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An Efficient and Practical Synthesis of Dimethyl 2-chloromalonate

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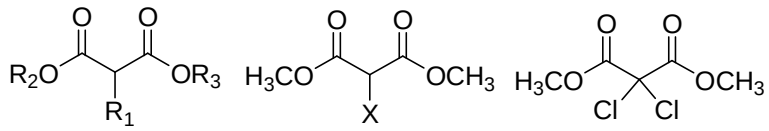
ABSTRACT

Dimethyl 2-chloromalonate, an important reagent unavailable commercially in high chemical purity, has now been successfully produced on pilot plant scale by chlorination of readily available dimethyl malonate with sulfuryl chloride.

Keywords: Dimethyl 2-chloromalonate, chlorination, dimethyl malonate, sulfuryl chloride, pilot plant.

INTRODUCTION

Dialkyl 2-substituted malonates (**Figure 1**) are known to be very useful reagents in the field of Organic Synthesis. These on cyclocondensation with dinucleophiles afford 5-, 6- and 7-membered rings generating a variety of heterocycles that possess as structure element a 1,3-dicarbonyl moiety or its enolized tautomeric 1-oxo-3-hydroxy form [1].



Dialkyl 2-subtituted malonates

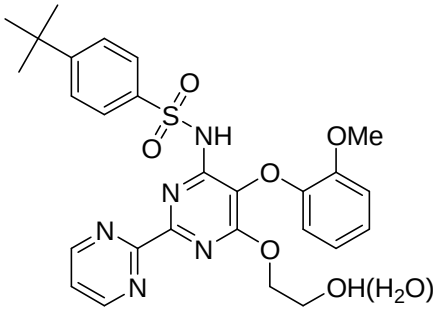
1a: X = -Cl
1b: X = -Br

2

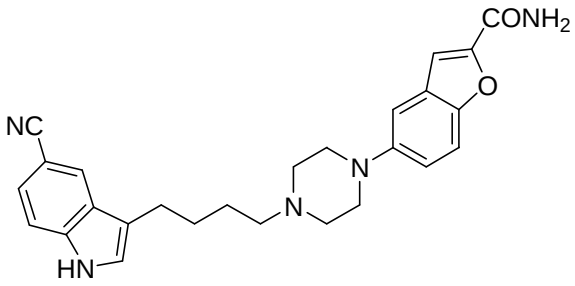
Figure 1. Structures of Dialkyl 2-subtituted malonates, Dimethyl 2-chloromalonate 1a, Dimethyl 2-bromo malonate 1b and Dimethyl 2,2-dichloromalonate.

Dialkyl 2-halo malonates are also important starting materials for the synthesis of various Active Pharmaceutical Ingredients (APIs) such as Bosentan, Viibryd™ (Vilazodone hydrochloride) and AG-2034 (**Figure 2**) [2]. Beside the preparation of simple derivatives such as dialkyl 2-aryloxy malonates, dialkyl 2-halo malonates are useful for construction of (i) pyrimidinediones by condensation with amidines [2a,3], (ii) cyclopropanated fullerenes by Bingel-Hirsch reaction [4], (iii) benzofurans by *O*-alkylation of corresponding salicyladehyde [5], (iv) *tetra*-alkoxycarbonylallylidenetri phenyl phosphoranes by a multi component reaction with

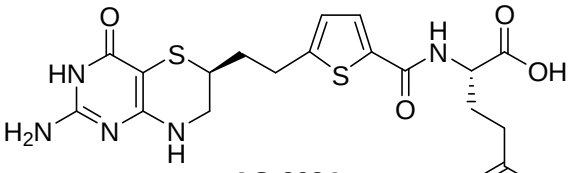
dialkylacetyl enedicarboxylates and triphenylphosphine [6], (v) 3-oxothio morpholine ring by condensation with corresponding *tert*-butyl 2-acetylmercaptoethyl carbamates [2c] and many others [7].



Bosentan



Viibryd (vilazodone hydrochloride)



AG-2034

Figure 2. Structures of Bosentan, Viibry (Vilazodone hydrochloride) and AG-2034.

MATERIALS AND METHODS

Dimethyl malonate and sulfuryl chloride were obtained from commercial sources and used without further purification. All reagents and solvents employed were of commercial grade and were used as such, unless otherwise specified. Reaction flasks were oven-dried at 200°C, flame-dried and flushed with dry nitrogen prior to use. Silica plug filtration was performed using Kieselgel 60 brand silica gel (60-120 mesh). The IR spectra were obtained on a Nicolet 380 FT-IR instrument (neat for liquids and as KBr pellets for solids). NMR spectra were recorded with a Varian 300 MHz Mercury Plus Spectrometer at 300 MHz (^{1}H) and at 75 MHz (^{13}C). Chemical shifts were given in ppm relative to trimethylsilane (TMS). Mass spectra were recorded on Waters quattro premier XE triple quadrupole spectrometer using either electron spray ionisation (ESI) or atmospheric pressure chemical ionization (APCI) technique.

Synthesis of Dimethyl 2-chlromalonate (1a). A 50-L all glass reactor was purged with nitrogen and charged dimethyl malonate **3** (20 Kg, 151.4 mol) at 25 °C. To this stirred content, sulfuryl chloride (24.5 Kg, 181.7 mol) was added over a period of 1 h, maintaining the batch temperature <25 °C. The reaction mixture was gradually heated to 40-45 °C and maintained for 4-5 h at same temperature (40-45 °C).GC of the sample indicated less than 6.0 area % of dimethyl malonate remaining in the reaction mixture. At this point the reaction mixture was cooled to 25 °C and stirred for 30 min. The liquid dimethyl 2-chloromalonate was unloaded from reactor and performed complete analysis. Compound **1a** was obtained as a yellow colored liquid in 98% yield, 24.71 Kg, with a GC purity of 90.3 area %.

Reprocess method for purification of dimethyl 2-chloromalonate. To a stirred solution of curde dimethyl 2-chloromalonate **1a** (24 Kg) in ethyl aceate (10 L), silica gel (10 Kg, 60-120 mesh) was slowly added over 15 min, maintaining the batch temperature <30 °C. The suspension was

stirred at 25 °C for 30 min and evaporated to dryness. The obtained material was triturated with hexanes (35 L) and made as a bed using nutch filter and bed was washed successively with 2 % EtOAc in hexanes (10 L), 5 % EtOAc in hexanes (10 L), 10 % EtOAc in hexanes (25 L), 15 % EtOAc in hexanes (25 L) and 25 % EtOAc in hexanes (25 L). The small aliquot of all five fractions were separately concentrated and analyzed using GC. The pure fractions were combined and concentrated to dryness until constant weight to obtain dimethyl 2-chloromalonate **1a** as a pale yellow colored liquid in 87 % yield (85 % overall yield from **3**), 20.9 Kg, with a GC purity of 97.5 area %, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.8 (s, 6H), 4.8 (s, 1H); IR (neat): ν 1017, 1161, 1752, 2963 cm^{-1}; ESI-MS: m/z 167 (100, M^++1), 169 (100, M^++3).

Synthesis of Dimethyl 2-(2-methoxyphenoxy)malonate (5). Guaiacol, **4** (200 g, 1.61 mol) was dissolved in toluene (1 L) at room temperature and sodium hydroxide (67.6 g, 1.692 mol) was added. The reaction mixture was heated to reflux temperature and separated water azeotropically. Thereafter, dimethyl 2-chloro malonate **1a** (321.8 g, 1.93 mol) was added at 65 °C over a period of 30 min and heated to reflux temperature and stirred for 3 h. The reaction mixture was cooled to room temperature, washed with purified water followed by 1% aqueous sodium hydroxide solution (1 L) and concentrated to yield dimethyl 2-(2-methoxyphenoxy) malonate, **5** in 94 % yield, 385 g, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.8 (s, 9H), 6.8 (m, 2H), 7.0 (m, 2H); IR (neat): ν 1446, 1503, 1770, 2514, 3231 cm^{-1}; ESI-MS: m/z 255 (M^++1).

RESULTS AND DISCUSSION

In our lab, we required dimethyl 2-chloromalonate, **1a** in larger quantities for the development of an advanced intermediate. Among dialkyl 2-halo malonates, it became apparent that dimethyl 2-chloromalonate **1a** proved superior to the corresponding bromo compound **1b**, both in terms of atom economy and cost of the final molecules. As per the information from our commercial suppliers, dimethyl 2-chloromalonate **1a** is available in limited purity (< 85 % by Gas Chromatography) and contains considerable amount of dimethyl 2,2-dichloromalonate **2** (Figure 1) as a major single impurity along with few others. However, lab grade material of dimethyl 2-chloromalonate **1a** available from Sigma-Aldrich (92-94% pure; USD 500 / 100 g).

A review of the literature revealed that this malonate **1a** can be made by chlorination of dimethyl malonate **3** either with sulfuryl chloride or dichlorantin, but these methods only provide material in 75 and 80% purity, respectively [8]. In literature it has also been mentioned the formation of 20-25 % of dimethyl 2,2-dichloromalonate **2** as impurity while chlorination of dimethyl malonate **3** [8b]. Other chlorination methods are available for malonates and those methods are not commercially viable [9].

Table 1. The effect of solvent on reaction progress and impurity 2 formation

Entry No.	Solvent	Content (%)*		
		3	**2**	**1**
1.	Methylene chloride (10 mL/g)	11.8	10.2	78.1
2.	Methylene chloride (5 mL/g)	13.2	11.9	72.3
3.	Toluene	14.7	6.2	67.4
4.	Acetonitrile	13.2	8.7	76.2

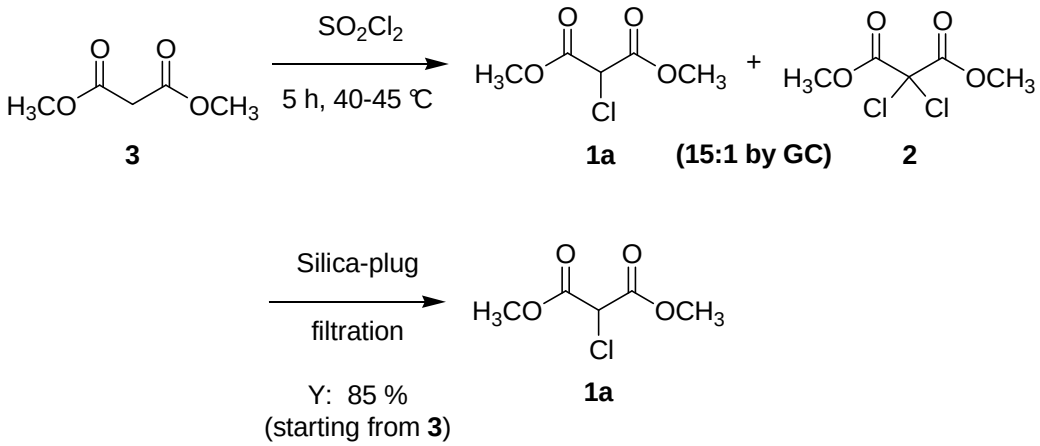
*Note. All the reactions were maintained in respective reaction condition for more than 72 h. *Area % by GC in the reaction mixture. Any other major single maximum impurity (> 1.0 %) was not observed.*

Herein we report an inexpensive synthesis of dimethyl 2-chloromalonate **1a** starting with readily available dimethyl malonate **3**. Our goal was to develop a high-throughput process that would yield chemically pure material **1a** on a consistent basis. In view of cost of the final molecule, we

focused on chlorination of dimethyl malonate **3** with commercially available sulfuryl chloride. The preparation of chloromalonate **1a** in methylene chloride solvent has been reported earlier. We studied readily formation of **1a** in a number of more EPA-friendly solvents such as toluene gave better results (other than methylene chloride) at elevated temperature. The results are depicted in **Table 1**.

However, in these solvents reaction doesn't reach to completion even after 3 days and conversion is only about 67 % (entry 3) and 76 % (entry 4) by GC. In both the solvents formation of dimethyl 2,2-dichloromalonate, **2** was observed in about 6.2 and 8.7 % respectively. The effect of other parameters such as mole ratio, concentration (solvent volumes), temperature and time on progress of reaction was studied and found no considerable impact on reaction conversion.

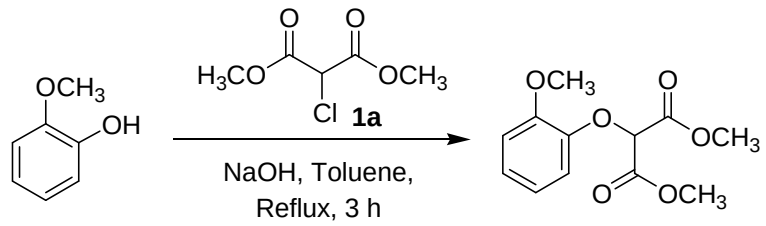
Apart from these, we also carried out reaction with equimolar ratio of both starting materials i.e. dimethyl malonate **3** and sulfuryl chloride, without any solvent (neat reaction) at 45 °C and observed positive reaction conversion (formation of **1a** about 83 % by GC) but no completion. With 1.2 mole equivalents of sulfuryl chloride in neat condition at same temperature, observed the formation of maximum % of product **1a** (88 %) after 5 h (Note: In this condition, left over starting material **3** is 5.9 % and dichloro compound **2** is 5.0 % by GC). After 48 h of reaction maintenance at same temperature, some of product also converts to dichloro impurity **2**. Finally after 48 h, GC analysis showed 75 % of dimethyl 2-chloromalonate **1a**, 15 % of dichloro impurity **2** and 6 % of starting material, **3**. Hence, we finalized to discontinue reaction after 5 h (cooled to room temperature) in order to obtain maximum amount of product and to reduce impurity **2** formation. Product **1a** was isolated without any work up and used for next reaction conversions as such. The isolated product **1a** contains purity about 90 % (by GC) with 5 % of dimethyl malonate **3** and 5 % of dichloro impurity **2** with almost quantitative yield (**Scheme 1**).



Scheme 1. Synthesis of Dimethyl 2-chloromalonate, 1a

O-Alkylation of the aromatic moiety with dimethyl 2-chloro malonate **1a** could easily be performed using the above mentioned crude product (90%) as neither the dichloro compound (impurity) nor the dimethyl malonate (starting material) can react with phenols under reaction conditions. Hence, these impurities could be removed easily during purification of *O*-alkylated products. We substantiated it by preparing a well known Bosentan intermediate, dimethyl 2-(2-methoxyphenoxy)malonate, **5**. Accordingly, guaiacol **4** is treated with dimethyl 2-chloromalonate **1a** (purity 90 area % by GC) using NaOH as a base in toluene affording dimethyl

2-(2-methoxyphenoxy)malonate **5**. We were able to get rid of the two impurities (dimethyl 2,2-dichloro malonate **2** and dimethyl malonate **3**).



Guaiacol, 4 **Bosentan intermediate, 5**

Scheme 2. Synthesis of Bosentan intermediate, dimethyl 2-(2-methoxyphenoxy)malonate 5

However, the same logic cannot be applied while either constructing pyrimidinediones by cyclocondensation with amidines or using compound **1a** as a reagent in final (or pre-final) stages to prepare a drug product. Manufacturers would generally expect high quality reagent for this type of reactions as the impurities react too. In these situations, raw materials with high purity (minimum 95 %) are appreciated in order to control the impurity levels of drug product. Hence, we took it upon ourselves to develop a reprocessing method to remove impurity **2** (from **1a**). The obvious choice for purification of dimethyl 2-chloromalonate **1a** would point to fractional distillation. However considerable yield loss prevented us from opting for this and we developed a simple and easily accessible purification method to remove impurity **2** through a silica-plug filtration. We achieved dimethyl 2-chloro malonate with required quality (purity NLT 95 area % by GC) in high yields.

CONCLUSION

We have described a practical, cost-effective chlorination of dimethyl malonate **3** for the preparation of pure dimethyl 2-chloromalonate **1a**. An examination of reaction parameters has revealed the factors crucial for the formation of dichloro impurity **2**. Additionally, a scalable reprocess has been developed that renders dimethyl 2-chloro malonate **1a** in purity that is NLT 95 area% by GC. This novel reprocess protocol was scaled up to prepare malonate **1a** about 25 Kg in pilot plant.

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