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STEREOSELECTIVE PREPARATION OF METHYL (Z)-CINNAMATES BY FAVORSKII REARRANGEMENT

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Abstract: 1,3-Dibromo-1-phenylacetones, readily prepared by direct bromination of the parent phenylacetone, react with methanolic sodium methoxide to yield stereoselectively methyl (Z) cinnamates in good yield.

In the previous paper, we described a highly stereoselective method for the preparation of (Z)-2,4-pentadienoic esters based on Favorskii rearrangement[1] and double elimination of hydrogen bromide from a series of 1,3,4-tribromo-2-butanones. In a survey of the literature, we were surprised to discover that although similar reactions with α,α'-dihaloketones are well known methods for preparing (Z)-acrylates,[2] a related, general procedure for the efficient synthesis of (Z)-α,β-unsaturated esters with extended γ,δ-unsaturation has not been developed. In the present study, the preparation of methyl (Z)-cinnamates was chosen to explore the potential of this new method. We are aware of only one report of a (Z)-cinnamate product from a Favorskii rearrangement of a dihalo-phenylacetone derivative.[3] In that case, 1,1-dichloro-3-phenylacetone gave methyl (Z)-cinnamate in 40% yield upon treatment with methoxide ion. In contrast, 1,1-dichloro-1-phenylacetone produced a 4.3:1 ratio of (E):(Z) methyl cinnamates under identical conditions.

We now report that 1,3-dibromo-1-phenylacetones **2a-f** yield methyl (Z)-cinnamates **3a-f**[4] in good yield and with high stereoselectivity upon addition to 2 equiv of sodium methoxide in methanol at -20 to 0°C (eq 1 and Table I).[5] The (Z):(E) ratios were determined by capillary VPC analyses of both the crude reaction mixtures [after neutral quench (pH=7.0 sodium phosphate buffer), ether extraction and concentration] and the chromatographically purified products.[6,7] No (E) isomers of **3d,e** could be detected in the crude reaction mixtures; however, small amounts (≤1.5%) were found after chromatography on silica gel.

The α,α'-dibromophenylacetones, **2a-f**, are conveniently prepared by direct bromination of the parent phenylacetones **1a-f**, respectively.[8] Thus, treatment of **1** in acetic acid or acetic acid/carbon tetrachloride (1:1) mixtures with bromine followed by addition of aqueous sodium bicarbonate and extractive isolation afforded the dibromides **2** which were used immediately without further purification.[5] Although the 1,3-dibromophenylacetones, **2**, could be isolated by chromatography on silica gel, extensive decomposition generally resulted and low yields were obtained. With regard to mechanism, the present work is notable in that it establishes that the presence of unsaturation at C-4 of a 1,3-dibromo-2-alkanone does not alter the (Z) selectivity of the Favorskii process.[11]

Table 1: Preparation of Methyl Cinnamates from Phenylacetones[a]

Compound	Yield of 3^b(%)	(Z):(E) (isolated)
1a	80	99:1
b	65	93:7
c	79	99:1
d	79	98.5:1.5
e	78	>99:1
f	70	99:1

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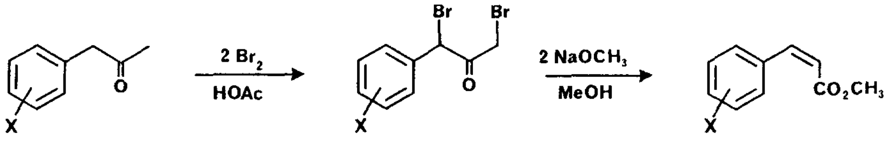
a) The phenylacetones were commercially available or readily prepared by literature procedures; see references 9 and 10.

b) Overall yield of **1** to **3**.



1a-f **2a-f** **3a-f** (1)

a, X = H
b, X = 4-CH_3
c, X = 3-CF_3
d, X = 4-Cl
e, X = 2,4-Cl_2
f, X = 3,4-Cl_2

References and Notes

1. For excellent reviews and discussions of the mechanism of the Favorskii rearrangement, see a) Baretta, A. and Waegell, B. In "Reactive Intermediates;" Abramovitch, R.A., Ed.; Plenum: New York, 1982; Vol. 2, Chpater 6. b) Hunter, D.H.; Stothers, J.B. and Warnhoff, E.W. In "Rearrangements in Ground and Excited States;" de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, Chapter 6. c) Rappe, C. In "The Chemistry of the Carbon Halogen Bond, Part 2;" Patai, S., Ed.; John Wiley and Sons: New York, 1973; Chapter 17. d) Akhrem, A.; Ustynyuk, T.K. and Titov, Y.A. Russ. Chem. Rev. (Engl. Trans.) **1970**, 39, 732 and references cited in the above.
2. Rappe, C. Org. Synth. **1973**, 53, 123.
3. Schamp, N.; De Kimpe, N. and Coppens, W. Tetrahedron **1975**, 31, 2081.
4. a) Compounds **3a-f** exhibited proper spectral characteristics (^1H and ^{13}C NMR, IR, and mass spectra including exact mass, if possible); b) dibromides **2a-f** were characterized by ^1H NMR and IR spectra.
5. Particularly noteworthy is that reaction of 1,3-dibromo-1-phenylacetone with trialkylamines in methanol gives phenylcyclopropenone; see, a) Eicher, T. and Pelz, N. Tetrahedron Lett. **1974**, 1631; b) Krebs, A. and Breckwoldt, J. ibid. **1969**, 3797.
6. Separation of the (Z) and (E) isomers of **3a-f** by column chromatography was not attempted or effected.
7. The minor (E) isomers of **3a-f** were identified by co-injection with authentic (E) methyl cinnamates prepared by diazomethane esterification of the corresponding commercially available trans-cinnamic acids.
8. Fry, A.J. and O'Dea, J.J. J. Org. Chem. **1975**, 40, 3625.
9. Kurz, M.E.; Baru, V. and Nguyen, P.N. J. Org. Chem. **1984**, 49, 1603 and references cited therein.
10. Magidson, O.Y. and Garkusha, G.A. J. Gen. Chem. (USSR) **1941**, 11, 339; CA 35:5868(5).
11. This research was supported financially by the State of Kansas and the Fulbright Scholars Program (as a fellowship to W.F.).

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