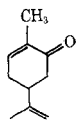
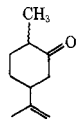
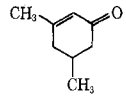
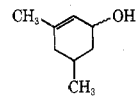
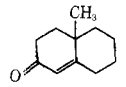
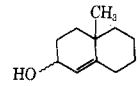
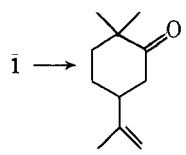
Table I

Enone	No.	Product[5]	No.	Yield,[b] %
	1		2	98
	3		4	99
	5		6	95
	7		8	83
	9		10	95

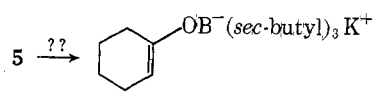
[a] This product was identical with an authentic sample. [b] Isolated yields of glc pure materials.

In those cases where conjugate enone reduction is successful, we have also been able to use the intermediate enolate in a second, alkylation, step.[7,8] For example, when carvone is treated with 1 mol equiv of K-Selectride™ followed by 1.3 equiv of methyl iodide, a 98% yield of 1-methyl-1,6-dihydrocarvone (11) can be realized.[5] A similar



11

experiment using cyclohexenone and 1.5 equiv of allyl bromide leads to a mixture of 2-allylcyclohexanone (55%), cyclohexanone (15%), and some dialkylated ketone (30%) in high yield.[9] The nature of the intermediate species, whether a simple potassium enolate or a borate such as 12, remains uncertain. If shown to be the former, this method



12

would afford a facile and convenient access to reactive potassium enolates in unhindered systems. Work is being continued in an effort to learn whether other unsaturated moieties, particularly esters and nitriles, can also experience 1,4 reduction, reductive alkylation, and perhaps even intramolecular reductive cyclization. A typical experimental procedure follows.

To a dry THF solution (5 ml) of carvone (0.366 g, 2.44 mmol) under nitrogen at −78° was added 1 equiv of K-Selectride™ (0.5 *M* solution, 4.9 ml). After the mixture was stirred for 1 hr at −78°, methyl iodide (1.3 equiv, .20 ml) was injected and the low temperature bath removed. The contents of the flask were brought to 0° for 10 min, by which time a white precipitate had appeared. Addition of 10% NaOH solution (7 ml) and 30% H_2O_2 (5 ml) sufficed to oxidize the trialkylborane by-product after stirring for 3 hr at room temperature. Excess peroxide was destroyed with sodium bisulfite and three hexane extractions afforded 0.400 g (98%) of 11 as a water-white liquid.[10]

References and Notes

(1) H. C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, **94**, 7159 (1972)
(2) C. A. Brown, *J. Amer. Chem. Soc.*, **95**, 4100 (1973)
(3) E. J. Corey, K. B. Becker, and R. K. Varma, *J. Amer. Chem. Soc.*, **94**, 8616 (1972)
(4) Sodium borohydride in pyridine has also been observed to effect 1,4 reduction of enones followed by carbonyl reduction thus affording saturated alcohols: W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965)
(5) All products exhibited ir and nmr data completely in accord with the assigned structures.
(6) This sensitivity may account for the apparently exclusive formation of allylic alcohol from the β-cyclopentyl-α,β-unsaturated ketone reported in reference 3.
(7) G. Stork, P. Rosen, and N. L. Goldman, *J. Amer. Chem. Soc.*, **83**, 2965 (1961)
(8) For examples of the alkylation of enol borates and enol borinates, see (a) D. J. Pasto and P. W. Wojtkowski, *J. Org. Chem.*, **36**, 1790 (1971); (b) J. Hooz and J. N. Bridson, *J. Amer. Chem. Soc.*, **95**, 602 (1973); (c) T. Mukaiyama, K. Inomata, and M. Muraki, *J. Amer. Chem. Soc.*, **95**, 967 (1973)
(9) Enolate equilibration during alkylation of enol borates has been observed by Pasto. *Cf.* ref 8a.
(10) The author thanks the Department of Chemistry at Cornell University for generous financial support.

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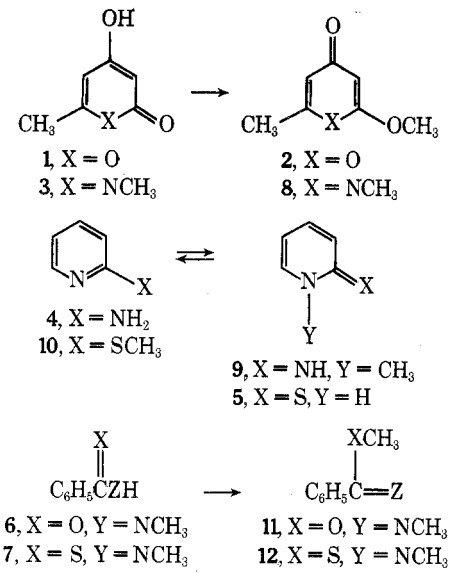
Received October 3, 1974

Methylation of Prototropic Ambident Nucleophiles. The Proton as a Formal Directing Group

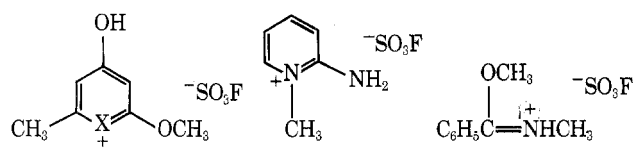
Summary: The fact that six different prototropic ambident nucleophiles react with methylfluorosulfonate and aqueous base to give, in high yields, the product resulting from methylation at the heteroatom which does not bear the proton in the major tautomer is taken to suggest a general regiospecific synthesis of potential synthetic value.

Sir: The mobility of an active hydrogen generally precludes its actually functioning as a blocking or directing group in the traditional sense. Nonetheless, the efficient alkylative conversion of monosubstituted amides to imidates[1] provides one of a number of precedents[2] which suggest, that under some conditions, the proton of a prototropic ambident nucleophile can formally direct alkylation away from its bonding site in the major tautomer. We wish to draw attention to the synthetic value of this prospect with the report that it applied to the reactions of at least six such nucleophiles with methylfluorosulfonate. Comment is also made on the mechanistic considerations which underlie such specificity.

The formation of 2-methoxy-6-methyl-4-pyrone (2) from 4-hydroxy-6-methyl-2-pyrone (1) has been reported after separation of isomers produced by reaction of 1 with diazomethane[3] or by multiple steps involving the trimethylsilyl blocking group[4] in <20% yields. Treatment of 1 with methylfluorosulfonate[5] followed by removal of excess methylating agent under reduced pressure and treatment of the resulting solid with 10% aqueous sodium hydroxide gives 2 in 90% yield. Similar reactions of 3–7 give 8–12,[1a,f,2a,b] in quantitative yields. In each case these products are the formal result of methylation at the heteroatom which does not bear the proton in the major tautomer. This sequence appears to be superior to alternative methods of preparation of these compounds.[1-5]



A scheme which accounts for these results has fast equilibration of the protomers with the ratio of products being determined by kinetically controlled methylation[6] in accord with the Curtin–Hammett principle.[8] Since the transition state energy differences are in the same direction as the ground-state energy differences[3,9,10] and the initial kinetic products are stable and can be deprotonated in the second step, a regiospecific synthesis results in which the proton appears to have acted as a directing group. Support for this interpretation is provided by the fact that the intermediate salts **13–16** can be isolated and identified by



13, X = O
14, X = NCH_3

15 **16**

nmr and ir spectroscopy after reaction of **1, 3, 4,** and **6** with methylfluorosulfonate.

Although cases can be anticipated in which the alkylating agent might not exhibit the requisite selectivity,[11] the synthetic potential of the regioselective synthesis suggested by these results appears to be significant. The fact that the less stable,[1,3,5b,12] and therefore often more reactive, alkyl substituted isomer may be produced easily and in high yield may prove of particular value.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for support of this work.

References and Notes

(1) (a) S. Julia and R. J. Ryan [*C. R. Acad. Sci., Ser. C,* 274, 1207 (1972)] report this conversion with methylfluorosulfonate; (b) E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem., Int. Ed. Engl.,* **3**, 490 (1964); (c) R. F. Borch, *Tetrahedron Lett.*, 61 (1968); (d) T. Oishi, M. Ochiai, M. Nagai, and T. Ban, *ibid.*, 491, 497 (1968); (e) A. Pilotti, A. Reuterhall, K. Torssell, and C. G. Lindblad, *Acta Chem. Scand.*, **23**, 818 (1969); (f) P. Beak and J. T. Lee, Jr., *J. Org. Chem.*, **34**, 2125 (1969); (g) L. A. Paquette, M. J. Wyvratt, and G. R. Allen, *J. Amer. Chem. Soc.*, **92**, 1763 (1970); (h) R. G. Glushkov and V. B. Granik, *Advan. Heterocycl. Chem.*, **12**, 185 (1970), and references cited therein.
(2) (a) R. Adams and J. S. Dix, *J. Amer. Chem. Soc.*, **80**, 4618 (1958); (b) **12**, B. Böttcher and F. Bauer, *Justus Liebigs Ann. Chem.*, **568**, 218 (1950); (c) A. Grimison, J. H. Ridd, and B. U. Smith, *J. Chem. Soc.*, 1357 (1960); (d) W. J. Theuer and J. A. Moore, *J. Org. Chem.*, **32**, 1602 (1967).
(3) J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.*, 502 (1960); H. Nakata, *Bull. Chem. Soc. Jap.*, **33**, 1688 (1960), and references cited therein.
(4) P. Beak, D. S. Mueller, and J. Lee, *J. Amer. Chem. Soc.*, **96**, 3867 (1974), and references cited therein.
(5) M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott, and M. C. Whiting *Chem. Commun.*, 1533 (1968); (b) R. W. Alder, *Chem. Ind. (London)*, 983 (1973).
(6) The methylation of **6** proceeds with a second-order rate constant of ~3 × 10^{-4} l./mol sec or at least ten orders of magnitude slower than proton transfer,[7] a process which provides a reasonable estimate of the rate of tautomerization of the protomeric isomers of the reactant.
(7) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(8) D. Y. Curtin, *Rec. Chem. Prog., Kresge-Hooker Sci. Library*, **15**, 111 (1954); L. P. Hammet, "Physical Organic Chemistry," McGraw-Hall, New York, N.Y., 1970, pp 119–120; E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N.Y., 1962, pp 237–239.
(9) The position at which a prototropic ambident nucleophile reacts with an electrophile has been a matter of interest for many years: L. Skulski, *Rocz. Chem.*, **46**, 2139 (1972); O. A. Reutov, "Fundamentals of Theoretical Organic Chemistry," Appleton-Century-Crofts, New York, N.Y., 1967, p 544–551, pp 559; A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **1**, 320 (1963).
(10) One possibility is that the respective transition states resemble the reactants. Practically the transition state energy difference should be greater than ~3 kcal/mol for regioselective synthesis.
(11) See, for example, M. G. Ahmed and R. W. Alder, *Chem. Commun.*, 1389 (1969).
(12) The less stable isomer will be produced under this hypothesis if the relative stabilities of structually similar methylthropic and prototropic isomers are in the same order.

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Received September 17, 1974

Applications of Sulfenylations of Ester Enolates. Synthesis of Pheromones of the Honey Bee

Summary: By the sulfenylation–dehydrosulfenylation method, the queen substance and the pollen attractant of honey bees have been synthesized and a new approach to α-keto esters by direct bissulfenylation has been demonstrated.

Sir: In conjunction with our continuing interest in the application of new synthetic methods to the chemistry of insect pheromones, we have developed short syntheses of the esters of the queen substance[1,2] and the pollen attractant of honey bees.[3,4] In the course of this study we have developed a new synthesis of α-keto esters and have determined the dependence of the sulfenylation reaction on the choice of carboxylic ester.

Sulfenylation[5] of the esters of linoleic acid in THF at 0° (generation of the enolate at −78°) led to the α-methylthiolinoleates in yields that paralleled enolate stability (see Scheme I). Since enolates of methyl and ethyl esters are frequently unstable at this temperature,[6a] decomposition competes with sulfenylation. On the other hand, the enolate of the *tert*-butyl ester[6b] is thermally stable and sulfenylation proceeds smoothly. Enhancing the rate of sulfeny-