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for the Preparation
of Organic Compounds

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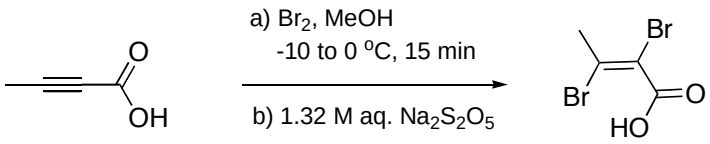
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.085.0231

STEREOSELECTIVE SYNTHESIS OF (*E*)-2,3-DIBROMOBUT-2-ENOIC ACID

(2-Butenoic acid, 2,3-dibromo-, (2*E*)-)



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Submitted by Samuel Inack Ngi, Elsa Anselmi, Mohamed Abarbri, Sandrine Langle, Alain Duchêne, Jérôme Thibonnet.[1]
Checked by Vikram Bhat and Viresh H. Rawal.

1. Procedure

Caution! All operations should be performed in a well-ventilated hood, and care should be taken to avoid skin contact with bromine.

An oven-dried, 100-mL, two-necked, round-bottomed flask protected from light (Note 1), equipped with a magnetic stir bar, a thermometer and a pressure-equalizing dropping funnel (fitted with a rubber septum and an argon inlet needle) is charged with tetrolic acid (3.0 g, 0.036 mol) (Note 2) and methanol (10 mL) (Note 3). The mixture is cooled to –10 °C (internal temperature) in an ice-salt bath.

Bromine (3.70 mL, 11.51 g, 0.072 mol, 2.0 equiv) (Note 4) is added dropwise via the addition funnel over 25 min (Note 5) while the reaction mixture is vigorously stirred. Complete bromine transfer is achieved by rinsing the addition funnel with 2 mL of methanol. The resulting dark-red solution is stirred for an additional 15 min while being cooled in the ice-salt bath. The reaction mixture is quenched by addition of 1.32 M aqueous sodium metabisulfite solution (30 mL) over 5-7 min (Note 6). The mixture is poured into a 250-mL separatory funnel and is rapidly extracted with Et_2O (4 x 50 mL) (Note 7). The combined organic layers are washed with brine (20 mL), dried over anhydrous $MgSO_4$ (7 g), filtered through a medium porosity fritted glass funnel, and concentrated on a rotary evaporator (room temperature, 25 mmHg) to provide a yellow solid (7.61 g, 0.031 mol, 87%). In a 200-mL beaker (Note 8) 7.61 g of crude product is dissolved in

dichloromethane (10 mL) (Note 9). Hexanes (10 mL) is added and the solution is kept in a fume hood at room temperature for 15 h. Much of the solvent gradually evaporates over this period, leaving a white crystalline product in an orange liquid. The liquid (ca. 3 mL) is removed using a Pasteur pipette and the product is transferred to a Büchner funnel lined with Whatman filter paper (2 layers of Grade 1, 50 mm diameter) and is washed with 3 x 50 mL of petroleum ether (Note 9). The product is then dried for 2 h under vacuum (< 1 mmHg, room temperature) to yield 6.69 g (76%) of (*E*)-2,3-dibromobut-2-enoic acid **(1)** as colorless, monoclinic crystals (Note 10).

2. Notes

1. The flask was protected from light with aluminum foil. All procedures were carried out in a room with overhead lights turned off.
2. Tetrolic acid was purchased from Aldrich Chemical Co. and was used it as received.
3. Methanol (99.8%) was purchased from Acros and was used as received.
4. Bromine (>99.8%) was purchased from Acros and was used as received. ***CAUTION****: Bromine is extremely corrosive and must be handled with great care and always in a fume hood*.
5. Because the bromination is exotherimic, the rate of addition of bromine was such that the internal temperature of the reaction mixture never exceeded –5 °C. Submitters found up to 6% of the *Z*-isomer was formed when the internal temperature was allowed to rise above 0 °C.
6. Quenching the reaction was exothermic as well. Sodium metabisulfite solution was added dropwise using the addition funnel such that the internal temperature 7was allowed to rise gradually to 20 °C. The reaction mixture turned pale yellow when the excess bromine was quenched.
7. The flasks, including the separatory funnel, were protected from light with aluminum foil. The product was found to be unstable under light when in solution.
8. The 200 mL beaker (10.2 cm high with 5.8 cm diameter) was wrapped with aluminum foil and was covered with perforated aluminum foil (ca. 40 holes were made using a PrecisionGlide 16G1 ½ needle).
9. Dichloromethane was purified by percolation through activated alumina. Hexanes (anhydrous, 99.9%) was obtained from Acros Petroleum

ether (bp range 36–60 °C) was obtained from Fisher Chemicals and was used as received.

10. (*E*)-2,3-Dibromobut-2-enoic acid (**1**), displayed the following physicochemical properties: mp 91–93 °C; IR (KBr) cm^{-1}: 3400-2300, 1703, 1600, 1274; ^{1}H NMR (500 MHz, $CDCl_3$ with 0.03% TMS) δ: 2.58 (3 H, s); 11.76 (1 H, bs); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 30.2, 107.4, 126.2, 168.9; MS *m/z* (EI) 244 (M^+, 49), 165 (99), 163 (100), 135 (21), 79 (23), 67 (22), 55 (24), 45 (26); HRMS calcd for $C_4H_3{}^{79}Br_2O_2$ (M^+–H): 240.8494, found 240.8505; Anal. Calcd. For $C_4H_4Br_2O_2$: C, 19.70; H, 1.65; Br 65.53; O, 13.12. Found: C, 19.54; H, 1.73; Br, 65.24; O, 13.02.

Safety and Waste Disposal Information

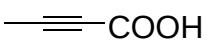
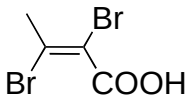
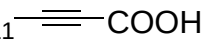
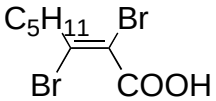
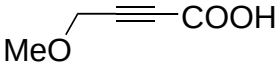
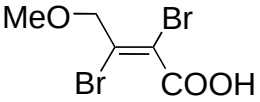
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The synthesis of α,β-dihalogeno-unsaturated systems has already been fully described and selectively achieved by addition of dihalogens on acetylenic systems.[2-14] On the other hand, little information is available regarding the synthesis of unsaturated α, β-dihalogeno carboxylic acids.[2-7, 15] Studies published up to now focus mainly on α, β-acetylenic ester dihalogenation by direct addition of dihalogen,[8-12] or in the presence of halonium ion sources.[6, 7] Direct site- and stereoselective dibromination of tetrolic acid is an easy procedure that can be carried out with good results and without secondary products.[16] The reaction is not seem effected by solvent, and similar yields were obtained when using MeOH, Et_2O, or $CHCl_3$. Maintaining the reaction temperature below 0 °C during the addition was imperative; above that temperature an *E/Z* mixture of the product was obtained. The crude dibrominated acid obtained before crystallization was pure enough for subsequent coupling reactions.

The same procedure can be applied to certain other α,β-acetylenic acids, and the results are summarized in Table 1.[16]

Table 1 - Stereoselective synthesis of (*E*)-2,3-dibromoalk-2-enoic acid

Entry	Alkyne	Solvent	Product	Yield, %
1		MeOH or Et_2O or $CHCl_3$	 **1**	87
2	C_5H_{11} 	MeOH or $CHCl_3$	 **2**	97
3		MeOH or neat	 **3**	87

The *E* configuration of the double bond in the products obtained was proven by X-ray analysis.[16]

Unfortunately, this procedure does not give good results with propiolic acid, for which a mixture of brominated alkane and alkene products are formed.[9]

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(*E*)-2,3-Dibromobut-2-enoic acid: (2-Butenoic acid, 2,3-dibromo-, (2*E*)- (9); (24557-17-3)
(*E*)-2,3-Dibromooct-2-enoic acid: (2-Octenoic acid, 2,3-dibromo- (4); (861041-43-2)
4-Methoxy-2-butynoic acid: 2-Butynoic acid, 4-Methoxy (9); (24303-64-8)
Tetrolic acid: 2-Butynoic acid (9); (590-93-2)
Pentylpropiolic acid: 2-Octynoic acid (6, 7, 8, 9); (5663-96-7)
Bromine (8, 9); (7726-95-6)

Jérôme Thibonnet, born in 1971 in Joinville (France), received his Ph.D. in 1999 from the University of Tours working on the total synthesis of retinoids under the supervision of Professor Alain Duchêne. After post-doctoral studies in the laboratory of Professor Paul Knochel at University of Munich, he joined the University of Aix-Marseille III as ingénieur de recherche at the laboratory of Professor Maurice Santelli (2000). He became Lecturer at the University of Tours in 2003. His research interests include new synthetic methods development of new organotin reagents and total synthesis of natural compounds.

Samuel Inack Ngi was born in Douala, Cameroon, 1977. He obtained his Master 2 of Organic Chemistry at the University of Orléans in 2005. He made his practical training under the guidance of Dr. Jérôme Thibonnet in the Organic Chemistry Laboratory of the Chemistry Department of Sciences at the University of Tours. During the same year he was allowed to begin his Ph.D. at the University of Tours under the direction of Pr. Alain Duchêne and Dr. Jérôme Thibonnet. His research focuses on the synthesis of heterocycles using reactions catalyzed by copper, in order to produce natural biologically active compounds or analogous.

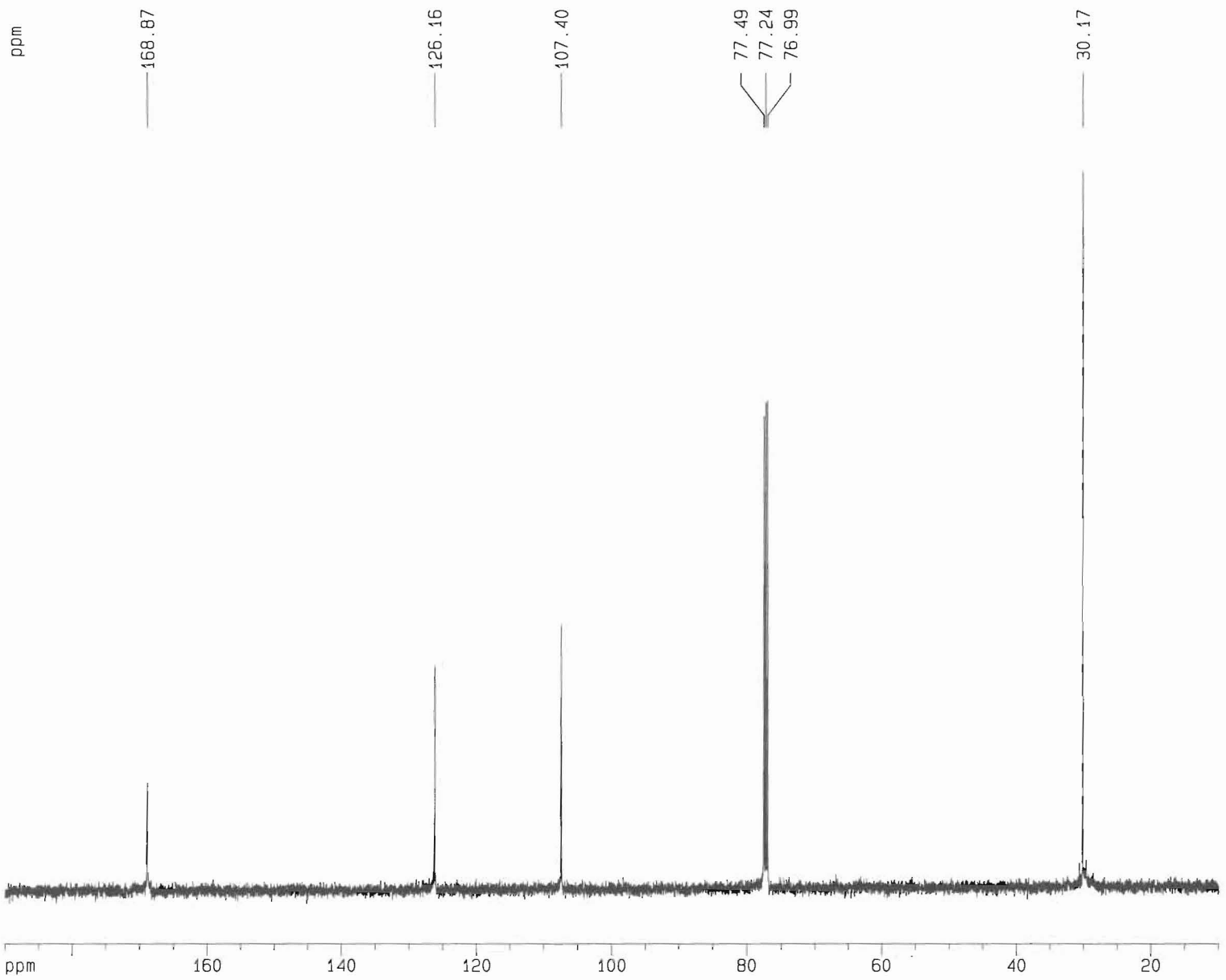
Elsa Anselmi was born in Suresnes (France, Hauts-de-Seine) in 1974. She obtained her Ph.D. degree in 2000 from the "University of Versailles St-Quentin en Yvelines" under the guidance of Dr. Claude Wakselman and Jean-Claude Blazejewski on the development of new trifluoromethylation methods. After three years of post-doctoral studies on the synthesis of new fluorinated or deuterated monomers and polymers (CEA-Monts), she became Lecturer at the University of Tours in 2004. Her research interests include new synthetic methods development of new organotin reagents, new monomers and total synthesis of natural compounds.

Mohamed Abarbri was born in 1966 in Alhoceima (Marocco). He obtained, in 1995, his Ph.D. in Chemistry at the University of Tours. After post-doctoral studies in the laboratory of Professor Paul Knochel at the University of Marbourg, he became Lecturer (1996) and full professor in 2002 at the University of Tours. His research interests include new synthetic methods, development of new organotin reagents, ultra-sound chemistry and synthesis of perfluoro compounds.

Sandrine Langle was born in 1977 in Tours (France), obtained her Ph.D. in 2004 from the University of Tours working on the synthesis and reactivity of dihalogeno-unsaturated systems. After post-doctoral studies in the Service Hospitalier Frédéric-Joliot (CEA) at Orsay in radiochemistry, she became Lecturer at the University of Nancy in 2006. Her research interests include new prosthetic groups and radiotracers development for PET imaging and radiolabelling of molecules with 18-fluorine.

Alain Duchêne was born in Tours (France) in 1947. He studied organic chemistry at the Faculty of Sciences, Bordeaux I University. After post-doctoral studies in the laboratory of Professor Ryoji Noyori at the University of Nagoya (1992) he was promoted full professor in 1997 at the University of Tours. His research interests include new synthetic methods development of new organogermanium or tin reagents, ultra-sound chemistry and synthetic organic materials.

Vikram Bhat was born in 1981 in Ajmer, India. He received his undergraduate education at the Indian Institute of Technology, Bombay, Mumbai. In 2005 he entered the graduate program at the University of Chicago where he joined the research group of Professor Viresh H. Rawal. Currently, his graduate research focuses on the total synthesis of welwitindolinone alkaloids.

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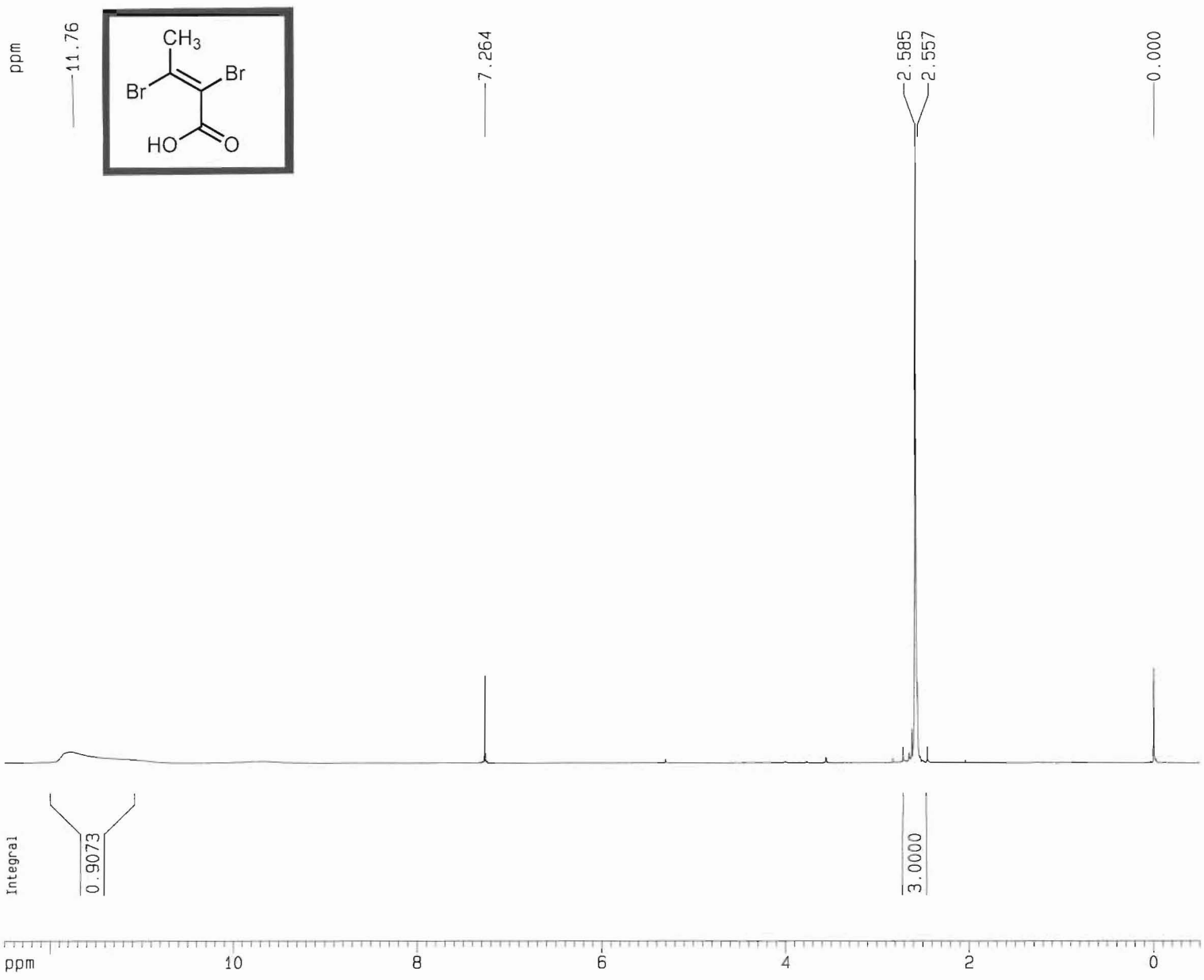

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