Pergamon

Tetrahedron Letters, Vol. 35, No. 26, pp. 4509-4510, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00880-9

An Expedient Synthesis of Isopropyl Anisoles and Veratroles

Jari T. Yli-Kauhaluoma and Kim D. Janda*

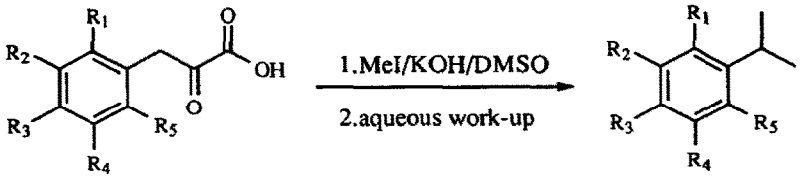
The Scripps Research Institute, The Departments of Molecular Biology and Chemistry, MB-20, 10666 North Torrey Pines Road, La Jolla, California 92037, U. S. A.

Abstract: Isopropyl-substituted anisoles and veratroles were obtained in high yields (89 - 93 %) on the aqueous work-up of the reaction of 3-(methoxyphenyl)-2-oxopropanoic acids with iodomethane and potassium hydroxide in dimethyl sulfoxide.

In the course of our studies on the applications of the twisted α-keto amides as potential transition-state analogues for acyl-transfer reactions[1,2] and peptide prolyl *cis-trans* isomerization of peptide substrates,[3] we have prepared several 2-ketocarboxylic acids as starting materials in our haptenic syntheses. From these investigations, we have discovered that methoxy-substituted isopropylbenzenes can be obtained in a convenient manner from the corresponding substituted 3-phenyl-2-oxopropanoic acids. Such monomethoxy-isopropylbenzenes (isopropyl anisoles) and dimethoxyisopropylbenzenes (isopropyl veratroles and homoveratroles) have been used to investigate substituent effects on the redox potential of arylmethyl radicals[4] and the stability of the benzyl cation in the gas phase.[5] Additionally, these anisoles and veratroles have found use in carbon-13 NMR studies of carbocations[6] and in mass spectrometry.[7]

Isopropyl anisoles and veratroles are typically obtained via Friedel-Crafts alkylation of anisoles[8] or through organolithium reactions with *o*-benzoquinone bisacetals.[9] A problem with these Friedel-Crafts reactions is that mixtures of ortho and para isomers arise. The ratio of these isomers is dependent on the catalyst and the solvent employed.[8] Similarly, the reaction of *o*-benzoquinone bisacetals with isopropyllithium yields a mixture of regioisomers as well as dialkylated veratrole as a byproduct.[9]

Herein we describe an expedient synthesis of several isopropyl anisoles and veratroles **2 a-f**. The advantage of our synthetic method is that it is not plagued with the problems of regioisomers and yields are excellent.



1 a-f **2 a-f**

Methoxy-substituted 3-phenyl-2-oxopropanoic acids, **1 a-f**, were prepared via the classical Erlenmeyer azalactone method.[10] Methoxyphenylaldehydes can be transformed to (*E*)-4-arylmethylene-2-oxazolin-5-ones[11] through the condensation reaction of *N*-benzoylglycine in the presence of acetic anhydride and anhydrous sodium acetate. All azalactones obtained were crystalline and were converted to the requisite

starting materials **1 a-f** by refluxing in aqueous sodium hydroxide.[12] A variety of isopropyl anisoles and veratroles **2 a-f** were secured when the α-keto acids **1 a-f** were treated with four equivalents of potassium hydroxide, an excess of iodomethane,[13] and by an aqueous work-up.[14,15]

Table. Reaction of 3-(Methoxyphenyl)-2-oxopropanoic Acids with KOH/MeI in DMSO.

Compound	R_1	R_2	R_3	R_4	R_5	Yield (%)	B. p. (°C/mmHg)
(2a)	H	OMe	OMe	H	H	93	55/2
(2b)	OMe	H	OMe	H	H	89	N.D.
(2c)	H	OMe	H	H	H	92	128/1
(2d)	H	H	OMe	H	H	90	N.D.
(2e)	H	OMe	H	OMe	H	88	N.D.
(2f)	OMe	OMe	H	H	H	91	49/5

N.D. = Not determined. The compound was purified by silica gel chromatography.

In a typical reaction, 0.50 g (8.92 mmol) of powdered potassium hydroxide was added to 10 ml of dimethyl sulfoxide. After stirring for 10 min, the methoxy-substituted 3-phenyl-2-oxopropanoic acid (2.23 mmol) was added, followed immediately by the addition of 0.42 ml of iodomethane (6.69 mmol). After the reaction was stirred at ambient temperature for 5 hours, the mixture was poured into water and extracted with CH_2Cl_2. The organic layer was subsequently washed with brine and dried with $MgSO_4$. The product was obtained in purified form by either silica gel chromatography or a fractional distillation.

In conclusion, we have demonstrated how isopropyl anisoles and veratroles can be prepared from α-keto acids in high yields and importantly, without the contamination of unwanted regioisomers. Because of the simplicity of our method, we view it as a viable alternative to the Friedel-Crafts reaction when preparing isopropyl anisoles and veratroles. Moreover, the use of other alkylating agents could expand the scope of this reaction to other alkyl derivatives of anisoles and veratroles.

Acknowledgments: This work was supported in part by The National Institutes of Health (GM-43858) and the Alfred P. Sloan Foundation.

REFERENCES AND NOTES

1. Yli-Kauhaluoma, J. T.; Janda, K. D. *Bioorg. Med. Chem.* in the press.
2. Yli-Kauhaluoma, J. T.; Janda, K. D. *Rep. Ser. Chem. Univ. Oulu* **1993**, *42*, 29.
3. Yli-Kauhaluoma, J. T.; Janda, K. D. unpublished work.
4. Sim, B. A.; Milne, P. H.; Griller, D.; Wayner, D. D. M. *J. Am. Chem. Soc.* **1990**, *112*, 6635.
5. Mishima, M.; Arima, K.; Usui, S.; Fujio, M.; Tsuno, Y. *Chem. Lett.* **1987**, 1047.
6. Brown, H. C.; Kelly, D. P.; Periasamy, M. *Proc. Natl. Acad. Sci. U. S. A.* **1980**, *77*, 6956.
7. Mohara, S.; Tanimoto, M.; Kikuchi, Y.; Hasegawa, Y.; Matsumoto, M. *Shitsuryo Bunseki* **1986**, *34*, 107; *Chem. Abstr.* **1986**, *106*, 83872s.
8. Olah, G. A.; Olah, J. A.; Ohyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 5284.
9. Kikuchi, Y.; Hasegawa, Y.; Matsumoto, M. *Tetrahedron Lett.* **1982**, *23*, 2199.
10. Erlenmeyer, E. *Liebigs Ann. Chem.* **1893**, *275*, 1.
11. Carter, H. E. *Org. React.* **1946**, *3*, 198.
12. Snyder, H. R.; Buck, J. S.; Ide, W. S. *Org. Synth., Coll. Vol.* **1955**, *2*, 333.
13. Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.
14. All the compounds were characterized by means of ^1H NMR spectra and mass spectra.
15. Interestingly, upon substituting potassium hydroxide for cesium carbonate, the same reaction afforded methyl 3-(methoxyphenyl)-3,3-dimethyl-2-oxopropanoates in good yield.

(*Received in USA* 30 *March* 1994; *revised* 27 *April* 1994; *accepted* 4 *May* 1994)