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AN EFFICIENT SYNTHESIS OF α-SUBSTITUTED α,β-UNSATURATED KETONES EMPLOYING A VERSATILE LATENT α-KETOVINYL ANION EQUIVALENT

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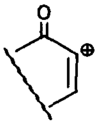
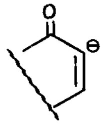
In connection with our synthetic program directed at the elaboration of cyclopentenoid antibiotics we required an efficient method for the construction of a variety of α-substituted α,β-unsaturated ketones directly from the parent enone (i.e. 1→2), which did not require intervention of the thermodynamic dienolate. To our knowledge a *general* solution for this recurring synthetic problem is unavailable, although Corey,[1] Fuchs[2] and Stork[3] have independently developed a reverse polarity (umpolung) strategy for α-alkylation and α-arylation of α,β-unsaturated ketones. Central to their approach was the generation of an effective latent equivalent for α-ketovinyl cation 3. Such a strategy, however, is limited in that it depends critically upon the availability of the requisite alkyl or aryl organocuprate or magnesium reagent.

1 2



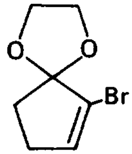
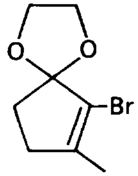
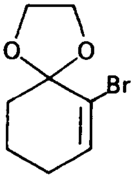
3
α-Ketovinyl cation



4
α-Ketovinyl anion

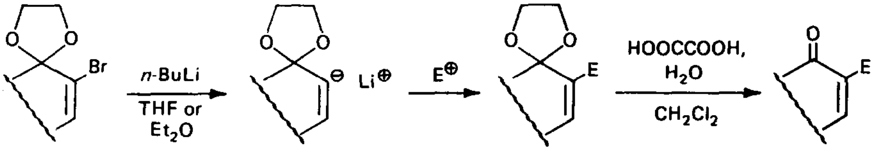
A more versatile and possibly more direct approach for the conversion of 1 to 2, albeit hypothetical, would be the generation of α-ketovinyl anion 4, followed by addition of an appropriate electrophile.[4] While the generation of such an anion, *per se*, is not feasible, recent studies by Ficini,[5a] House[5b] and Swenton[5c] suggest that α-bromoketal 5 could serve as a viable latent equivalent of 4, providing the following criteria could be met successfully: a) metalation of 5; b) electrophilic

Table 1: Synthesis of α-Substituted α,β-Unsaturated Ketones

Entry	*Substrate*	*Electrophile* (E⊕)	*Solvent*	*Overall yield from 5a–c (percent)*	*Product*
5a		D_2O	THF	79	**8a**
		CH_3I	THF/HMPA	53	**8b**
		n-$C_5H_{11}I$	Et_2O/HMPA	71	**8c**
		HCHO	THF	84	**8d**
		CH_3COCH_3	THF/HMPA	62	**8e**
		ClCOOEt	THF	53	**8f**
		TMSCl	THF	56	**8g**
		CH_3SSCH_3	THF	73	**8*l***
5b		n-$C_5H_{11}I$	Et_2O/HMPA	60	**8i**[10]
		ClCOOEt	THF	62	**8j**
5c		n-$C_5H_{11}I$	Et_2O/HMPA	69	**8k**
		ClCOOEt	THF	81	**7*l***[11]

capture of the resultant anion (6); and c) hydrolysis of ketal 7. Assuming that each step in the above sequence is efficient, the entire transformation could be effected in "one-pot."

We are most pleased to report that this is indeed the case. For example, treatment of bromoketal 5a[6] with 1.3 eq of n-butyl lithium in THF at -76°C led smoothly to anion 6a as determined by quenching with deuterium oxide. In particular, NMR analysis (220 MHz) of both ketal 7a and cyclopentenone, derived from 7a via mild acid hydrolysis, indicated > 95% monodeuterium incorporation specifically at the α-carbon.



5 6 7 8

Repetition of the above experiment employing bromoketals 5a-c and a variety of electrophiles including methyl and n-pentyl iodide, formaldehyde, acetone, ethyl chloroformate, trimethylsilyl chloride and dimethyl disulfide afforded the respective α-substituted enone derivatives 8b-l in good to excellent yield[7] (see Table I).[8] Optimum results with methyl and n-pentyl iodide were obtained when the alkylations were carried out in ether or THF containing 10-12 eq. of HMPA as co-solvent. Hydrolysis of the individual ketals could then be conveniently effected without purification by treatment with 2-3 eq of oxalic acid employing a two phase ($CHCl_2$-H_2O) system. The overall efficiency for this sequence (i.e. 5→ 8) was 51-84%.[7] The requisite bromoketals 5a-c[6] in turn were readily prepared from the corresponding parent enone in 76-84% yield via a three step protocol: a) bromination (Br_2/CCl_4); b) dehydrobromination; and c) ketalization of the resultant α-bromoenone (1.1 eq ethylene glycol/TsOH/C_6H_6/-H_2O via Dean-Stark).

A typical experimental procedure for the metalation of 5a-c is illustrated by the preparation of 2-carbethoxy-2-cyclopentenone (8 f). A mixture containing 1.02 ml (2.05 mmol, 2.0M) of n-butyl lithium in 30 ml of dry THF was treated under N_2 at -76 °C over a 5 min period with 325.4 mg (1.58 mmol) of ketal 5a in 10 ml of THF. After 1 hr, 0.45 ml (4.7 mmol) of freshly distilled ethyl chloroformate in 10 ml of THF was added and the resultant solution stirred at -78° for 3 hr, whereupon the cooling bath was removed, and after an additional 10 min the reaction quenched with

20% aq NaH_2PO_4. The usual extractive work-up (Et_2O) followed by drying with $MgSO_4$ gave a yellow oil which after TLC [2000μ silica gel/(4:1) pentane EtOAc/rf ∿ 0.3] and Kugelrohr distillation gave 181 mg (58%) of pure 2-carbethoxy-2-cyclopentenone ethylene ketal. Hydrolysis of this ketal [3.2 eq. HOOCCOOH/$CH_2CL_2H_2O$/18 hr] afforded 2-carbethoxy-2-cyclopentenone[9] in 91% yield.

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References and Footnotes

1. E. J. Corey, L. S. Melvin, Jr. and M. F. Haslanger, *Tetrahedron Lett.*, 3117 (1975).
2. P. L. Fuchs, *J. Org. Chem.*, 41, 2935 (1976).
3. G. Stork and A. A. Panaras, *J. Org. Chem.*, 41, 2937 (1976):
4. A latent equivalent of a β-ketovinyl anion was recently reported by Okamura; see: M. L. Hammond, A. Mourino and W. H. Okamura, *J. Am. Chem. Soc.*, 100, 4908 (1978).
5. a) J. Ficini and J.-C. Depezay, *Tetrahedron Letters*, 4797 (1969); b) H. O. House and W. C. McDaniel, *J. Org. Chem.*, 42, 2155 (1977); c) M. J. Manning, P. W. Raynolds and J. S. Swenton, *J. Am. Chem. Soc.*, 98, 5008 (1976); also see P. W. Raynolds, M. J. Manning and J. S. Swenton, *J. Chem. Soc.*, *Chem. Commun.*, 499 (1977).
6. The structure assigned to each new compound was in accord with its infrared and 60 MHz nmr spectra. Analytical samples of each new compound, obtained by preparative vapor phase chromatography or preparative thin layer chromatography gave C and H combustion analysis within 0.4% of theory. The 60 MHz spectra (CCl_4 δ) for enones 8b-1 are recorded below: 8b: 1.73(d, J=2Hz, 3H), 2.16-2.78 (m, 4H), 7.10-7.31 (m, 1H); 8c: 0.89(t, J=6Hz, 3H), 1.09-1.65 (m, 6H), 1.89-2.39 (m, 4H), 2.39-2.74 (m, 2H), 7.11-7.30 (m, 1H); 8d: 2.27-2.84 (m, 4H), 3.00 (broad s, 1H), 4.33 (d, J=1Hz, 2H), 7.60 (m, 1H); 8e: 1.32 (s, 6H), 2.25-2.72 (m, 4H), 2.88-3.08 (m, 1H), 7.25 (t, J=2Hz, 1H); 8f: 1.25 (t, J=7Hz, 3H), 2.30-2.55 (m, 2H), 2.61-2.90 (m, 2H), 4.14 (q, J=7Hz, 2H), 8.25 (t, J= 2Hz, 1H); 8g; 0.13 (s, 9H), 2.00-2.40 (m, 2H), 2.40-2.80 (m, 2H), 7.70 (t, J= 2.5Hz, 1H); 8h; 2.25 (s, 3H), 2.05-2.83 (m, 4H), 6.93 (t, J= 2.5Hz, 1H); 8i; 0.92 (t, J= 6Hz, 3H), 1.10-1.72 (m, 6H), 1.95 (s, 3H), 1.90-2.53 (m, 6H); 8j; 1.31 (t, J= 7Hz, 3H), 2.28 (s, 3H), 2.23-2.51 (m, 2H), 2.51-2.81 (m, 2H), 4.22 (q. J= 7Hz, 2H); 8k; 0.80 (t, J= 5Hz, 3H), 1.04-1.52 (m, 6H), 1.67-2.53 (m, 8H), 6.51 (t, J= 3.5Hz, 1H); 7; 1.25 (t, J= 7Hz, 3H), 1.54-2.54 (m, 6H), 3.69-4.40 (m, 6H), 6.95 (t, J= 4Hz, 1H).
7. All yields recorded here were based on isolated material after purification via distillatio, recrystallization or chromatography (TLC or LC on silical gel), and are not maximized.
8. In each case a 3-5 fold excess of electrophile was employed.
9. The ir and 200 MHz NMR spectra was identical in all respects with an authentic sample prepared by the method of Reich *et al.*; see H. Reich, J. M. Renga and I. L. Reich, *J. Am. Chem. Soc.*, 97, 5434 (1975); For the original synthesis of 8f see J. N. Marx, J. H. Cox and L. R. Norman, *J. Org. Chem.*, 37, 4489 (1972).
10. Identical in all respects with an authentic sample of dihyrojasmone kindly provided by Dr. W.T. Taylor of International Fragrances and Flavors.
11. All attempts to effect the hydrolysis of 71 to 81 led either to the recovery or distruction of 71.

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