 8.60 (br, 2 H), 7.81 (m, 1 H), 7.6–7.4 (m, 2 H), 5.72 (s, 1 H), 0.96 (s, 9 H), 0.20 (s, 3 H), 0.08 (s, 3 H). Anal. Calcd for $C_{13}H_{22}N_2OSSi$: C, 55.28; H, 7.85; N, 9.92. Found: C, 54.90; H, 7.68; N, 9.69.

2-Hydroxy-2-phenylthioacetamide (8b). A mixture of 1.65 g (5.9 mmol) of 2-(*tert*-butyldimethylsiloxy)-2-phenylthioacetamide (**5b**) and 65 mL of dry THF was stirred at 0 °C, and 3.72 g (11.8 mmol) of tetra-*n*-butylammonium fluoride was added in one portion. The mixture was allowed to stir at room temperature for 1 h, and then the mixture was concentrated. The oil residue was partitioned between 100 mL of water and 100 mL of ether. The ether portion was separated and the aqueous solution extracted twice more with 50-mL portions of ether. The combined ether extracts were dried (Na_2SO_4), filtered, and evaporated leaving a solid. Recrystallization from toluene afforded 965 mg (98%) of **8b** as a white crystalline solid: mp 113.5–116 °C; NMR (Me_2SO-d_6, D_2O) 7.6–7.2 (m, 5 H), 5.33 (s, 1 H). Anal. Calcd for C_8H_9NOS: C, 57.46; H, 5.42; N, 8.38; O, 9.57; S, 19.18. Found: C, 57.62; H, 5.59; N, 7.95; O, 9.30; S, 18.65.

2-Hydroxythioheptanamide (8c). With the same procedure outlined for the synthesis of **8b**, 2-(*tert*-butyldimethylsiloxy)-thioheptanamide was converted into **8c**. This product was initially isolated as an oil but was crystallized by trituration with 2:1 hexane/toluene and scratching with a glass rod. Recrystallization from 2:1 hexane/toluene afforded the product as a white crystalline solid, mp 68–70 °C, in 54% yield: NMR (Me_2SO-d_6): 9.78 (br, 1 H), 9.06 (br, 1 H), 5.67 (d, 1 H), 4.17 (br 1 H), 1.91–1.1 (m, 8 H), 0.90 (t, 3 H). Anal. Calcd for $C_7H_{15}NOS$: C, 52.14; H, 9.38; N, 8.69. Found: C, 52.31; H, 9.21; N, 8.78.

2-[(1-Benzyl-2-imidazolyl)hydroxymethyl]-4-(2-methyl-4-imidazolyl)thiazole (7). A mixture of 17.8 g (87.5 mmol) of 1-(2-methyl-4-imidazolyl)-2-bromoethanone (**2**),[5] 31.6 g (87.5 mmol) of 2-(*tert*-butyldimethylsiloxy)-2-(1-benzyl-2-imidazolyl)thioacetamide (**5a**), and 2 L of acetone was stirred at room temperature. After 15 min, the mixture became homogeneous, and, after another 15 min, a precipitate began to form. After the mixture was stirred at room temperature for 48 h, the precipitate was collected, washed with acetone, and dried in vacuo, giving adduct **6** as its hydrobromide, mp 179–180 °C. This was converted to its free base by partitioning between 500 mL of ethyl acetate and 300 mL of saturated sodium bicarbonate solution. The organic portion was separated, and the aqueous solution was extracted twice more with 150-mL portions of ethyl acetate. The combined ethyl acetate layers were dried (Na_2SO_4), filtered, and evaporated, leaving 34.6 g (85%) of **6** as a yellow solid. This was generally deprotected directly.

A mixture of 9.74 g (21 mmol) of **6** in 250 mL of dry THF was stirred at −10 °C under nitrogen and 15.8 g (50 mmol) of tetra-*n*-butylammonium fluoride was added directly. The mixture was stirred at −10 °C for 1 h and then at room temperature for 30 min. The mixture was concentrated, and the residue was repeatedly triturated with water and decanted, all the while being sure to break up the yellow solid into tiny particles. The yellow solid was collected, washed with water, and dried in vacuo to afford 4.0 (54%) of pure **7**: mp 230–232.5 °C; NMR (Me_2SO-d_6) 7.37 (s, 1 H), 7.3–7.1 (m, 5 H), 7.0 (s, 1 H), 6.90 (d, 1 H), 6.68 (d, 1 H), 5.96 (s, 1 H), 5.09 (s, 2 H), 2.12 (s, 3 H). Anal. Calcd for $C_{18}H_{17}N_5SO$: C, 61.52; H, 4.88; N, 19.93; S, 9.12. Found: C, 61.81; H, 5.16; N, 19.45; S, 8.87.

2-(1-Benzyl-2-keto-2-imidazolyl)-4-(2-methyl-4-imidazolyl)thiazole (1). A mixture of 315 mg (0.9 mmol) of 2-[(1-benzyl-2-imidazolyl)hydroxymethyl]-4-(2-methyl-4-imidazolyl)thiazole (**7**), 3 g of MnO_2, and 20 mL of dry THF was stirred 0 °C for 2 h. The mixture was filtered through Celite and the filtrate concentrated. The resulting yellow solid was triturated with ether, finely powdered with a glass rod, and then stirred in ether for 30 min. The solid was collected, washed with ether, and dried in vacuo to afford 228 mg (73%) of pure **1**: mp 198.5–199.5 °C; NMR (Me_2SO-d_6) 8.06 (s, 1 H), 7.90 (s, 1 H), 7.5–7.2 (m, 7 H), 5.74 (s, 2 H), 2.32 (s, 3 H). Anal. Calcd for $C_{18}H_{15}N_5OS$: C, 61.87; H, 4.33; N, 20.04. Found: C, 61.53; H, 4.54; N, 19.89.

Registry No. **1**, 99808-97-6; **2**, 92049-88-2; **3**, 10045-65-5; **4a**, 99808-98-7; **4b**, 99808-99-8; **4c**, 99809-00-4; **4d**, 99809-01-5; **5a**, 99809-02-6; **5b**, 99809-03-7; **5c**, 99809-04-8; **5d**, 99809-05-9; **6**, 99809-10-6; **6**·HBr, 99809-09-3; **7**, 99809-08-2; **8b**, 99809-06-0; **8c**, 99809-07-1; diphenylphosphinodithioic acid, 1015-38-9; *tert*-butyldimethylsilyl cyanide, 56522-24-8; benzaldehyde, 100-52-7; hexanal, 66-25-1; pyridine-2-carboxaldehyde, 1121-60-4; tetra-*n*-butylammonium fluoride, 311-28-4.

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Palladium-Catalyzed Double Carbonylation of Aryl Halides Affording α-Keto Amides. Applications to Synthesis of Isatin and Quinoline Derivatives

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Recently developed palladium-catalyzed double carbonylation reactions provide convenient synthetic means for introducing two reactive carbonyl groups into organic moieties. Various organic halides can be readily converted into corresponding α-keto acid derivatives in these reactions.[1-3] Since α-keto acid derivatives are known to be potentially useful starting materials of various organic

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