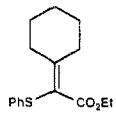
propylidenemalononitrile (**15**) and cyclohexylidenemalononitrile (**18**) reacted much more slowly (−78 °C, 12 h)[9a] with dienolates to provide, in most cases, the product of double Michael addition.[5q,s,10] The reasons for this difference in reactivity are not clear, but we speculate that coordination of lithium ion may play a role in accelerating additions to cyano esters.

Several other features of this reaction are noteworthy. Double Michael addition products **16**, **19a**, and **19c** contain *four* contiguous quaternary centers. The occurrence of the second Michael addition to form bicyclo[2:2:2] ring systems appears to be limited to those cases where activation is provided by two cyano substituents and depends upon a combination of electronic and steric buttressing factors. The formation of uncyclized **20** from **1b** and **18** may be rationalized on the basis of the absence of methyl buttressing (R_1 = H) along with deactivation of the enone (R_3 = OCH_3).

Although this reaction is remarkably capable of accommodating steric bulk at the reacting centers, we believe that the lower yields of **5**, **13**, **14**, and **17** result from remote steric interference with the cyclohexanone enolate ring. In support of this hypothesis, we have observed that the kinetic lithium enolate of isophorone completely fails to react with **2**.

Hindered Michael acceptors bearing other activating groups were generally found to react less readily. For example, sulfide ester **21**[5r-t] failed to react with **1a**.[12] Diethyl cyclohexylidenemalonate and diethyl isopropylidenemalonate were also unreactive. Ethyl isopropylideneacetoacetate (**22**) formed no Michael adduct with **1a** but reacted with **1b** to give **23**[7] in 50% yield.[8]



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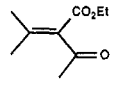

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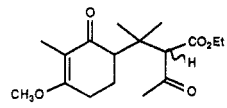

23

These results unambiguously demonstrate, for the first time, that contiguous quaternary carbon centers can be formed under very mild conditions via the aprotic Michael addition. We are currently investigating the possibility of diastereoselectivity in these processes[13] as well as their utility in the total synthesis of natural products.

Acknowledgment. We thank the National Cancer Institute for generous financial support of our programs.

(9) (a) In all cases, reactions were quenched at −78 °C by rapid addition to a large excess of saturated sodium bicarbonate solution. (b) Temperatures higher than −78 °C appear to favor either competing proton transfer or retro Michael reaction, or both. (c) In a typical experiment, a solution of 0.154 g (1.0 mmol) of 3-methoxy-2,6-dimethylcyclohexenone in 2 mL of THF was added to a solution of 1.1 mmol of LDA in 7 mL of dry THF at −78 °C. The mixture was stirred at −78 °C for 15 min before addition of a solution of 0.193 g (1.0 mmol) of ethyl cyclohexylidenecyanoacetate in 2 mL of dry THF. After being stirred at −78 °C for 15 min, the mixture was rapidly poured into a mixture of 75 mL of saturated aqueous $NaHCO_3$ and 20 mL of 40% ethyl acetate/hexane. The aqueous layer was extracted with an ethyl acetate/hexane mixture, and the organic layers were combined, dried, and concentrated to yield a light yellow oil. Flash chromatography (20% EtOAc/hexane) afforded 0.338 g (98%) of pure Michael adduct.

(10) (a) White, K. B.; Reusch, W. *Tetrahedron* **1978**, *34*, 2439. (b) Lee, R. A. *Tetrahedron Lett.* **1973**, 3333. (c) Spitzner, D. *Ibid.* **1978**, 3349. (d) Gibbons, E. G. *J. Org. Chem.* **1980**, *45*, 1540. (e) Narula, A. S.; Birch, A. J. *Tetrahedron Lett.* **1981**, *22*, 591. (f) Hagiwara, H.; Nakayama, K.; Uda, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3769. (g) Roberts, M. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 724. (h) Quesada, M. L.; Schlessinger, R. H.; Parsons, W. H. *J. Org. Chem.* **1978**, *43*, 3968. (i) Ohnuma, T.; Oishi, T.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 301. (j) Cory, R. M.; Chan, D. M. T.; Naguib, Y. M. A.; Rastall, M. H.; Renneboog, R. M. *J. Org. Chem.* **1980**, *45*, 1852 and references cited therein.

(11) The stereochemistry of **5**, **14**, and **16** was determined by ^1H NMR decoupling and NOE difference experiments. The stereochemistry of **19a**, **19c**, and **19d** was assigned by analogy with **16**.

(12) The reaction of the corresponding sulfoxide with **1a** has provided interesting preliminary results. Because of their increased complexity, these reactions are still under investigation and will be described in a future communication.

(13) Krafft, M. E.; Kennedy, R. M.; Holton, R. A. *Tetrahedron Lett.* **1986**, *27*, 2087.

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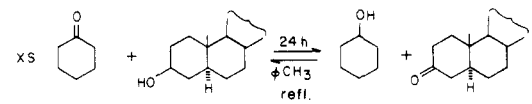
Oxidation of Secondary Alcohols Using Raney Nickel

Summary: A high yield, one-step oxidation procedure has been developed for the selective oxidation of secondary alcohols.

Sir: We report that Raney nickel in refluxing benzene can be used to efficiently oxidize secondary alcohols to ketones. Numerous methods exist for the oxidation of alcohols to ketones[1] and for the selective oxidation of primary–secondary diols.[2] The use of Raney nickel provides a mild and inexpensive means of oxidizing secondary alcohols to the corresponding carbonyl compounds.

Oxidation of secondary alcohols to ketones using Raney nickel has been reported. However, the reaction was either carried out at very high temperatures[3] or under equilibrating conditions in the presence of a large excess of a reversible hydrogen acceptor, cyclohexanone, to drive the reaction to completion[4] (eq 1). It would be more desirable if one could use an irreversible hydrogen acceptor and eliminate the need for an excess of cyclohexanone.



(1)

(1) House, H. O. *Modern Synthetic Reactions*; W. A. Benjamin: Menlo, CA, 1972, and references cited therein. Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*; Springer-Verlag: Berlin, 1984, and references cited therein.

(2) (a) For oxidation of the primary alcohol of a primary–secondary diol, see: Doyle, M. P.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 4806. Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605. Kanemoto, S.; Oshima, K.; Matsubara, S.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 2185. (b) For oxidation of the secondary alcohol of a primary–secondary diol, see: Trost, B. M.; Masuyama, Y. *Tetrahedron Lett.* **1984**, *25*, 173. Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 539. Jung, M. E.; Brown, R. W. *Tetrahedron Lett.* **1978**, 2771. June, M. E.; Speltz, L. M. *J. Am. Chem. Soc.* **1976**, *98*, 7882. Ueno, Y.; Okawara, M. *Tetrahedron Lett.* **1976**, 4597. Posner, G. H.; Perfetti, R. B.; Runquist, A. W. *Tetrahedron Lett.* **1976**, 3499. Neirabeyeh, M. A.; Ziegler, J. C.; Gross, B. *Synthesis* **1976**, 811. Barton, D. H. R.; Kitchin, J. P.; Lestor, D. J.; Motherwell, W. B.; Papoula, M. T. B. *Tetrahedron* **1981**, *37*, W73. Wicha, J.; Zarecki, A. *Tetrahedron Lett.* **1974**, 3059. Jones, R. E.; Kocher, F. W. *J. Am. Chem. Soc.* **1954**, *76*, 3682.

(3) Paul, R. *Compt. Rend.* **1939**, *208*, 1319. Palfray, L.; Sabatay, S. *Compt. Rend.* **1939**, *208*, 107, 1654. See also: Sandner, M. R.; Trecker, D. J. *J. Org. Chem.* **1973**, *38*, 3954. Badin, E. J. *J. Am. Chem. Soc.* **1943**, *65*, 1809.

(4) Kleiderer, E. C.; Kornfield, E. C. *J. Org. Chem.* **1948**, *13*, 455. Mahato, S. B.; Banerjee, S. K.; Chakravarti, R. N. *Tetrahedron* **1971**, *27*, 177. Forsek, J. *Tetrahedron Lett.* **1980**, *21*, 1071.

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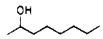
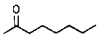
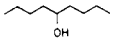
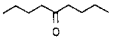
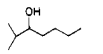
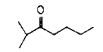
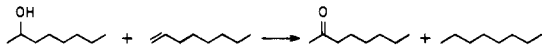
Table I

entry	alcohol	product	yield (%)[a]	procedure[b]	time (h)
1			93	A	4
			91	B	3
2			93	A	9
					
3	n=2		93	A	2
4	n=3		95	A	1.5
			94	B	2
5	n=5		98	A	7
6	n=7		96	A	1
			95	B	3
7			70	A	13
					
8	R=CH3		85	A	20
9	R=nBu		89	A	24
10			–[c]	A	0.5
			90	B	1

[a] All yields refer to isolated materials. [b] Reactions were carried out on a 1–2-mmol scale. See text for a description of procedures A and B. [c] See text for discussion.

Heating a benzene solution of 2-octanol and 2 equiv of 1-octene with Raney nickel for 3 h gave 2-octanone in 91% yield (eq 2). Unfortunately, the reaction was sluggish with



(2)

other secondary alcohols and did not proceed to completion. Longer reaction times and the use of other hydrogen acceptors[5] did not facilitate the complete conversion of alcohol to ketone.

We found that the oxidation proceeded cleanly and in high yield in the absence of a hydrogen acceptor as is illustrated by the results in Table I. For example, the oxidation of 5-nonanol with Raney nickel in the presence of 1-octene (procedure B) proceeded only to ca. 25% completion after 9 h at 80 °C; however, 5-nonanone was obtained in 93% isolated yield by using Raney nickel in refluxing benzene for 9 h in the absence of a hydrogen acceptor (entry 2, procedure A).

Although secondary alcohols were readily oxidized, primary alcohols appeared to be unreactive. For example, both cyclohexanemethanol and 1-dodecanol were recovered unchanged after 1.5 h in refluxing benzene in the presence of Raney nickel. Furthermore, competition experiments showed that secondary alcohols were selectively oxidized in the presence of primary alcohols. Oxidation of an equimolar mixture of cyclooctanol and cyclohexanemethanol with Raney nickel in refluxing benzene for 1.5 h yielded cyclooctanone and recovered cyclohexanemethanol in essentially quantitative yields. These results seemed to indicate a high degree of selectivity in the oxidation reaction. However, oxidation of 1,12-dihydroxytridecane gave 1-hydroxy-12-tridecanone as well as 2-tridecanone which resulted from competing hydrogenolysis of the primary alcohol.

Hydrogenolysis of benzylic alcohols presented a minor problem.[4] Oxidation of *sec*-phenethyl alcohol (entry 10) using Raney nickel yielded a 1:1 mixture of acetophenone and ethylbenzene when the reaction was carried out in the absence of 1-octene, but yielded exclusively acetophenone in 90% yield when the reaction was carried out in the presence of 1-octene. Benzyl alcohol yielded toluene[6] as the only product upon attempted oxidation with Raney nickel. No benzaldehyde was detected in the 270-MHz ^{1}H NMR spectrum of the reaction mixture. Oxidation of benzhydrol, even in the presence of 1-octene, yielded a 2:1 mixture of benzophenone and diphenylmethane in 95% yield.

Under the reaction conditions, cyclohexanol and substituted cyclohexanols reacted sluggishly and only low conversions (~25–40%) to the corresponding ketones were obtained. Further investigations to address the low reactivity of cyclohexanols and the hydrogenolysis of primary alcohols are in progress.

Although large quantities of nickel are used in the oxidation reaction, Raney nickel is inexpensive and is not as toxic as the standard chromium(VI) oxidizing reagents. One major advantage this route offers over many other oxidation methods is the ease with which the ketones are isolated from the reaction mixture—by filtration and solvent removal.

Representative experimental procedures follow: Procedure A. A solution of 200 mg (1.54 mmol) of 2-octanol in 2.2 mL of benzene was added to 800 mg of a Raney nickel[7] slurry. [The Raney nickel was weighed as an aqueous slurry where most of the liquid had been removed before weighing. The weight of the Raney nickel slurry was equal to four times the weight of the alcohol. Five of the alcohols required the addition of more Raney nickel during the course of the reaction.[8] Immediately before each use the slurry was washed ten times with vigorous stirring using 8 mL of distilled water.] The water from the slurry was azeotropically removed rapidly by using an efficient Dean–Stark trap and a hot oil bath (~125 °C). Less than 10 min was necessary for complete removal of the water. The remaining suspension was refluxed for 3 h with vigorous stirring, cooled to room temperature, and filtered through a pad of Celite using 30% ethyl acetate in hexane. (Caution, the Raney nickel may still be pyrophoric!) The solvent was removed in vacuo leaving a pale oil which was then filtered through a plug of silica gel using 30% ethyl acetate in hexane. Removal of the solvent in vacuo yielded 184 mg of 2-octanone (93%).[9] Procedure B. The same as procedure A except that a solution of 2 equiv of 1-octene and 1 equiv of alcohol in 2.2 mL of benzene were added to the Raney nickel slurry.

Note Added in Proof: We have recently found that washing the nickel with 1-propanol (after the distilled water washes) and using toluene as the reaction solvent allowed shorter reaction times and the use of reduced amounts of nickel in some cases.

Acknowledgment. The Florida State University Department of Chemistry is gratefully acknowledged for financial support. B.Z. acknowledges the F.S.U. Center for Yugoslav–American Studies for a fellowship.

Registry No. 2-Octanol, 123-96-6; 5-nonanol, 623-93-8; cycloheptanol, 502-41-0; cyclooctanol, 696-71-9; cyclodecanol,

(5) Other irreversible hydrogen acceptors include 1-hexyne, diethyl maleate, and valeraldehyde.

(6) The reaction was carried out in benzene-d_6 so direct ^{1}H NMR analysis of the reaction mixture was possible.

(7) Fresh Raney nickel, available from Aldrich Chemical Company (50% slurry in water, pH 10), was used for the oxidation reaction.

(8) The total weight of the Raney nickel used was equal to four times the weight of the alcohol with the following exceptions: An additional portion of Raney nickel equal to 2–3 times the weight of the alcohol (washed as previously described) was added to entries 2, 5, 7, and 8 after 6 h and to entry 9 after 7 h and 12 h. The use of a large excess of Raney nickel at the outset of the reaction resulted in lower yields.

(9) All compounds gave satisfactory spectral data. All yields refer to chromatographically homogeneous materials of >98% purity.

1502-05-2; cyclododecanol, 1724-39-6; 2-methyl-3-heptanol, 18720-62-2; 1-cyclohexylethanol, 1193-81-3; 1-cyclohexyl-1-pentanol, 7338-43-4; 1-phenylethanol, 98-85-1; 2-octanone, 111-13-7; 5-nonanone, 502-56-7; cycloheptanone, 502-42-1; cyclooctanone, 502-49-8; cyclodecanone, 1502-06-3; cyclododecanone, 830-13-7; 2-methyl-3-heptanone, 13019-20-0; 1-cyclohexylethanone, 823-76-7; 1-cyclohexyl-1-pentanone, 5445-35-2; acetophenone, 98-86-2; Raney nickel, 7440-02-0; 1-octene, 111-66-0; ethylbenzene, 100-41-4.

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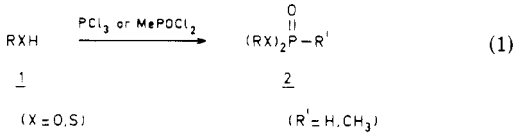
Enantiomeric Excess Determination without Chiral Auxiliary Compounds. A New ^{31}P NMR Method for Amino Acid Esters and Primary Amines

Summary: Amino acid esters and primary amines yield diastereoisomeric methylphosphonic diamides **5** upon reaction with $MePSCl_2$. The enantiomeric excess of amino acid esters and amines is easily determined by measurement of the ratio of diastereoisomers of **5** by ^{31}P NMR spectroscopy.

Sir: We recently developed a facile method for enantiomeric excess (ee) determinations of alcohols[1a] and thiols.[1b] The principle is a coupling reaction of chiral alcohols or thiols **1** with an achiral phosphorus reagent to afford diastereoisomeric phosphonates **2** (eq 1). PCl_3 is



(1)

used for alcohols and $MePOCl_2$ for both alcohols and thiols. The enantiomeric purities of the alcohols or thiols **1** are easily determined by ^{31}P NMR measurement of the ratio of diastereoisomers of **2**.

The increasing use of amino acids,[2] either natural or synthetically obtained, in asymmetric syntheses made the extension of our ^{31}P NMR method for fast and accurate ee determination of these and amines derived therefrom a major goal of our research. Extensive investigations[3] showed, however, that neither phosphorus trichloride nor alkylphosphonic dichloride is a satisfactory reagent for this purpose.

We now report a completely effective method for the ee determination of amino acids and primary amines based on the principles described above. Alkylphosphonothioic dichlorides are well-suited for the coupling reaction of

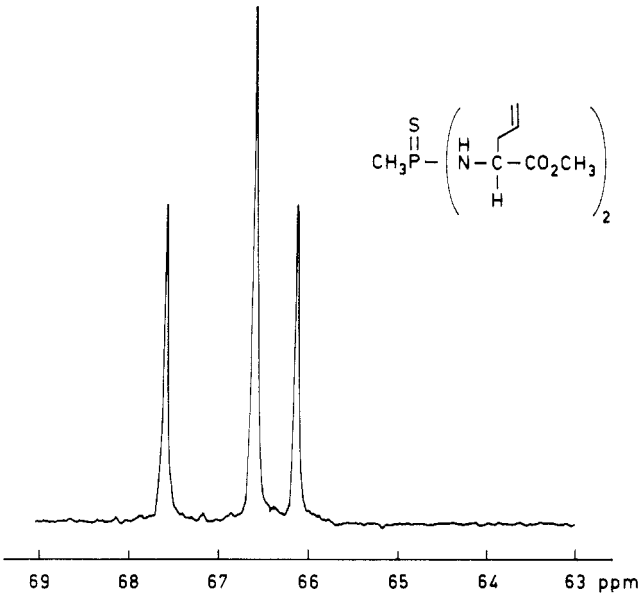
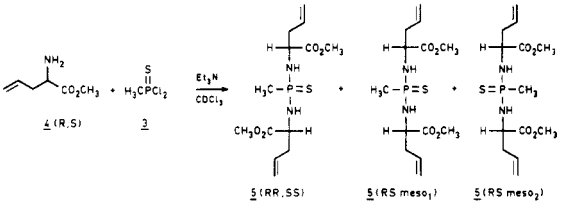


Figure 1. ^{31}P NMR spectrum of **5** obtained from racemic allylglycine and $MePSCl_2$ ($CDCl_3$).

primary amines. Thus, methylphosphonothioic dichloride (**3**)[4] in the presence of 2 equiv of triethylamine reacts quantitatively in 10 min at −20 °C with 2 equiv of (*R*,*S*)-allylglycine methyl ester (**4**) to afford diastereoisomeric methylphosphonothioic diamides **5** (eq 2).[5]



(2)

The ^{31}P NMR spectrum of **5** shows three well-separated singlets for the racemate (*RR* + *SS*) and two meso (*RS* meso$_1$, *RS* meso$_2$) diastereoisomers with a meso/*dl* ratio of 49:51 (Figure 1).[6] The ratio of these singlets is directly related to the enantiomeric excess of the amino acid esters.[7] For 96.6% enantiomerically pure **5** (as determined by optical rotation) the two meso peaks could just be observed; an ee of 97% was calculated from the integration. Although $MePSCl_2$ has to be used at −20 °C to avoid byproduct formation whereas commercially avilable $C_6H_5P-SCl_2$ can be used at room temperature, we prefer the former for this ee determination because it gives superior chemical shift differences for the diastereoisomers (see

(1) (a) Feringa, B. L.; Smaardijk, A. A.; Wynberg, H. *J. Am. Chem. Soc.* **1985**, *107*, 4798. (b) Feringa, B. L.; Smaardijk, A. A.; Wynberg, H.; Strijtveen, B.; Kellogg, R. M. *Tetrahedron Lett.* **1986**, *27*, 997.

(2) For example: Martens, J. In *Topics in Current Chemistry*; Boschke, F. L., Ed., Springer Verlag: Berlin, Vol. 125, p 165. Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1984**, *25*, 2545. Vriesema, B. K.; Ten Hoeve, W.; Wynberg, H.; Kellogg, R. M.; Boesten, W. H. J.; Meijer, E. M.; Schoemaker, H. E. *Tetrahedron Lett.* **1986**, *27*, 2045. Vriesema, B. K.; Kellogg, R. M. *Tetrahedron Lett.* **1986**, *27*, 2049. Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783. Seebach, D.; Imwinkelreid, R.; Weber, T. "Enantiomerically Pure Compound Syntheses with C,C Bond Formation *via* Acetals and Enamines" in *Modern Synthetic Methods*, Springer Verlag: Berlin, in press.

(3) Feringa, B. L.; Smaardijk, A. A., unpublished results. For example, $MePOCl_2$ does not give quantitative reaction, byproduct formation is excessive, and ratios for the diastereomers deviate from statistical for primary amines.

(4) Hoffmann, F.; Wadsworth, D.; Weiss, H. *J. Am. Chem. Soc.* **1958**, *80*, 3945.

(5) Only one enantiomer of racemic **5** is shown.

(6) All spectra were recorded in $CDCl_3$ at 80.988 MHz on a Nicolet 200 NT spectrometer; chemical shift values are in hertz with 85% H_3PO_4 (δ 0.0 Hz) as an external standard.

(7) The enantiomeric purity (p) was calculated from the integrated peak area's Q and Q′ of the *d*,*l* isomer and the meso isomers, respectively (with *dl*/meso ratio $K = Q/Q'$) using Horeau's[8] formula, $p^2 = (K - 1)/(K + 1)$.

(8) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055.

(9) Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* **1985**, *50*, 4508.

(10) Johnson, C. R.; Elliott, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 5019.

(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(12) Frank, H.; Nicholson, G. J.; Bayer, E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 364. Davankov, V. A. *Adv. Chromatog.* **1980**, *18*, 139. Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 352.

(13) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732. McCreary, M. O.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038. Pirkle, W. H.; Beare, S. D. *Ibid.* **1969**, *91*, 5150.

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