Versatile β-Keto Ester and β-Keto Nitrile Synthesis through Sulfide Contraction

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A versatile and efficient synthesis for various β-keto esters, including those which are α substituted, is described. The α-thio iminium salt prepared from a thioamide and a primary or secondary alkylating agent is subjected to sulfur extrusion upon addition of base and a phosphine thiophile, and the result is an enamino ester which may be hydrolyzed to the desired β-keto ester. The method is also applicable to the preparation of various substituted β-keto nitriles.

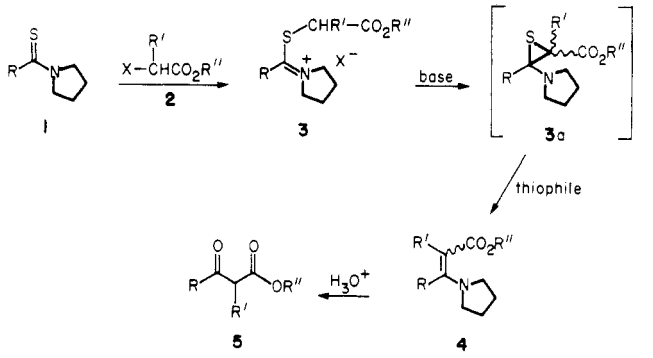
β-Keto esters are highly versatile synthetic intermediates, and their value is reflected in the myriad of methods for their preparation described in the literature. These varied syntheses may be conveniently divided into two groups: those that proceed from malonic acid derivatives, the most widely exploited route, and the remainder that do not.

Those preparations that proceed from malonic acid derivatives all derive from a common set of reactions. The starting malonic acid derivative is chosen such that one of the ester groups can be readily removed in the presence of the other to effect decarboxylation, thus limiting to some extent the type of ester group that can be preserved in the final product. The malonates are then acylated with acid halides, anhydrides, or imidazolides under treatment with a variety of bases including alkoxides, hydrides, lithium alkyls and amides, and Grignard reagents.

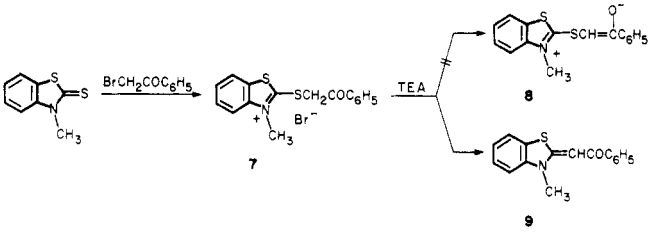
Some specific examples include the acylation of *tert*-butyl ethyl malonate by treatment with magnesium ethoxide and various acid chlorides followed by acid treatment and decarboxylation to yield various β-keto ethyl esters.[2] Improvements on the malonic ester approach were made by acylation of the dilithium dianion of ethyl hydrogen malonate[3] and treatment of the neutral salt of the malonate half ester with imidazolides, the latter being useful for alkali-sensitive systems.[4] Recently[5] Meldrum's acid has been utilized to yield various β-keto esters whose ester moiety could be more broadly substituted.

With regard to methods that do not proceed from malonic acid derivatives, improvements on the classic Claisen condensation using potassium hydride as the base have been reported.[6] Several modifications of the addition of an acetate unit to an acid chloride were described,[7] including the use of silylketene acetals and treatment of various acid chlorides with a stabilized Wittig reagent[8] to yield various β-keto esters. Acyl interchange via treatment of acetoacetate with an acid chloride and subsequent loss of the acetyl group under alkaline conditions[9] has been improved by methods which allow for nearly exclusive C-acylation.[10,11]

Scheme I



Scheme II



The process we have investigated to produce β-keto esters begins with the S-alkylation of the starting thioamide **1** with an α-activated ester **2** to form the α-thio imidinium salt **3** (Scheme I). Abstraction of the remaining acidic proton α to the ester creates a nucleophilic carbon and leads to the episulfide intermediate **3a**. Sulfur is extruded from **3a** with the aid of a phosphine thiophile, generating an enamino ester **4**, and mild acid hydrolysis of **4** yields the desired β-keto ester **5**. The synthesis of any arbitrarily substituted β-keto ester should thereby be possible by selecting the requisite thioamide and alkylating agent.

Sulfur extrusion as a method to effect carbon–carbon bond formation was first observed by Knott[12] in his investigation of sulfur-containing chromophores. He noted that the product he obtained while attempting to dehydrobrominate a (phenacylthio)benzothiazolium bromide **7** with triethylamine was not the expected sulfide **8** but the α,β-unsaturated ketone **9** resulting from the loss of a sulfur atom (Scheme II). A mechanism proceeding through an episulfide intermediate followed by the extrusion of sulfur was proposed to explain these observations.

This sulfide-contraction technique as a synthetic tool was implemented by Eschenmoser.[13] Various systems

(1) Fellow of the Deutsche Forschungsgemeinschaft.
(2) Breslow, D. S.; Baumgarten, E.; Hauser, C. R. *J. Am. Chem. Soc.* **1944**, *66*, 1286.
(3) Wierenga, W.; Skulnick, H. I. *J. Org. Chem.* **1979**, *44*, 310.
(4) Brooks, D. W.; Lu, L. D.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72.
(5) Oikawa, Y.; Sugamo, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087.
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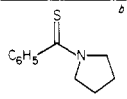
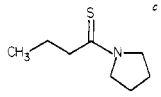
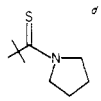
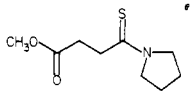
(7) Rathke, M. W.; Sullivan, D. F. *Tetrahedron Lett.* **1973**, 1297.
(8) Bestmann, H. J.; Graf, G.; Hartung, H.; Kolewa, S.; Vilsmaier, E. *Chem. Ber.* **1970**, *103*, 2794.
(9) Vincontini, M.; Merckling, N. *Helv. Chim. Acta* **1952**, *35*, 2280.
(10) Durst, H. D.; Liebeskind, L. *J. Org. Chem.* **1974**, *39*, 3271.
(11) Brandstrom, A.; Junggren, U. *Acta Chem. Scand.* **1969**, *23*, 2204.
(12) Knott, E. B. *J. Chem. Soc.* **1955**, 916.

0022-3263/81/1946-3230$01.25/0

Table I. Preparation of Thiopyrrolidides

thioamide	method	% yield[a]	IR (film), cm^{-1}	NMR ($CDCl_3$), δ
 [b]	A	85	1495, 1490, 1480, 1260, 960, 762, 716, 690	1.85 (m, 4 H), 3.33 (t, 2 H, J = 6 Hz), 3.86 (t, 2 H, J = 6 Hz), 7.39 (s, 5 H)
 [c]	A	74	2950, 1975, 1940, 1890, 1350, 1260, 1210	0.89 (t, 3 H, J = 6 Hz), 1.6-2.0 (m, 6 H), 2.54 (t, 2 H, J = 6 Hz), 3.49 (t, 2 H, J = 8 Hz), 3.69 (t, 2 H, J = 8 Hz)
 [d]	A	83	2990, 1495, 1460, 1405, 1355, 1260, 1150	1.35 (s, 9 H), 1.95 (br s, 4 H), 3.79 (br s, 4 H)
 [e]	B	70	2995, 1725, 1480, 1440, 1360, 1210	1.92 (m, 4 H), 2.74-2.84 (m, 4 H), 3.58 (s, 3 H), 3.48-3.82 (m, 4 H)

[a] Yield for method A refers to two-step process from acid chloride to thioamide; method B is for one-step transformation from amide to thioamide. [b] Mp 73-75 °C. [c] Bp 100 °C (150 μm). [d] Bp 90 °C (150 μm). [e] Bp 100 °C (100 μm).

amenable to this process were investigated as well as the conditions required to efficiently invoke the extrusion. This led to the development of a reagent which served the dual role of base to abstract the α-proton and thiophile to assist in extrusion of the sulfur. Several β-keto ethyl esters also were prepared by starting with thioesters and using this methodology.

Several other examples of β-keto ester synthesis employing sulfide contraction have subsequently appeared. Treatment of various *N*-(thioacyl)urethanes with a resonance-stabilized phosphorus ylide effected both alkylation and sulfur extrusion and, after hydrolysis, yielded various substituted β-keto ethyl esters.[14] Application of Eschenmoser's base–thiophile reagent to an α-thio iminium salt prepared from the alkylation of a thioamide with bromo- or iodoacetates according to the previously described scheme, and anticipating our process to some extent, was recently reported to yield various β-keto esters upon hydrolysis.[15]

We have expanded the latter application from a specifically directed preparative method to a versatile and practical scheme to produce variously substituted β-keto esters in which substitution on the acyl group, the α-methylene carbon, or the ester can be broadly varied. Investigations of the steric limitations inherent in our scheme as well as the development of mild reaction conditions to effect each step of the sequence were conducted. The mild reaction conditions should allow the incorporation of added functionality in the β-keto esters, thereby increasing their synthetic utility. This should also render the scheme applicable to systems containing racemizable centers.

Our process can be conveniently divided into four stages: (1) preparation of the starting thioamide, (2) subsequent alkylation to the α-thio iminium salt, (3) sulfur extrusion to yield the enamino ester, (4) hydrolysis to produce the desired product.

Various methods have been described for the preparation of thioamides. A particularly convenient transformation has been described of an acid chloride to the thioamide, without isolation of the intermediate amide, in high yields of pure alkyl and simple aryl products.[16] Milder techniques necessary for further functionalized examples are also available.[17]

The choice of thiopyrrolidides in all our examples stemmed from the necessity to satisfy two criteria: a secondary or tertiary thioamide to prevent competitive abstraction of the nitrogen proton during sulfur extrusion (e.g., primary amides are converted to nitriles) was required, and the enhanced extrusion from the least sterically demanding tertiary amide was desired, thus minimizing interactions in any sterically demanding β-keto ester production.

The production of α-thio iminium salts was initially conducted by using various bromoacetates which required highly concentrated solutions and extended periods of time to effect alkylation. Such methods were successful in producing nonsterically demanding β-keto esters. However, when the production of a β-keto ester beginning with thiopivalamide was attempted, the propensity for the nucleophilic bromide ion to reverse thioiminium salt formation and re-form the starting materials became an obvious problem. A series of equilibria are established from starting materials to episulfide, and when a bulky substituent such as the pivaloyl group is introduced, closure to the congested episulfide is inhibited. Bromide ion now competitively attacks the α-thio iminium ion to yield the starting materials. The position of equilibrium between the starting materials and the α-thio iminium ion is sensitive to various factors, including heat, which favors the former, and the solvent. Complete reversal to starting materials within several hours is observed when the α-thio iminium salt is dissolved in tetrahydrofuran, while a slow though incomplete reversal is observed in methylene chloride at room temperature.

Various unsuccessful attempts made to curtail or eliminate the nucleophilic back-reaction included cooling the solution and exchanging the bromide for a less nucleophilic anion by the addition of silver acetate or silver nitrate. A successful solution to the problem was achieved when silver trifluoromethanesulfonate was used. The α-thio iminium ion now carried a nonnucleophilic trifluoromethanesulfonate counterion and was found to be stable in refluxing methylene chloride for an extended period without detectable reversal.

The success of the counterion exchange prompted further investigation in the utilization of this concept directly. Since the more reactive triflates can be readily prepared

(13) Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.
(14) Gossauer, A.; Roessler, F.; Zilch, H. *Liebigs Ann. Chem.* **1979**, 1309.
(15) Ireland, R. E.; Brown, F. R. *J. Org. Chem.* **1980**, *45*, 1868.
(16) Voss, J.; Walter, W. *Justus Liebigs Ann. Chem.* **1968**, *716*, 209.
(17) Schreen, J. W.; Ooms, P. H. J.; Nivard, R. J. F. *Synthesis* **1973**, 149. Tamaru, Y.; Harada, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1980**, *102*, 2392.

from the requisite α-hydroxy ester,[18] their use was examined as an alternative to bromides and iodides. Thus the triflate prepared from benzyl glycolate readily alkylated the thiopivalamide in minutes and proceeded to yield the desired β-keto ester in excellent overall yield.

The ease with which the triflate produced α-thio iminium salt prompted a search for similar alkylating agents, and the mesylate and tosylate of benzyl glycolate were prepared and applied to our process. These reagents, however, failed to completely alkylate the thioamide, regardless of the conditions invoked. Their failure may be attributed to their poorer leaving group abilities as reflected in their dissociation constants. Hydrobromic and trifluoromethanesulfonic are the stronger acids, but the disadvantage of the nucleophilicity of bromide ion establishes triflates as our alkylating agent of choice.

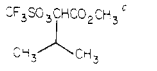
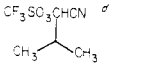
Sulfur extrusion from the α-thio iminium ion to form the enamino ester is conveniently performed by the dual base–thiophile reagent[13] which can also be readily removed with an aqueous acid wash, thereby greatly simplifying product isolation. In seeking milder reaction conditions, we developed a new dual base–thiophile reagent which substitutes the more weakly basic morpholinyl group for the dimethylamino group. This reagent, bis(3-morpholinylpropyl)phenylphosphine, was found to be equally effective in sulfur extrusion and as readily removed from the final product. Incorporation of a milder base could render the process more compatible with the presence of chiral centers susceptible to racemization with stronger bases.

Hydrolysis of the enamino ester can be readily accomplished under mild conditions in dilute acidic solutions at room temperature. The resulting β-keto esters, which were oils in all our examples, were easily isolated from the relatively clean crude products by simple bulb-to-bulb vacuum distillation.

β-Keto nitriles can also function as useful synthetic intermediates. Although various preparative methods for substituted aroylacetonitriles are reported, general methods for β-keto nitrile preparation are limited. Examples include the early work by Claisen,[19] who prepared benzoylacetonitrile through condensation of benzoylacetaldehyde with hydroxylamine in alkaline solutions. Subsequently[20] the same compound was prepared from ethyl benzoate and the anion of acetonitrile, generated with sodium ethoxide. The latter method was extended[21] to prepare other acylacetonitriles. Benzyl sodiocyanomalonate was acylated then decarboxylated after hydrogenolysis to yield various β-keto nitriles,[22] and aroylacetonitriles have been prepared[23] by treatment of α-bromoacetophenones with potassium cyanide and by the condensation of the anion of acetonitrile with variously substituted benzonitriles followed by hydrolysis.[24]

Application of the sulfide-contraction method to a general β-keto nitrile synthesis may be readily realized by substitution of a bromoacetonitrile or cyanohydrin triflate in lieu of the ester alkylating reagent. Thiobenzamide was thus treated with bromoacetonitrile, and upon subsequent sulfur extrusion and hydrolysis the benzoylacetonitrile was isolated in good yield.

Table II. Triflates Prepared from Corresponding α-Hydroxy Esters and Nitriles

triflate	% yield	NMR ($CDCl_3$), δ
$CF_3SO_3CH_2CO_2CH_2C_6H_5$ [a]	77	4.94 (s, 2 H), 5.30 (s, 2 H), 7.46 (s, 5 H)
$CF_3SO_3CH(CH_3)CO_2^-$	56	1.28 (t, 3 H, J = 5 Hz), 1.67 (d, 2 H, J = 7 Hz), 4.27 (q, 2 H), 5.18 (q, 1 H)
 [c]	84	0.99 (t, 6 H), 2.32 (m, 1 H), 3.82 (s, 3 H), 4.92 (d, 1 H, J = 4 Hz)
 [d]	40	1.15 (d, 3 H), 1.22 (d, 3 H), 2.27 (br, 1 H), 5.12 (d, 2 H, J = 5 Hz)

[a] Purified by passage through a short silica gel column. [b] Bp 40 °C (150 μm). [c] Bp 60 °C (150 μm). [d] Bp 30 °C 150 μm).

Introduction of an alkyl substituent at the α-carbon of a β-keto ester is commonly effected after the synthesis of the ester itself. However, this method suffers from the problems created by possible mono- vs. dialkylation and the tedious separation of mono-, di-, and unsubstituted β-keto esters. In the present process, however, the α substituent would be incorporated at the start of the synthesis through the use of a secondary alkylating agent. It is for this purpose that the advantage of employing the triflates becomes fully evident. Esters of secondary bromo acids failed to yield α-thio iminium salts. Forcing conditions were of no avail; even if the salt were formed, the more drastic conditions in the presence of bromide ion would lead to complete reversal. However, the secondary triflates successfully alkylated the thioamides. Their advantage was clearly demonstrated by the preparation of an α-methyl-β-keto ester in good yield by utilizing the triflate of ethyl lactate as the alkylating agent.

As a starting material, an aldehyde provides a convenient and common intermediate for either alkylating agent for β-keto ester or β-keto nitrile synthesis. The aldehyde is condensed with potassium cyanide to form the cyanohydrin which upon transformation to the triflate serves as the alkylating agent in β-keto nitrile synthesis. Carrying the cyanohydrin through hydrolysis to the α-hydroxy acid which is esterified and transformed to the triflate provides the educt necessary for β-keto ester production.

Introduction of a branched, bulky substituent such as an isopropyl group at the α-carbon according to our process was possible in good yield for β-keto nitriles, but lower yields were obtained in the synthesis of α-isopropyl-β-keto esters. Steric interaction at the episulfide stage between the isopropyl group in opposing the cyano vs. a bulkier carboalkoxy group may account for this difference in yields.

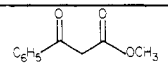
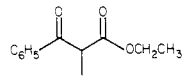
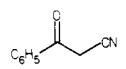
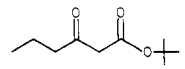
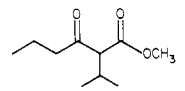
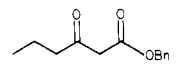
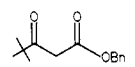
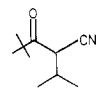
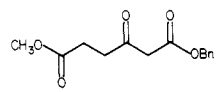
Finally, the convenience of the process is demonstrated by its ability to yield the isolated product from the starting thioamide and triflate reagent within 1 day, with the total reaction time consuming less than 2 h.

Experimental Section

All boiling points are uncorrected. Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer

(18) Vedejs, E.; Engler, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3109.
(19) Claisen, L.; Stock, R. *Chem. Ber.* **1891**, *24*, 130.
(20) Dorsh, J. B.; McElvain, S. M. *J. Am. Chem. Soc.* **1932**, *54*, 2960.
(21) Long, R. S. *J. Am. Chem. Soc.* **1947**, *69*, 990.
(22) Bowman, R. E.; Fordham, W. D. *J. Chem. Soc.* **1951**, 2758.
(23) Gakhar, H. K.; Gill, G. S.; Multani, J. S. *J. Indian Chem. Soc.* **1971**, *48*, 953.
(24) Ridge, D. N.; Hanifin, J. W.; Harten, L. A.; Johnson, B. D.; Menschik, J.; Nicolau, G.; Sloboda, A. E.; Watts, D. E. *J. Med. Chem.* **1979**, *22*, 1385. See also recent examples of β-keto nitriles prepared from enolates by displacement of benzyl mercaptide from benzyl thiocyanate: Rodriguez, C.; Lamazouere, A.; Sotiropoulos, J. *C. R. Hebd. Seances Acad. Sci. Ser. C* **1980**, *291*, 179.

Table III. β-Keto Esters and β-Keto Nitriles Prepared Via Thiopyrrolidides

product[a]	method	% yield[b]	IR (film), cm^{-1}	NMR ($CDCl_3$), δ
	A	89	2930, 1790, 1760, 1680, 1650, 1610, 733, 690	3.67 (s, 3 H), 3.98 (s, 2 H), 7.2-7.9 (m, 5 H)
	B	85	3000, 1750, 1700, 1620, 1600, 1460, 709, 693	1.15 (t, 3 H, J = 6 Hz), 1.49 (d, 3 H, J = 6 Hz), 3.9-4.4 (m, 3 H), 7.2-7.9 (m, 5 H)
	A	89	2930, 2280, 1720, 1460, 1380, 760, 690	4.05 (s, 2 H), 7.3-7.8 (m, 5 H)
	A	85	2930, 1750, 1720, 1460	0.92 (t, 3 H, J = 6 Hz), 1.47 (s, 9 H), 1.56 (m, 2 H), 2.48 (t, 3 H, J = 6 Hz), 2.34 (s, 2 H)
	D	15	3400, 2930, 2860, 1740, 1690, 1620, 1420	0.08-1.0 (m, 9 H), 1.68 (m, 2 H), 2.18 (m, 1 H), 2.55 (t, 2 H, J = 7 Hz), 3.69 (s, 3 H), 4.07 (d, 1 H, J = 6 Hz)
	B	95	3400, 2980, 1750, 1720, 1630, 1410, 698	0.86 (t, 3 H, J = 5 Hz), 1.61 (6, 2 H), 2.44 (t, 2 H, J = 6 Hz), 3.39 (s, 2 H), 5.12 (s, 2 H), 7.42 (s, 5 H)
	B	95	3000, 1750, 1720, 1640, 1460, 698	1.17 (s, 9 H), 3.52 (s, 2 H), 7.38 (s, 5 H), 5.13 (s, 4 H), 7.39 (s, 5 H)
	C	80	2900, 2220, 1710, 1600, 1420, 1390	0.9-1.2 (m, 13 H), 2.29 (s, 1 H), 3.52 (d, 1 H, J = 4 Hz)
	A	80	2920, 1690, 1590, 1390, 709	2.5-2.9 (m, 4 H), 3.49 (s, 2 H), 3.64 (s, 3 H), 5.16 (s, 2 H), 7.42 (s, 5 H)

[a] Satisfactory elemental analyses or comparison with literature values were obtained for all samples. [b] Yields calculated from starting thioamide.

317. ^1H NMR spectra were recorded on a Varian EM-390 spectrometer, and the chemical shifts are reported as δ values in parts per million relative to internal tetramethylsilane. Solvents were distilled shortly prior to use. Methylene chloride was dried and distilled from P_2O_5. Pyridine was distilled first from tosyl chloride and then from calcium hydride; THF was dried and distilled from sodium and benzophenone. Ether was anhydrous grade (Mallinckrodt); all other solvents were reagent grade.

Acid chlorides were distilled prior to use. Pyrrolidine was refluxed then distilled from barium oxide. P_4S_{10} was purified by extraction through a Soxhlet apparatus with carbon disulfide. Trifluoromethanesulfonic anhydride was prepared as reported.[25] All other reagents were reagent grade and used without further purification.

Bis(3-morpholinylpropyl)phenylphosphine. To 6.07 g of Mg (0.25 mol, dried at 400 °C for 18 h) covered with 40 mL of THF was added over a period of 1 h with stirring in a nitrogen atmosphere 36.5 g of 3-morpholinylpropyl chloride[26] (0.25 mol) dissolved in 40 mL of THF. Reaction was initiated by addition of 0.5 mL of ethylene bromide and local heating. After complete addition of the chloride, the mixture was refluxed for 3 h and then cooled in an ice bath, and 14.9 g of dichlorophenylphosphine (0.083 mol) dissolved in 25 mL of THF was added over a period of 0.5 h with continued stirring. The reaction mixture was then refluxed for 2 h, cooled to room temperature, and allowed to stand overnight covered with 75 mL of ether. The supernatant was added to 40 mL of 40% KOH and 150 g of ice, with a solution of ether/methylene chloride (5/1) to transfer the residue. The organic phase was dried (Na_2SO_4), the solvent evaporated, and the residue bulb-to-bulb vacuum distilled; 20.8 g (69%) of product was obtained: bp 180 °C (500 μm); IR (film) 2970, 2900, 1480, 1460, 1360, 1120, 1070, 1010, 746, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.32–1.83 (m, 8 H), 2.14–2.34 (m, 10 H), 3.46–3.67 (m, 8 H), 7.23–7.53 (m, 5 H). Anal. Calcd for $C_{20}H_{33}N_2O_2P$: C, 65.9; H, 9.1; N, 7.7. Found: C, 66.2; H, 9.1; N, 7.6.

Preparation of Thioamides. Method A. To a stirring solution of 1.40 g of pyrrolidine (19.7 mmol) in 25 mL of dry pyridine was slowly added via syringe pump over 15 min 2.12 g (19.9 mmol) of butyryl chloride. The solution was refluxed for 0.5 h under a nitrogen atmosphere and then allowed to cool to room temperature, at which time 3.57 g (8.06 mmol) of P_4S_{10} was added and the reflux continued for an additional 2 h. The cooled solution was poured into 100 mL of 1 N HCl, stirred for 1 h, and then extracted with $CHCl_3$ (3 × 25 mL). The combined extracts were washed twice with 40 mL of each of 1 N HCl, H_2O, saturated $NaHCO_3$, and H_2O, dried (Na_2SO_4), and evaporated. Bulb-to-bulb vacuum distillation yielded 2.35 g (74%) of 1-(thiobutyryl)-pyrrolidine as a clear yellow oil.

Method B. A mixture of 0.82 g (4.43 mmol) of 1-[β-(methoxycarbonyl)pyropionyl]pyrrolidine,[27] in 25 mL of THF, 0.98 g (2.21 mmol) of P_4S_{10}, and 0.74 g (8.86 mmol) of $NaHCO_3$ was refluxed under nitrogen for 4 h. After the mixture cooled, the solvent was evaporated and the residue dissolved in 25 mL of ethyl acetate which was washed with water and saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was bulb-to-bulb vacuum distilled to give 0.61 g (70%) of the thiopyrrolidide as a clear, yellow oil.

Preparation of Triflates. The triflates were prepared as reported by using procedure B.[18] The reaction residue was passed through several inches of silica gel packed into a Pasteur pipet followed by several rinsings with hexane and then isolated by bulb-to-bulb vacuum distillation, giving the triflates in 80–90% yields as clear, colorless liquids.

Preparation of β-Keto Esters and Nitriles. Method A. A mixture of 0.21 g (1.05 mmol) of 1-[[β-(methoxycarbonyl)thio]-propionyl]pyrrolidine and 0.29 g (1.27 mmol) of benzyl bromoacetate[28] was stirred for 0.5 h and then allowed to stand for 24 h under a blanket of nitrogen. The mixture was dissolved in 10 mL of dry CH_2Cl_2 and 0.57 g (1.47 mmol) of bis(3-morpholinylpropyl)phenylphosphine was added at room temperature. After 18 h the solution was diluted with 10 mL of CH_2Cl_2 and washed with 1 N HCl (3 × 10 mL). The methylene chloride was evaporated and the residue dissolved in 25 mL of methanol/water (4/1) to which was added 1.25 mL of 1 N HCl.

(25) Burdon, J.; Farazmand, I.; Stacy, M.; Tatlow, J. C. *J. Chem. Soc.* **1957**, 2574.
(26) Adams, R. R.; Whitmore, F. C. *J. Am. Chem. Soc.* **1945**, *67*, 735.
(27) The acid chloride was prepared according to: Cason, J. "Organic Synthesis"; Wiley: New York, 1955; Collect. Vol. III, p 169. The amide was prepared as described in method A except that it was isolated prior to sulfurization.
(28) Bradley, J.; Buchi, G. *J. Org. Chem.* **1976**, *41*, 699.

After the mixture was stirred at room temperature for 4 h, the methanol was evaporated and the aqueous solution extracted with fractions of $CHCl_3$ (2 × 15 mL) which were combined and washed with 1 N HCl, dried (Na_2SO_4), and evaporated. The benzyl δ-(methoxycarbonyl)-γ-oxovalerate was isolated by bulb-to-bulb vacuum distillation in 0.20 g (70%) yield as a clear, colorless oil.

Method B. A mixture of 0.26 g (1.50 mmol) of 1-(thiopivaloyl)pyrrolidine and 0.54 g (1.80 mmol) of [(benzyloxy)carbonyl]methyl trifluoromethanesulfonate in 5 mL of CH_2Cl_2 was stirred at room temperature for 15 min under a nitrogen atmosphere. To the solution was added 0.82 g (2.25 mmol) of bis(3-morpholinylpropyl)phenylphosphine, and the sulfur extrusion was allowed to proceed for 0.5 h at room temperature under nitrogen. The mixture was diluted with 15 mL of CH_2Cl_2 and washed several times with 10 mL of 1 N HCl, the solvent was evaporated, and the residue was dissolved in 50 mL of methanol/water (4/1) to which was added 3.0 mL of 1 N HCl. After 1 h, the methanol was evaporated, the aqueous solution was extracted with $CHCl_3$ (3 × 15 mL), and the combined extracts were washed with 20 mL of 1 N HCl and then dried (Na_2SO_4). Evaporation of solvent and bulb-to-bulb vacuum distillation of the residue yielded 0.33 g (94%) of **benzyl γ,γ-dimethyl-β-oxovalerate.**

Method C. A mixture of 0.26 g (1.50 mmol) of 1-(thiopivaloyl)pyrrolidine and 0.42 g (1.80 mmol) of α-cyanoisobutyl trifluoromethanesulfonate was stirred for 0.5 h and allowed to stand 18 h under a nitrogen atmosphere. Sulfur extrusion, hydrolysis, and isolation proceeded as described in method A to yield 0.20 g (80%) of **γ,γ-dimethyl-α-isopropyl-β-oxovaleronitrile.**

Method D. Method C was followed except that after the addition of the bis(3-morpholinyl)propylphenylphosphine, the reaction was refluxed for 15 h under a nitrogen atmosphere. After hydrolysis, the product was separated on a silica gel preparative plate (1/1 ether/hexane).

Registry No. 1 (R = Ph), 15563-45-8; 1 (R = Pr), 66343-95-1; 1 R = *t*-Bu), 77902-87-5; 1 (R = $(CH_2)_2C(O)OMe$), 77902-88-6; 2 (R^1 = H; R^{11} = CH_2Ph; X = SO_3CF_3), 77902-89-7; 2 (R^1 = Me; R^{11} = Et; X = SO_3CF_3), 77902-90-0; 2 (R^1 = *i*-Pr; R^{11} = Me; X = SO_3CF_3, 77902-91-1; 5 (R = Ph; R^1 = H; R^{11} = Me), 614-27-7; 5 (R = Ph; R^1 = Me; R^{11} = Et), 10488-87-6; 5 (R = Pr; R^1 = H; R^{11} = *t*-Bu), 61540-30-5; 5 (R^1 = Pr; R^1 = *i*-Pr; R^{11} = Me), 77924-73-3; 5 (R = Pr; R^1 = H; R^{11} = CH_2Ph), 5006-35-9; 5 (R = *t*-Bu; R^1 = H; R^{11} = CH_2Ph), 77902-92-2; 5 (R = $(CH_2)_2C(O)OMe$; R^1 = H; R^{11} = CH_2Ph), 53314-75-3; α-cyanoisobutyl α-trifluoromethanesulfonate, 77924-74-4; β-oxo-β-phenylpropionitrile, 614-16-4; γ,γ-dimethyl-α-isopropyl-β-oxovaleronitrile, 77902-93-3; bis(3-morpholinylpropyl)phenylphosphine, 77902-94-4; 3-morpholinylpropyl chloride, 7357-67-7; dichlorophenylphosphine, 644-97-3; pyrrolidine, 123-75-1; butyryl chloride, 109-69-3; 1-[β-(methoxycarbonyl)propionyl]pyrrolidine, 77902-95-5; benzyl bromoacetate, 5437-45-6.

Stereochemistry of Imino Group Reduction. 2. Synthesis and Assignment of Configuration of Some *N*-(1-Phenylethyl)-1,2-diaryl-2-aminoethanols

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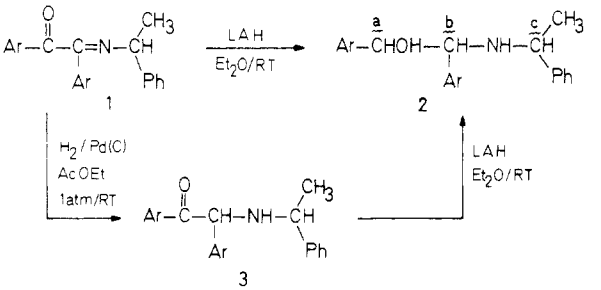
Lithium aluminum hydride reduction of the monoimines prepared by reaction of benzils and 1-phenylethylamine yields a mixture of the related diastereomeric *N*-(1-phenylethyl)-1,2-diaryl-2-aminoethanols. After separation of the diastereomers, assignment of their configuration is made on the basis of their infrared and NMR spectra. Catalytic hydrogenation of the monoimine prepared from benzil yields the amino ketone, which when treated with lithium aluminum hydride yields a mixture of aminoethanols. The composition of this shows that the stereochemical result of this reduction is different from that of the direct reduction. Stereochemical results are analyzed on the basis of models which take into account different initial conformations of the monoimine and the higher probability of attack of hydride at the less hindered side of each conformer.

Previously[1] we reported stereochemical results for the lithium aluminum hydride (LAH) reduction of a series of imines, ArCOCAr=NCHRPh (1).[2] Analysis of the mixture of aminoethanols obtained in this way showed that the reduction process is highly stereoselective for R = Me. With the purpose of obtaining all possible stereoisomers for one imine type, we have further investigated the product of the one-step LAH reduction and also studied the reduction of imine 1 (Ar = C_6H_5) by a two-step process

Scheme I



involving the intermediacy of an amino ketone (Scheme I).

Results

Assignment of Configuration to LAH Reduction Products. The amino alcohols (2) considered in this paper

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(2) For the synthesis and structure of this type of compounds, see: (a) J. L. García-Ruano, R. Haro, C. Pascual, R. Pérez-Ossorio, and J. Plumet, *An. Quim.*, **75**, 165 (1979); (b) S. García-Blanco, I. Fonseca, and S. Martínez Carrera, *Acta Crystallogr., Sect. B*, **35**, 2643 (1979); (c) J. L. García-Ruano, M. A. Henao, D. Molina, R. Pérez-Ossorio, and J. Plumet, *Tetrahedron Lett.*, 3123 (1979); (d) J. L. García-Ruano, M. A. Henao, D. Molina, R. Pérez-Ossorio, and J. Plumet, *An. Quim.*, **76C**, 260 (1980).

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