A NEW SYNTHESIS OF 3-(BROMOMETHYL) FURAN-2,5-DIONE

A. Arfaoui, T. Ben Ayed, H. Amri *

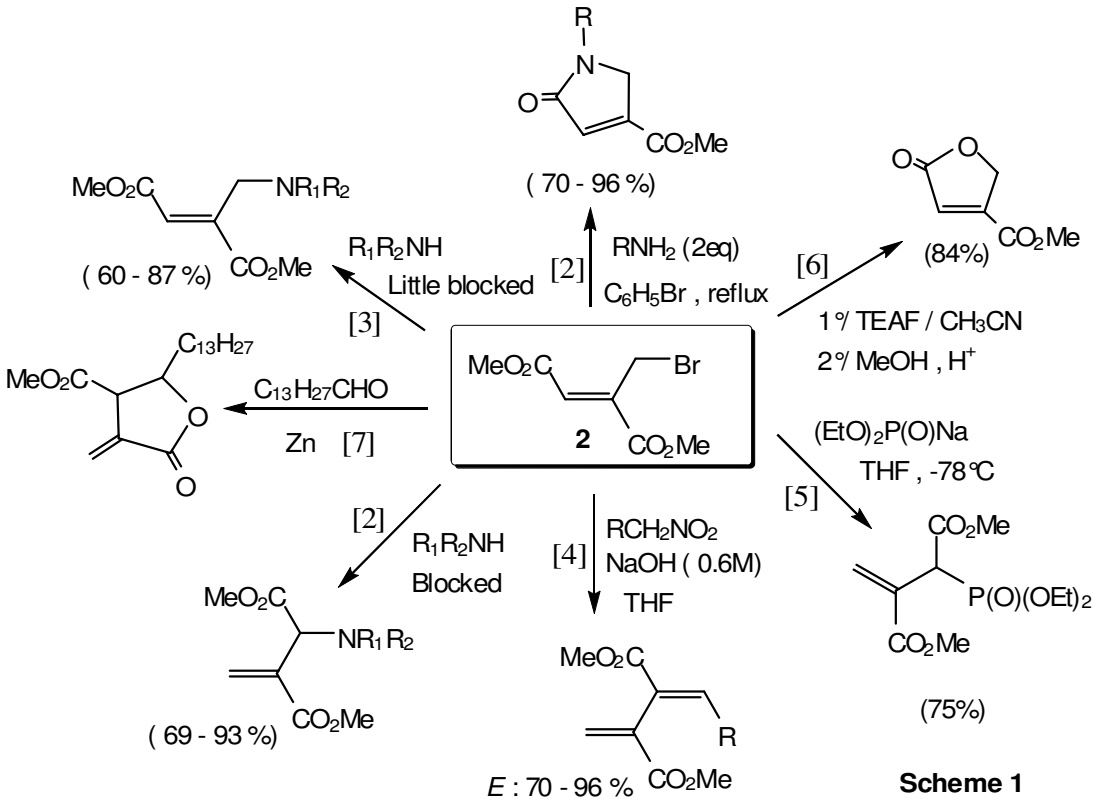
Laboratoire de Chimie Organique et Organométallique
Faculté des Sciences de Tunis-Campus Universitaire 2092 Tunis- TUNISIE

(Reçu le 2 Octobre 2007, accepté le 12 Février 2008)

Abstract: 3-(Bromomethyl) furan-2,5-dione **5**, a highly functionalized and reactive compound was prepared in three steps with an excellent yield starting from the dimethyl itaconate **1**.

Key words: Allyl bromide, 3-(bromomethyl) furan-2,5-dione , dimethyl itaconate.

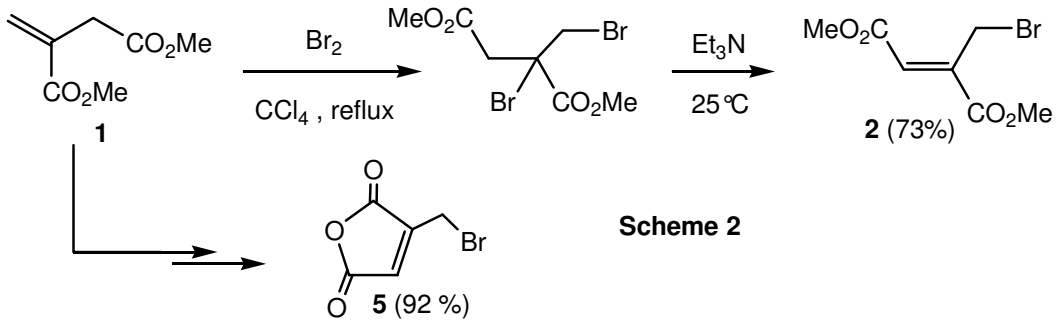
During the last years, dimethyl α-(bromomethyl) fumarate **2** [1] revealed a considerable synthetic potentiality due to its easy conversion into aliphatic and heterocyclic functionalized organic compounds (Scheme 1).



Scheme 1

* corresponding author, e-mail : hassen.amri@fst.rnu.tn.

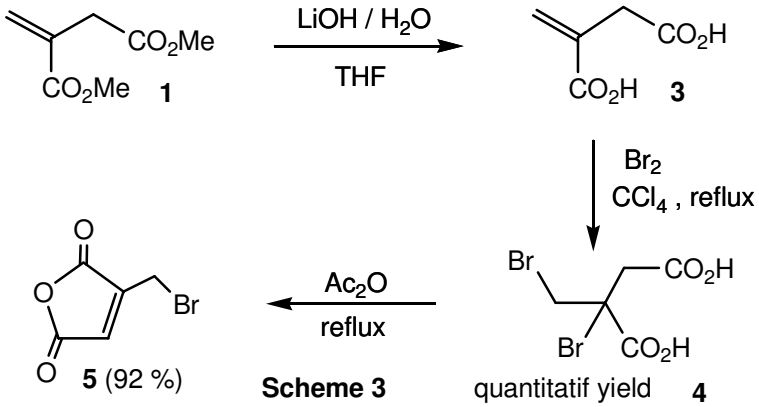
The bromination of commercially available dimethyl itaconate **1** with bromine under reflux of carbon tetrachloride, gives rise to an intermediate dibromide compound which can be easily converted into a regio- and stereoselective dehydrobromination process [8] induced with triethylamine, to give the dimethyl α-(bromomethyl) fumarate **2** in 73% overall yield (Scheme 2).



Scheme 2

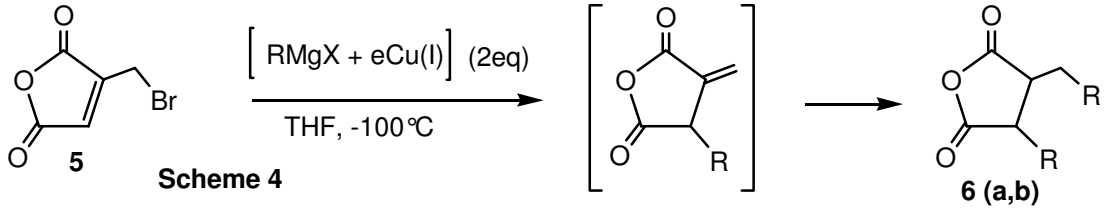
In this way, it appeared plausible to search a new synthetic ways [9-13] to elaborate some analogous cyclic models such as the derivative of maleic anhydride **5** (Scheme 2) which known to be an efficient therapeutic agent against the neurological mess and also for its increased reactivity toward nucleophilc reagents as it is reported for the first time in an international patent in 1986 [14].

Our continued interest in the synthesis of allyl bromide derivatives led us to reinvestigate the methodology that has been used to prepare the aliphatic allyl bromide **2** and further in the preparation of the cyclic model **5**. Our strategy was based on three transformations, the hydrolysis of the dimethyl itaconate **1** followed by the α-bromination and intramolecular cyclization with very fast loss of hydrogen bromide, to give the 3-(bromomethyl) furan-2,5-dione **5** with an excellent yield (Scheme 3).



Scheme 3

During this study, we also observed that the elimination of the bromine atom in the allyl position [15] of α,β-unsaturated diester **5** *via* a Michael reaction type [16-18] provides an increased reactivity of the anhydride **5** toward organocopper reagents [19-21]. This resulting in any case in a double attacks S_N2' leading to 3,4-dialkyl dihydofuran-2,5-diones **6** with a good yields (Scheme 4).

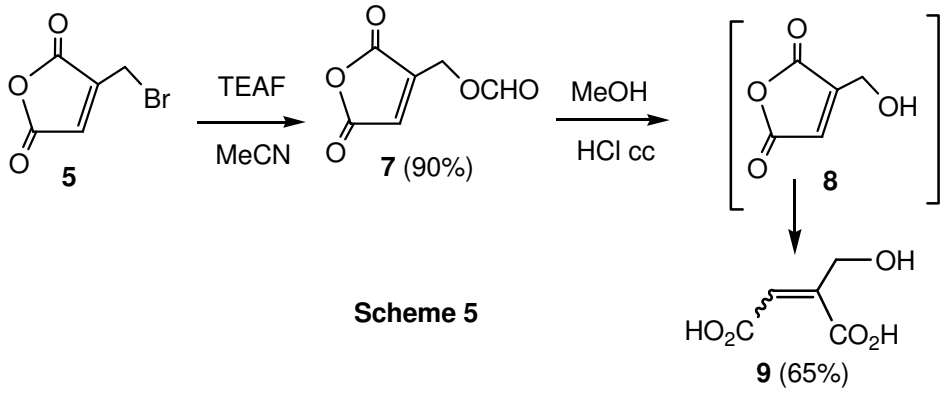


Scheme 4

Table 1: *Synthesis of the 3,4-dialkyl dihydrofuran-2,5-diones* ***6***

Product	RMgX	Yields (%)
6 a	MeMgBr	70
6 b	EtMgBr	74

As for the formylation [22] of the allylic bromide **5** by the use of triethylammonium formate (TEAF) in acetonitrile [23-27] after stirring for 2h, it permits to cover only the substitution S_N2 product of the ion bromide by the ion formate [28]. The formic ester **7** so isolated gets ready to an easy conversion into the hydroxymethyl intermediate **9** *via* a catalytic acidification using two drops of concentrated hydrochloric acid in methanol at room temperature [29]. Considering its instability in acidic media, the isomerization process of anhydride **8** involved the ring opening of the furanic cycle to give the α-hydroxymethyl butendioïc acid **9** (Scheme 5).



Scheme 5

In conclusion, we report in this work a simple and direct methodology consisting in the synthesis of the 3-(bromomethyl) furan-2,5-dione **5**, a highly reactive product from the commercially available dimethyl itaconate **1**. This procedure proves to be very useful and efficient compared to the unique reported one up to date in the literature [14].

EXPERIMENTAL SECTION

Structures of compounds obtained after distillation were identified by: ^{1}H and ^{13}C NMR on Bruker device AM 300 (300 MHz), IR on a spectrometer PERKIN ELMER PARAGON 1000 PC and by elementary analysis in certain cases. All NMR ^{1}H and ^{13}C spectra were achieved on samples dissolved in $CDCl_3$ and DMSO-D6, using TMS as an internal reference. The chemical displacements (δ) were expressed in ppm.

2-Methylene succinic Acid 3

In 1000 mL round-bottomed flask, fitted with 100 mL pressure-equalizing addition funnel, was introduced 16,3g (0,1 mol) of dimethyl itaconate **1** in 450 mL of THF then 15g (0,62 mol) of lithium hydroxide solubilized in 150 mL of distilled water was added quickly under magnetic agitation. The saponification reaction required 18 h of contact. To the obtained salt, was added 250 mL of a hydrochloric acid solution (2N) until acidic pH. The mixture was left under agitation during 2h. After extraction with ethyl acetate, the organic phase was dried on $MgSO_4$ then evaporated in vacuum conditions to give the 2-methylenesuccinic acid **3** in the form of a white powder. (Yield = 95%) ; IR (cm^{-1}) : 1703 (C=O), 1627 (C=C) ; NMR ^{1}H (DMSO-D6 / TMS) :

12.5 (s *br*, 2H, -CO_2H), 3.2 (s, 2H, CH_2-CO_2H); 5.7 and 6.1 (2s, 2H, =CH_2). NMR ^{13}C (DMSO-D6 / TMS) : 37.2 (CH_2), 127.3 (=CH_2), 135.2 (=*C*), 167.3 (=C-CO_2H), 171.9 (CH_2-CO_2H). Anal. calcd. for $C_5H_6O_4$: C, 46.16 ; H, 4.65. Found: C, 45.96 ; H, 4.56.

2-Bromo-2-(bromomethyl) succinic acid 4

To a mixture of 13g (0,1 mol) of 2-methylenesuccinic acid **3** dispersed in 500 mL of anhydrous carbon tetrachloride and carried to the ebb previously, was added drops by drops, under magnetic agitation, 10 mL (0,18 mol) of bromine in 150 mL of CCl_4. The solution discolours with the progression of the addition of bromine until persistence of a red coloration indicating the end of the reaction. After cooling, the excess of bromine was eliminated by addition of a saturated solution of sodium thiosulfate. After extraction with ethyl acetate, the organic layer was washed with a saturated NaCl solution then with water and dried on magnesium sulfate. The evaporation of the solvent provides a brown clear solid. (Yield = 100%); NMR ^{1}H (DMSO-D6 / TMS) : 4.27 (s, 1H, CH_2-CO_2H) ; 3.22 (s, 1H, CH_2-Br) ; NMR ^{13}C (DMSO-D6 / TMS) : 39 (CH_2-Br), 39.6 (CH_2-CO_2H), 57.3 (Br-*C*-CO_2H), 168.7 (CH_2-CO_2H), 169.9 (C-CO_2H). Anal. calcd. for $C_5H_6Br_2O_4$: C, 20.71 ; H, 2.09 ; Br, 55,12. Found: C, 20.25 ; H, 1.99 ; Br, 55,02.

3-(Bromomethyl) furan-2,5-dione 5

In 500 mL round-bottomed was introduced under nitrogen atmosphere 29g (0,1 mmol) of diacid dibromide **4** solubilized in 235 mL of acetic anhydride and the reaction mixture was stirred during one night. After evaporation the excess of anhydride under vacuum conditions, the mixture is cooled then diluted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The black residue was distilled under reduced pressure (Yield = 92%), $Eb_{0,2}$ = 81°C pale yellow liquid to 25°C crystallizing to 0°C . NMR ^{1}H ($CDCl_3$ / TMS) : 4.3 (s, 2H, CH_2-Br); 7 (s, 1H, =C*H*-). NMR ^{13}C ($CDCl_3$ / TMS) : 18.7 (CH_2-Br), 131.8 (=*C*H), 148 (=*C*), 162.7 (=CH-*C*O-), 163.5 (=C-*C*O-). Anal. calcd. for $C_5H_3BrO_3$: C, 31.44 ; H, 1.58 ; Br, 41,84. Found: C, 30.56 ; H, 1.71 ; Br, 41.96.

3,4-Dialkyl dihydofuran-2,5-dione 6 a,b

THF solution of alkylmagnesium halide RMgX was added dropwise over a period of 20-30 min to a mixture of 3-(bromomethyl) furan-2,5-dione **5** (5 mmol) and 1M solution of $LiCuBr_2$ (0.5 mL, 10 mol%) diluted in 30 mL dry THF at -70 °C under nitrogen atmosphere. A magnetic stirring was maintained at this temperature. After a few minutes (TLC), the reaction mixture was quenched with a 10 mL saturated NH_4Cl solution then extracted with ether (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (AcOEt / Hexane, 0.5:9.5) to afford anhydride 3,4-dialkyl dihydofuran-2,5-diones **6 a,b**.

3-Ethyl-4-propyl dihydofuran-2,5-dione 6a :
NMR ^{1}H ($CDCl_3$ / TMS) : 1.0 (t, 3H, *J*=6.82Hz, CH_3-CH_2); 1.1 (t, 3H, *J*=6.85Hz, CH_3-CH_2); 1.45 (m, 2H, CH_2-CH_2); 1.7 (m, 2H, CH_2-CH); 1.9 (m, 1H, CH_2-CH_3); 2.8 (m, 2H, C*H*-*C*O-). NMR ^{13}C ($CDCl_3$ / TMS) : 11.7 (CH_3-CH_2), 14.6 (CH_3-CH_2), 19.2 (CH_2- CH_2), 20.9 (CH_2-CH), 29.1 (CH_2-CH), 52.1 (*C*H-CO-), 55.7 (*C*H-CO-), 173.1 (CH-*C*O-).

3-Ethyl-4-methyl dihydofuran-2,5-dione 6b :
NMR ^{1}H ($CDCl_3$ / TMS) : 1.0 (t, 3H, *J*=6.81Hz, CH_3-CH_2); 1.5 (d, 3H, *J*=6.94Hz, CH_3-CH); 1.51 (m, 2H, CH_2-CH); 2.8 (m, 1H, C*H*-CH_3); 3.2 (m, 1H, C*H*-CH_2) 2.8 (qd, 1H, *J*=6.94Hz, *J*=6.86Hz, C*H*-*C*O-). NMR ^{13}C ($CDCl_3$ / TMS) : 11.1 (CH_3-CH_2), 14.2 (CH_3-CH_2), 20.9 (CH_2- CH_3), 33.1 (*C*H-CH_3), 57.8 (*C*H-CH_2), 170.3 (CH-*C*O-), 172.9 (CH-*C*O-).

2-(Hydroxymethyl)but-2-enedioic acid 9

In 25 mL flask fitted with a condenser protected by calcium drying tube, were placed 3-(bromomethyl) furan-2,5-dione **5** (5 mmol)**,** triethylammonium formate (TEAF) (10 mmol) in 10mL of acetonitrile. After hydrolysis, the organic layer was extracted with (3×20 mL) of ether then dried over $MgSO_4$. After evaporation of the solvent, the formate **7** was purified by chromatography on silica gel (AcOEt / Hexane, 2:8). Two drops of concentrated hydrochloric acid were added to **7** diluted in 10 mL absolute methanol and the mixture was stirred during 2 hours at 25°C then diluted with l0 mL of ether and dried over $MgSO_4$. The evaporation of the solvent under reduced pressure afforded the crude diacid **9**. NMR ^1H ($CDCl_3$ / TMS) : 4.23 (s, 2H, C*H*$_2$-OH); 6,45 (s, 1H, =C*H*-); 11,3 (s *br*, 2H, -CO_2*H*). NMR ^{13}C ($CDCl_3$ / TMS) : 62.7 (*C*H$_2$-OH), 132.3 (=*C*H), 151,2 (=*C*), 170.9 (=CH-*C*O_2H), 171.1 (=C-*C*O_2H).

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