Zinc Perchlorate Hexahydrate Catalyzed Mono- and Bis-Transesterification of Malonic Esters

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Commercially available zinc perchlorate hexahydrate [$Zn(ClO_4)_2 \cdot 6H_2O$] was found to be a highly effective catalyst for the transesterification of malonic esters with alcohols. The treatment of methyl-, ethyl-, or α-substituted malonic esters with primary or secondary alcohols in the presence of a catalytic amount of zinc perchlorate results in good to high yields of the corresponding esters (68%-99%). Mono-transesterification products are also obtained in moderate to good yields (22%-42%). The reaction was also carried out with 2-mono- and di-substituted malonic esters, and in the case of 2-mono- and di-substituted malonic esters, the reaction time is, in some cases, shorter, in which the yields are comparable with unsubstituted derivatives. The cyanomethyl and bis-cyanomethyl malonic ester derivatives are also used for transesterification and the corresponding products are obtained in high yields. No reaction occurs with the CN group during the reaction.

Key Words: Transesterification, zinc perchlorate, malonic esters, mono-substituted malonic esters, unsymmetrical malonic esters.

Introduction

Transesterification is one of the classic organic reactions that possess extensive laboratory uses and industrial applications. Transesterification is more advantageous than the ester synthesis from carboxylic acids and alcohols. For instance, some carboxylic acids are sparingly soluble in organic solvents, and accordingly, are difficult to subject to homogeneous esterification, whereas esters are commonly soluble in most organic solvents. The ester-to-ester transformation is particularly useful when the parent carboxylic acids are labile and difficult to isolate. Some esters, especially methyl and ethyl esters, are readily or commercially available, and therefore, they serve conveniently as starting materials in transesterification. Transesterification is a process where an ester is transformed into another ester through the interchange of the alkoxy moiety. Since the reaction is an equilibrium process, the transformation essentially occurs by simply mixing the 2 components together. However, it has long been known that the reaction is accelerated by acid or base catalysts.

The transesterification reactions are well studied and reviewed.[1] Various esters are used for transesterification reactions but rather few generally applicable methods are known about the transesterification reactions carried out with malonic acid esters.

Malonic esters are among the most important intermediates in organic synthesis, since they can be transformed into useful building blocks and serve as a valuable tool for the synthesis of various complex compounds and for pharmaceutics. The transesterification of these compounds has been recognized as a rather important and useful process because it allows the preparation of more complex products from more easily accessible synthons.[1,2]

Transesterification of malonic esters with various types of alcohols in the presence of alkali and acidic catalysts has been studied. Transesterification of esters catalyzed by alkali proceeds via an attack of alkoxide ion on the acyl carbon, and when catalyzed by acids, proceeds according to a polycentric mechanism. In the former case, transesterification of a malonic ester is facilitated by way of enolization, and in the latter case, by the formation of a cyclic intermediate. The corresponding alcohol and the catalysts are heated, and then a lower ester of malonic acid (dimethyl, diethyl, or dipropyl) is added and the mixture is boiled. The alcohol formed in the reaction is continuously distilled. Esters of malonic acid were obtained in good yields (70%-96%).

Another method is described by Iskra et al., wherein malonic acid esters are prepared by continuous transesterification between dimethyl malonate and alcohols. Thus, dimethyl malonate was continuously treated with some higher homologues of methanol in the presence of tetraethyltitanate in a bubble tower to give dialkyl malonates in good yields.[2] Some additional methods involve the use of phosphorus ylid,[3−6] and aluminum isopropoxide mediated transesterification.[1,7,8] A green process for the esterification of malonic acids with alcohols and transesterification of malonic esters in good to excellent yields by $K_5CoW_{12}O_{14} \cdot 3H_2O$ (0.1 mol%) as a catalyst is reported.[9] Enzyme-catalyzed formation of chiral monosubstituted mixed diesters and half esters of malonic acid in organic solvents is also reported.[10]

In connection with our work on the synthesis and cyclization reactions of β-ketoester derivatives that are catalyzed by zinc perchlorate in order to form pyrroles, we found that this reagent is an effective catalyst for the activation of the C=O bond.[11−14] Therefore, we investigated the transesterification reactions of malonic acid esters catalyzed by zinc perchlorate under neutral and mild conditions, and explored the scope of the reaction (Scheme 1).
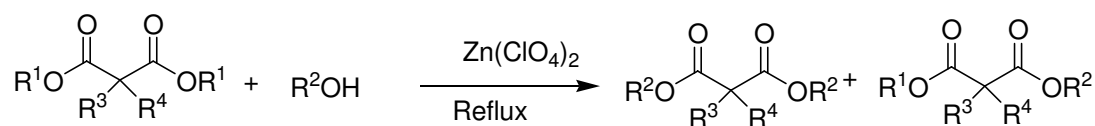
Scheme 1. $Zn(ClO_4)_2 \cdot 6H_2O$ catalyzed transesterification of malonic ester.

Experimental

General

All solvents were dried before use according to the standard procedures. Melting points were obtained using an electrothermal digital melting point apparatus (Gallenkamp). ^1H and ^{13}C NMR spectra were measured with a Bruker 400 MHz NMR spectrometer using $CDCl_3$ as solvent at room temperature. Chemical shifts

(ppm) were reported relative to Me_4Si. The coupling constant was expressed as J values in Hertz unit. Infrared spectra were recorded on a Mattson 1000 FTIR spectrometer. MS: ThermoQuest Finnigan multi Mass (EI, 70 eV). All reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel plates (60 F-254) using UV light or phosphomolybdic acid in methanol. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Commercially available metal salts were used without further purification or drying.

General procedure for zinc perchlorate hexahydrate catalyzed transesterification

Malonic ester (1 mmol) was dissolved in the corresponding alcohol (10 ml) together with a catalytic amount of $Zn(ClO_4)_2 \cdot 6H_2O$ (5 mol%). The reaction was refluxed (Dean–Stark apparatus) for 3-98 h and monitored by TLC. The reaction mixture was extracted with ethyl acetate. The extract was dried over MgSO4 and the solvent was evaporated under reduced pressure, in which the crude product was purified by column chromatography.

Spectral data of representative compounds

1-Ethyl 3-methyl 2-(cyanomethyl)malonate (2f). (74 mg, 40%) colorless oil; R_f (EtOAc/Hexane 1:3) 0.40; IR (neat) ν_{max}: 2984, 2948, 2255, 1729(br), 1461, 1450, 1420, 1370, 1093, 1039, 961 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$)δ: 4.21 (2H, q, J =7.1 Hz, C$\underline{H}_2$ CH$_3$), 3.74 (3H, s, MeO) 3.67 (1H, t, J =7.4 Hz, C$\underline{H}$CH$_2$CN), 2.86 (2H, d, J =7.4 Hz, C$\underline{H}_2$CN), 1.24 (3H, t, J =7.1 Hz, CH$_2$C$\underline{H}_3$). ^{13}C NMR (100 MHz, CDCl$_3$)δ: 166.5, 114.8, 63.8, 53.3, 47.9, 22.3, 13.9. Anal.Calcd for C$_8$H$_{11}$NO$_4$ (185.18): C, 51.89; H, 5.99; N, 7.56. Found: C, 51.81; H, 5.94; N, 7.48.

1-Isopropyl 3-methyl 2-(cyanomethyl)malonate (2g). (70 mg, 35%) colorless oil; R_f (EtOAc/ Hexane 1:3) 0.46; IR (neat) ν_{max}: 2998, 2936, 2274, 1728(br), 1461, 1445, 1411, 1351, 1099, 1011, 838 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$)δ: 5.03 (1H hept., J =6.2Hz, C$\underline{H}$(CH$_3$)$_2$), 3.74 (3H, s, MeO), 3.63 (1H, t, J =7.4 Hz, C$\underline{H}$CH$_2$ CN), 2.83 (2H, d, J =7.4 Hz, C$\underline{H}_2$ CN), 1.21 (6H, d, J =6.2 Hz, CH(C$\underline{H}_3$)$_2$). ^{13}C NMR (100 MHz, CDCl$_3$)δ: 166.7, 116.7, 70.7, 53.2, 48.1, 21.5, 16.9. Anal.Calcd for C$_9$H$_{13}$NO$_4$ (199.2): C, 54.26; H, 6.58; N, 7.03. Found: C, 54.30; H, 6.63; N, 6.84.

1-Ethyl 3-isopropyl 2-(cyanomethyl)malonate (2h). (47 mg, 22%)colorless oil; R_f (EtOAc/ Hexane 1:3) 0.58; IR (neat) ν_{max}: 2996, 2923, 2259, 1728(br), 1458, 1435, 1409, 1381, 1071, 1020, 820 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$)δ: 5.05 (1H hept., J =6.4Hz, C$\underline{H}$(CH$_3$)$_2$), 4.13-4.26 (2H, m, C$\underline{H}_2$O), 3.57 (1H, t, J =7.4 Hz, C$\underline{H}$CH$_2$ CN), 2.82 (2H, d, J =7.4 Hz, C$\underline{H}_2$ CN), 1.20-1.25 (3H and 6H , m, C$\underline{H}_3$CH and CH(C$\underline{H}_3$)$_2$). ^{13}C NMR (100 MHz, CDCl$_3$)δ: 166.0, 116.7, 70.5, 62.5, 48.2, 21.5, 16.9, 13.9. Anal.Calcd for C$_{10}$H$_{15}$NO$_4$ (213.23): C, 56.33; H, 7.09; N, 6.57. Found: C, 56.15; H, 6,98; N, 6.32.

1-Butyl 3-ethyl 2-(cyanomethyl)malonate (1i). (86 mg, 38%) colorless oil; R_f (EtOAc/Hexane 1:3) 0.62; IR (neat) ν_{max}: 2990, 2963, 2253, 1729(br), 1487, 1448, 1418, 1373, 1093, 1043, 855 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$)δ: 4.10-4.28 (4H, m, OC$\underline{H}_2$), 3.63 (1H, t, J =7.4 Hz, C$\underline{H}$CH$_2$CN), 2.84 (2H, d, J =7.4 Hz, C$\underline{H}_2$CN), 1.58 (2H, m, CH$_2$ C$\underline{H}_2$ CH$_2$), 1.21-1.36 (3H and 2H, m, C$\underline{H}_3$CH$_2$ and CH$_3$ C$\underline{H}_2$ CH$_2$), 0.87 (3H, t, J =7.3 Hz, C$\underline{H}_3$CH$_2$)^{13}C NMR (100 MHz, CDCl$_3$)δ: 166.5, 114.8, 66.4, 63.8, 48.1, 30.3, 22.3, 18.9, 16.9, 13.9. Anal.Calcd for C$_{11}$H$_{17}$NO$_4$ (227.26): C, 58.14; H, 7.54; N, 6.16. Found: C, 58.22; H, 7.43; N, 6.01.

Dimethyl 2,2-bis(cyanomethyl)malonate (1g)[15]**.** (193 mg, 92 %) white solid (mp 52-53^{0}C); R_f

(EtOAc/Hexane 1:3) 0.20; IR (KBr) ν_{max}: 2996, 2985, 2161, 1729(*br*), 1487, 1448, 1418, 1373, 1250,1093, 1043, 855 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$)δ: 3.81 (6H, s, Me), 3.12 (4H, s,C$\underline{H}_2$CN). ^{13}C NMR (100 MHz, CDCl$_3$)δ: 166.3, 114.8, 54.4, 53.2, 22.4. Anal.Calcd for C$_9$H$_{10}$N$_2$O$_4$ (210.19): C, 51.43; H, 4.80; N, 13.33. Found: C, 51.54; H, 4.84; N, 13.11.

Diethyl 2,2-bis(cyanomethyl)malonate (1h)[15]. (236 mg, 99%) colorless oil; R_f (EtOAc/Hexane 1:3) 0.32; IR (neat) ν_{max}: 2994, 2981, 2254, 1729(*br*), 1483, 1462, 1410, 1371, 1280,1124, 1033, 976cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$)δ: 4.25 (4H, q, J =7.1 Hz, C$\underline{H}_2$CH$_3$), 3.10 (4H, s, C$\underline{H}_2$CN), 1.25 (6H, t, J =7.1 Hz, Me). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 165.8, 114.8, 63.8, 53.2, 22.3, 13.8. Anal.Calcd for C$_{11}$H$_{14}$N$_2$O$_4$ (238.24): C, 55.46; H, 5.92; N, 11.76. Found: C, 55.39; H, 6,01; N, 11.58.

Dibutyl 2-methyl malonate (1k). (177 mg, 77%) colorless oil; R_f (EtOAc/Hexane 1:10) 0.60; IR (neat) ν_{max}: 2998, 2952, 1731(br), 1480, 1410, 1312, 1280, 1114, 1010, 1090, 910 cm^{-1}.^{1}H NMR (400 MHz, CDCl$_3$)δ: 4.01-4.11 (4H, m, OC$\underline{H}_2$), 3.36 (1H, q, J =7.2 Hz, C$\underline{H}$CH$_3$), 1.55 (4H, pent., J =7.4 Hz, CH$_2$ C$\underline{H}_2$ CH$_2$), 1.26-1.35 (4H and 3H, m, CH$_3$C$\underline{H}_2$CH$_2$ and C$\underline{H}_3$CH), 0.86 (6H, t, J =7.3 Hz, C$\underline{H}_3$CH$_2$)^{13}C NMR (100 MHz, CDCl$_3$)δ: 170.2, 65.1, 46.2, 30.5, 18.9, 13.6, 13.5. Anal.Calcd for C$_{12}$H$_{22}$O$_4$ (230.3): C, 62.58; H, 9.63. Found: C, 62.63; H, 9.69.

Diisopropyl 2-(cyanomethyl)malonate (1l). (182 mg, 80%) colorless oil; R_f (EtOAc/Hexane 1:3) 0.66; IR (neat) ν_{max}: 2996, 2981, 2144, 1727(*br*), 1510, 1464, 1410, 1368, 1215, 1112, 1043, 954 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$)δ: 5.03 (2H hept., J =6.2Hz, C$\underline{H}$(CH$_3$)$_2$), 3.55 (1H, t,J =7.3Hz C$\underline{H}$CH$_2$), 2.83 (2H, d, J =7.3 Hz, C$\underline{H}_2$ CN), 1.21 (6H, d, J =6.2 Hz, CH(C$\underline{H}_3$)$_2$), 1.19 (6H, d, J =6.2 Hz, CH(C$\underline{H}_3$)$_2$). ^{13}C NMR (100 MHz, CDCl$_3$)δ: 166.0, 116.7, 70.5, 48.4, 21.5, 16.9. Anal.Calcd for C$_{11}$H$_{17}$NO$_4$ (227.26): C, 58.14; H, 7.54; N, 6.16. Found: C, 58.22; H, 7.61; N, 6.19.

Dibutyl 2-(cyanomethyl)malonate (1m). (235 mg, 92%) colorless oil; R_f (EtOAc/Hexane 1:3) 0.70;IR (neat) ν_{max}: 2994, 2964, 2262, 1729(*br*), 1495, 1432, 1412, 1344, 1225, 1050, 1020, 954 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$)δ: 4.10-4.19 (4H, m, OC$\underline{H}_2$), 3.64 (1H, t, J =7.4 Hz, C$\underline{H}$CH$_2$CN), 2.84 (2H, d, J =7.4 Hz, C$\underline{H}_2$CN), 1.58 (4H, pent., J =7.3 Hz, CH$_2$ C$\underline{H}_2$ CH$_2$), 1.34 (4H, hext., J =7.3 Hz, CH$_3$ C$\underline{H}_2$ CH$_2$), 0.87 (6H, t, J =7.3 Hz, Me) ^{13}C NMR (100 MHz, CDCl$_3$)δ: 166.5, 116.7, 66.4, 48.1, 30.3, 18.9, 16.9, 13.5. Anal.Calcd for C$_{13}$H$_{21}$NO$_4$ (255.31): C, 61.16; H, 8.29; N, 5.49. Found: C, 61.20; H, 8.34; N, 5.41.

Dibutyl 2,2-bis(cyanomethyl)malonate (1n). (274 mg, 93 %) colorless oil; R_f (EtOAc/Hexane 1:3) 0.56;IR (neat) ν_{max}: 2994, 2965, 2264, 1731(*br*), 1510, 1485, 1425, 1385, 1288, 1075, 1043, 970 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$)δ: 4.20 (4H, t, J =6.6 Hz, OC$\underline{H}_2$), 3.11 (4H, s, C$\underline{H}_2$CN), 1.59 (4H, pent., J =7.4 Hz, CH$_2$ C$\underline{H}_2$ CH$_2$), 1.32 (4H, hext., J =7.4 Hz, CH$_3$ C$\underline{H}_2$ CH$_2$), 0.87 (6H, t, J =7.4 Hz, Me) ^{13}C NMR (100 MHz, CDCl$_3$)δ: 165.9, 114.9, 67.5, 53.2, 30.3, 22.3, 18.8, 13.7. Anal.Calcd for C$_{15}$H$_{22}$N$_2$O$_4$ (294.35): C, 61.21; H, 7.53; N, 9.52. Found: C, 61.11; H, 7.57; N, 9.46.

Diisopropyl 2-methylmalonate (1o). (68 mg, 34%) colorless oil; R_f (EtOAc/Hexane 1:10) 0.44;IR (neat) ν_{max}: 2991, 2950, 1732(br), 1465, 1401, 1310, 1283, 1100, 1010, 1090, 928 cm^{-1}.^{1}H NMR (400 MHz, CDCl$_3$)δ: 4.99 (2H sept., J =6.4Hz, C$\underline{H}$(CH$_3$)$_2$), 3.28 (1H, q, J =7.3 Hz, C$\underline{H}$CH$_3$), 1.32 (3H, d, J =7.3 Hz, C$\underline{H}_3$CH), 1.18 (12H, d, J =6.4Hz, (C$\underline{H}_3$)$_2$CH). ^{13}C NMR (100 MHz, CDCl$_3$)δ: 168.9, 67.7, 45.3, 20.6, 13.0. Anal.Calcd for C$_{10}$H$_{18}$O$_4$ (202.25): C, 59.39; H, 8.97. Found: C, 59.32; H, 9.01.

Results and Discussion

Transesterification of unsubstituted malonic esters

Metal-coordinated dicarbonyl compounds such as dialkyl malonate can easily undergo $C = O$ activation to react with nucleophiles. The 'electrophilic activation' property of $Zn(ClO_4)_2 \cdot 6H_2O$ was well demonstrated for $C = O$ and CN groups among the other metal salts.[11−14,16] In an initial reaction, dimethyl malonate (**1a**) was refluxed with ethanol in the presence of a catalytic amount of $Zn(ClO_4)_2 \cdot 6H_2O$ (5-10 mol%), in which the reaction was monitored by TLC, GC-MS, and NMR. After 4 h, 2 different products were formed and identified as diethyl malonate (**1b**) and ethyl-methyl malonate (**2a**). The reflux was continued until no more starting material was present (12h). After the work up, diethyl malonate (**1b**) was obtained in 96% yield. By repeating the reaction with different amounts of zinc perchlorate (2, 5, 10 mol%), 5 mol% was the best choice, and in the absence of zinc perchlorate, no reaction was observed (Scheme 2).
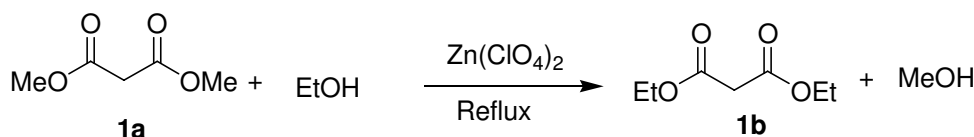
Scheme 2. $Zn(ClO_4)_2 \cdot 6H_2O$ catalyzed bis-transesterification of malonic ester.

To find the role of metal salts, $Zn(ClO_4)_2$, $Mg(ClO_4)_2$, $Cu(ClO_4)_2$, $LiClO_4$, $Co(ClO_4)_2$, $NaClO_4$, $Zn(OAc)_2$, $Mn(ClO_4)_2$, and $ZnCl_2$ were used as the catalyst during the reaction of **1a** with ethanol, in which the best result was obtained with $Zn(ClO_4)_2 \cdot 6H_2O$ (yield 96%). The other salts were given less than 10% yield and in some cases no product formations were observed.

Under the same conditions, commercially available dialkyl malonate furnished the corresponding dialkyl malonate by ethanol, methanol *i*-propanol, and *n*-butanol in high yield as shown in Table 1. We also carried out a reaction of **1b** in refluxing toluene: MeOH(v/v:10:2) with a Dean–Stark trap, in which the formation of the product was observed but the time of the reaction increased (96 h, 71% yield).
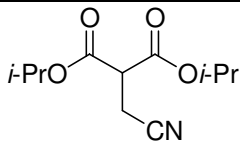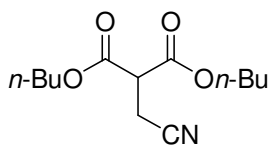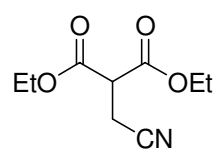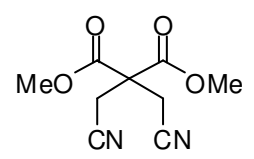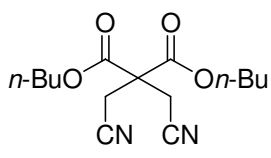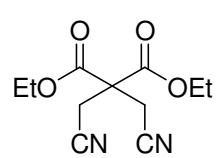
Transesterification of substituted malonic esters

Mono- and di-substituted malonic esters are interesting starting materials and, especially substituents with functional groups, are important for further derivatization. The $Zn(ClO_4)_2 \cdot 6H_2O$ catalyzed reaction was also carried out with 2-mono- and bis-substituted malonic esters. Commercially available ethyl 2-methyl malonate (**1c**) gave, under the conditions described above with *n*-butanol, the corresponding diester **1k** in 77% yield. 2-Bromo substituted derivative **1d** furnished a transesterification product with *i*-propanol **1i,** and debromination occurs during the reaction. The transesterification reactions were also carried out with 2-cyanomethyl and 2-bis-cyanomethyl malonic ester derivatives **1f-h.** These compounds were synthesized according to the related literature procedures in 53%-60% and 15%-25% yields with NaH/bromoacetonitrile in THF as shown in Scheme 3.[11−14] Depending on the equivalency of the base and bromoacetonitrile, it is possible to selectively synthesize the mono- and di-cyanomethylation product as the major product. The transesterification reaction with these compounds works in good to excellent yields (68%-99%). No reaction occurs with the CN group during the reaction. The transesterification reaction with 2-mono- and di-substituted malonic esters in general shows that the reaction time is in some cases shorter and the yields are comparable with unsubstituted derivatives as shown in Table 1; entries 10-18.

Table 1. Bis-transesterification of malonic esters.

h	Ester	Alcohol	Product	Yield (%)	Reaction time (h)
1	**1a**[17]	EtOH	**1b**	96	12
2	**1a**	i-PrOH	**1i**[17]	87	28
3	**1a**	n-BuOH	**1j**[17]	95	22
4	**1b**[17]	i-PrOH	**1i**	77	88
5	**1b**	n-BuOH	**1j**	93	28
6	**1b**	MeOH	**1a**	89	18
7	**1c**[17]	n-BuOH	**1k**	77	65
8	**1d**[17]	i-PrOH	**1i**	68	45
9	**1d**	n-BuOH	**1j**	95	12
10	**1e**[18-20]	EtOH	**1f**	87	22

Table 1. Contunied.

h	Ester	Alcohol	Product	Yield (%)	Reaction time (h)
11	**1e**	*i*-PrOH	**1l**	80	48
12	**1e**	*n*-BuOH	**1m**	92	18
13	**1f**[18-20]	*i*-PrOH	**1l**	78	60
14	**1f**	*n*-BuOH	**1m**	81	20
15	**1g**[15]	EtOH	**1h**	99	5
16	**1g**	*n*-BuOH	**1n**	93	9
17	**1h**[15]	MeOH	**1g**	92	10
18	**1h**	*n*-BuOH	**1n**	90	12

Mono-transesterification of malonic esters; Synthesis of unsymmetrical malonic esters

Unsymmetrical alkyl esters of malonic acids are rather important because the further regioselective functionalization is possible by chemical and enzymatic methods. During the transesterification reactions, mono-transesterification products are also formed (monitoring of the reaction by TLC GC-MS and NMR). Termination of the reaction by the maximum amount formation of an unsymmetrical ester gave the possibility to isolate mono-transesterification products after separation by way of column chromatography in 22%-42% yields (Scheme 4). Some representative examples are shown in Table 2.

Table 2. Mono-transesterification of malonic esters: Synthesis of unsymmetrical malonic esters.
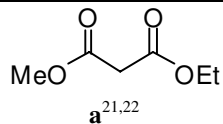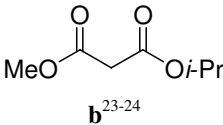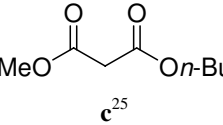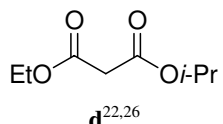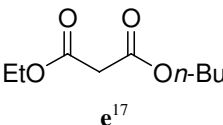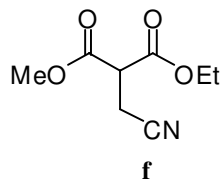
Entry	Ester	Alcohol	Unsymmetrical malonic ester 2	Yield (%)	Symmetrical malonic ester 1	Yield (%)	Reaction time (h)
1	1a	EtOH	MeO...OEt **a**[21,22]	42	1b	51	3
2	1a	i-PrOH	MeO...Oi-Pr **b**[23-24]	35	1i	45	24
3	1a	n-BuOH	MeO...On-Bu **c**[25]	40	1j	47	6
4	1b	MeOH	**a**	28	1a	38	34
5	1b	i-PrOH	EtO...Oi-Pr **d**[22,26]	33	1i	33	45
6	1b	n-BuOH	EtO...On-Bu **e**[17]	42	1j	50	7
7	1e	EtOH	MeO...OEt CN **f**	40	1f	45	6

Table 2. Contunied.

Entry	Ester	Alcohol	Unsymmetrical malonic ester **2**	Yield (%)	Symmetrical malonic ester **1**	Yield (%)	Reaction time (h)
8	**1e**	*i*-PrOH	MeO—C(O)—CH(CH₂CN)—C(O)—O*i*-Pr **g**	35	**1l**	44	26
9	**1f**	MeOH	**f**	28	**1e**	25	30
10	**1f**	*i*-PrOH	EtO—C(O)—CH(CH₂CN)—C(O)—O*i*-Pr **h**	22	**1l**	30	34
11	**1f**	*n*-BuOH	EtO—C(O)—CH(CH₂CN)—C(O)—O*n*-Bu **i**	38	**1m**	44	6
12	**1c**	*i*-PrOH	EtO—C(O)—CH(CH₃)—C(O)—O*i*-Pr **J**[21]	23	*i*-PrO—C(O)—CH(CH₃)—C(O)—O*i*-Pr **1o**	34	98
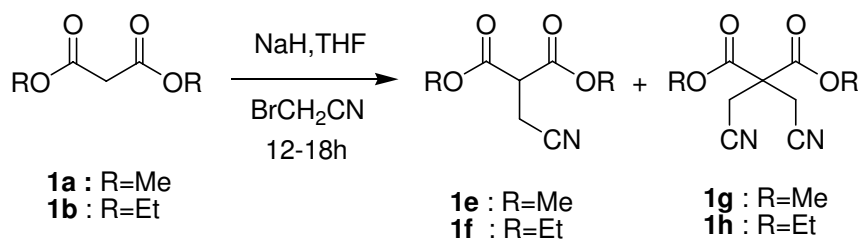
Scheme 3. Synthesis of mono- and di-cyanomethyl malonic esters.

RO—C(O)—CH₂—C(O)—OR
1a : R=Me
1b : R=Et

NaH,THF / BrCH₂CN / 12-18h

RO—C(O)—CH(CH₂CN)—C(O)—OR
1e : R=Me
1f : R=Et

RO—C(O)—C(CH₂CN)₂—C(O)—OR
1g : R=Me
1h : R=Et
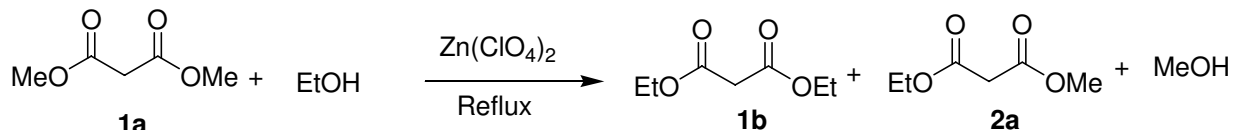
Scheme 4. Zn(ClO₄)₂·6H₂O catalyzed mono- and bis-transesterification of malonic ester.

MeO—C(O)—CH₂—C(O)—OMe **1a** + EtOH

Zn(ClO₄)₂ / Reflux

EtO—C(O)—CH₂—C(O)—OEt **1b** + EtO—C(O)—CH₂—C(O)—OMe **2a** + MeOH

The interaction between zinc perchlorate and carbonyl oxygen atom increases the electrophilic reactivity of the carbonyl carbon, and thereby enhances the reaction with the donor oxygen of the alcohol in order to generate transesterification.

Conclusion

We presented a practical 'one-pot' transesterification of malonic esters from commercially available malonic esters and alcohols in the presence of commercially available $Zn(ClO_4)_2 \cdot 6H_2O$ (5%) under neutral conditions. Bis-transesterification products can be obtained in high yield. The present procedure makes it possible to synthesize mono-transesterification products in moderate yields. C-2 mono- and di-substituted malonic esters with functional groups also furnished the transesterification products in high yields. No dry conditions and no further purification of the starting materials are necessary. This method is simple, cost efficient, mild, and cheap compared to the previously described methods.

Acknowledgements

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