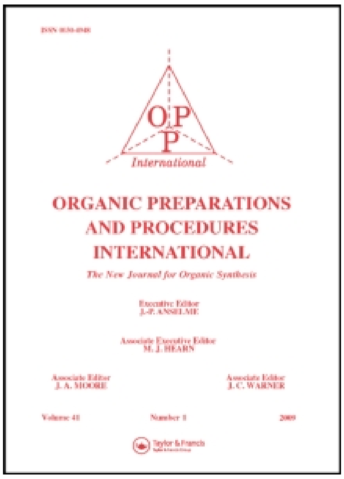

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PREPARATION OF MONOMETHYL FUMARATE

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To cite this Article Dymicky, Michael(1983) 'PREPARATION OF MONOMETHYL FUMARATE', Organic Preparations and Procedures International, 15: 4, 233 — 238
To link to this Article: DOI: 10.1080/00304948309356647
URL: http://dx.doi.org/10.1080/00304948309356647

ORGANIC PREPARATIONS AND PROCEDURES INT. 15(4), 233-238 (1983)

PREPARATION OF MONOMETHYL FUMARATE

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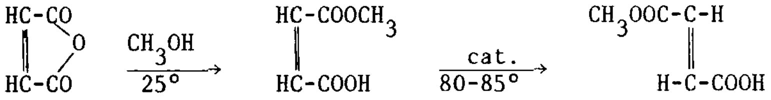
Monomethyl fumarate has been shown to display significant activity against Clostridium botulinum in canned meat.[1] Since monomethyl fumarate could be used as a potential substitute for sodium nitrite for the preservation of the meat, it appeared of interest to develop a practical and economical procedure for its preparation.



In general, the classical methods of preparation of monomethyl fumarate are impractical and inconvenient due to the time required, and the need for anhydrous hydrogen chloride as a catalyst for the esterification.[2] Furthermore, the partial hydrolysis of the diester[3,4] is potentially hazardous because of the large volume of ether required for the process[3,4]. The preparation of the ester from fumaryl chloride by partial reaction with methanol[5] is also unsuitable since it yields a mixture of the esters and free acid. Furthermore, fumaryl chloride is too expensive for industrial use, since it cannot be prepared by conventional methods from fumaric acid. The latter, upon heating with thionyl chloride, phosphorus tri- or oxychloride undergoes decomposition; only about 25% yield of fumaryl chloride was obtained from heating the acid with phosphorus pentachloride by the procedure of Perkin.[6] Treatment of the acid with oxalyl chloride at 65° for several hours, afforded maleic and monochlorosuccinic anhydride as the main products, with only about 10% fumaryl chloride. Though the acid chloride is easily prepared from maleic anhydride with phthaloyl chloride,[7] it is an expensive process. Attempts were made to prepare monomethyl fumarate from dimethyl fumarate, which was easily prepared by our procedure of esterification,[8] but extensive difficulties were encountered in the step of partial hydrolysis.[4] The stated limitations and difficulties were overcome by preparing monomethyl fumarate by isomerization of monomethyl maleate. The latter was easily prepared from maleic anhydride and methanol,[9] as outlined in the scheme.

Most of the methods suitable for isomerization of free acids,[10-13] and dimethyl fumarate[14-21] are not suitable for the isomerization of the monoester. A number of methods used for isomerization of the monoester[15,22,23] did not yield satisfactory results. Irradiation with ultraviolet light has been avoided since that procedure converts monomethyl fumarate to a dimer, cyclobutane-1,2,3,4-tetracarboxylic acid.[24] Only about 10% isomerization could be achieved using catalytic amounts of thiourea.[25] It was also not possible to achieve isomerization by heating monomethyl maleate with aqueous solutions of hydrochloric acid in presence of nitric acid.[26,27] Using the stated procedure, catalytic amounts of conc. hydrochloric acid and a number of other chlorides were found to be effective catalysts for isomerization of monomethyl maleate (Table 1); however, it appears that the chlorides of strong acids have a tendency to cause acidolysis of the ester[28,29] and yield a product containing 10%-15% of free acid. No isomerization occurred with milder, neutral chlorides. Excellent results were obtained with anhydrous aluminum chloride or phthaloyl dichloride, but the best results were obtained with fumaric monomethyl ester monochloride or fumaryl chloride (Table 1). These afforded good yields of high purity (99%-99.5%) monomethyl fumarate. The yields and purities in Table 1 refer to the product after a single recrystallization. It appears that ~2.0% of the catalysts Nos. 5 and 7 represents an optimum amount to effect a complete isomerization, as evident from the yields and the purities of the products (Table 1).

TABLE 1. Catalysts Used for Isomerization of Monomethyl Maleate

			Monomethyl fumarate (once recryst.)			
No.	Catalysts	g/mole	Yield (%)	mp. (°C)	Purity (%)	Ref.
1	Thiourea	6.00	13.4	142-3	95.5	24
2	Conc. HCl	1.25	82.1	"	96.5	18,9
3	$AlCl_3$	2.00	81.4	142	98.2	30
4	Phthaloyl dichloride	1.25	80.5	"	98.8	-
5	Fumaric acid monomethyl ester monochloride	"	81.5	141-141.5	99.3	-
6	"	2.50	85.4	"	99.3	-
7	Fumaryl chloride	1.25	82.3	"	99.4	-
8	"	2.50	85.1	"	99.5	-
9	"	3.50	84.2	"	99.2	-

EXPERIMENTAL

The purity of monomethyl fumarate was determined with a Water Associates[31] HPLC, model 440, with two pumps at 2000 psi, solvent programmer model 660, Hewlett-Packard integrator, model 3390, and μ-Bondapak C-18 column. Measured absorption at 280 nm in a solvent system 60% water, 32% methanol, and 8% acetic acid, flow rate 1 ml/min, sensitivity of the absorbance detector 0.1. IR (KBr) spectra were determined on Perkin-Elmer 421 grating spectrophotometer. Maleic anhydride (99%) and most of the chemicals were obtained from commercial sources. Fumaryl chloride was prepared as described by Kyrides,[7] fumaric monomethyl ester monochloride was prepared using procedure of Erlenmeyer and Schoenauer[4] and monomethyl maleate was synthesized using modified procedure of Siegel and Moran.[9]

Monochlorosuccinic Anhydride.- A mixture of 58.03 g (0.5 mole) of fumaric acid and 60 ml oxalyl chloride was placed into a 200-ml reaction flask, equipped with a condenser, magnetic stirrer, and the mixture was heated at 65° (silicone bath) for 11 hr with stirring. It was then cooled to 25°, filtered, residue (unreacted fumaric acid, 10 g) washed with ether, and the filtrates combined. After evaporation of ether, the residue was distilled to yield 14.70 g (30%) of maleic anhydride, bp. 56-60°/0.3 mm., 33.65 g (~50%) monochlorosuccinic anhydride, bp. 68-80°/0.1 mm., and 7.65 g (~10%) fumaryl chloride, bp. 88°/0.5 mm. Monochlorosuccinic anhydride was recrystallized twice from ether, mp. 43.5-44°, lit.[32] 40-41°.

Anal. Calcd. for $C_4H_3ClO_3$: C, 36.54; H, 2.30; Cl, 26.96

Found: C, 36.30; H, 2.28; Cl, 26.82

IR(KBr): 3020-2960,1880-1870, 1780-1745, 1395, 1290, 1275, 1230-1210, 1160, 1060-1050, 1040-1030, 950, 920-910, 895, and 755 cm^{-1}. This compound was originally prepared[32] by heating fumaric acid, acetic acid, and acetyl chloride in a sealed tube.

Monomethyl Fumarate.- A mixture of 19.60 g (0.2 mole) of maleic anhydride and 6.40 g (0.2 mole) methanol was placed into a 100-ml freeze-drying flask,[33] tightly closed and stirred (magnetic stirrer) for ~1 hr at room temperature until the solution became clear. At that point, a quantitative yield of the monomethyl maleate was obtained, as evident from HPLC determinations. This product, to which was added 0.25-0.5 g fumaric acid monomethyl ester monochloride (or some other catalyst, listed in Table 1), was immersed in a silicone bath at 50-55°, the flask closed and gradually heated to 80-85°, whereupon in about 5 min, at 65-70° the isomerization occurred, as evident from the formation of a white solid. At 75-80° the reaction mixture solidified. It was heated at 80-85° for about 2 hrs, cooled and the hard cake transferred to a mortar and pulverized, mp. 139.5-140°. Determination by HPLC indicated this material to contain ~98% of monomethyl fumarate. Recrystallization from hot water (80-85°) using 5 ml/g, yielded a crystalline material which was dried at 56°/0.1 mm to yield 22.19 g (~85%) of product, mp. 141 -141.5°, 99.3% purity by HPLC. IR (KBr): 3080, 1720, 1685, 1630, 1445, 1315, 1260, 1170, 995, 955, 775, and 645 cm^{-1}. Monomethyl fumarate was also prepared in the same way using fumaryl chloride and the other catalysts listed in Table 1. Iodine, 0.125-0.250 g/mole, did not cause isomerization.

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(Received February 8, 1983; in revised form May 9, 1983)