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A Convenient one-pot synthesis of n-arylmalonamic acid via in-situ generation of malonyl monoacyl chloride

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A CONVENIENT ONE-POT SYNTHESIS OF N-ARYLMALONAMIC ACID VIA IN-SITU GENERATION OF MALONYL MONOACYL CHLORIDE

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Abstract: *A convenient one-pot synthesis of N-arylmalonamic acid has been demonstrated based on the in-situ generation of malonyl monoacyl chloride, followed by reaction with aniline.*

N-Arylmalonamic acids possess biological activities such as plant growth regulators[1,2] or fungicides[3]. Procedures for the direct preparation of N-arylmalonamic acids that have been described previously involve refluxing the appropriate aniline with malonic acid, treating the aniline with diethyl malonate [1, 4] or with ethyl malonyl chloride[1] followed by alkaline hydrolysis of the ester group,

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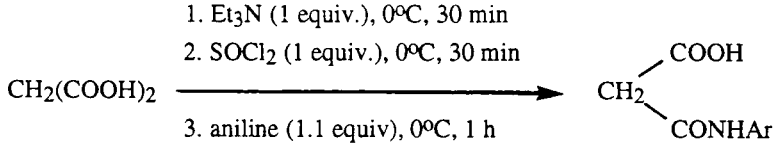
or treating the Meldrum's acid with a silylated aniline followed by hydrolysis of the malonic silyl ester.[5] Herein, we report a convenient synthesis of N-arylmalonamic acids *via* treatment of malonic acid consecutively with 1 equivalent of triethylamine and 1 equivalent of thionyl chloride under nitrogen, followed by reaction with the appropriate aniline at 0°C. Under these conditions, triethylamine, which provides a temporary protection at one of the carboxylic groups of malonic acid as the monoanion, can be neutralized with HCl, resulting from the subsequent addition of 1 equivalent of thionyl chloride. The *in-situ* generation of a malonyl monoacyl chloride species allows reaction with an aniline to give the desired product. This approach was applied in the successful preparation of a series of N-arylmalonamic acids with reasonable yields (31.5-56%) within 2 h. The wide range of yields of these reactions could possibly result from the electron-withdrawing effect of the chloride substituent(s) on the aniline ring, which in turn affected the nucleophilicity of amino group toward the acyl group.



In summary, we have demonstrated a convenient one-pot synthesis of N-arylmalonamic acids based on the reaction of *in-situ* generated malonyl monoacyl chloride with aniline derivatives. The method described may be useful in the selective preparation of related compounds such as malonyl monoamides, malonyl monoesters, or related derivatives from compounds containing multiple carboxylic acid functionalities.

Experimental Section

General procedure. To a mixture of malonic acid (2 gm, 19.2 mmole) in dry THF (30 ml) under nitrogen was added dropwise 1 equivalent of triethylamine with stirring for 30 min at 0°C, followed by the addition of 1 equivalent of thionyl chloride with stirring for another 30 min at 0°C. To the resulting mixture under nitrogen was added dropwise a solution of 1.1 equivalent of the appropriate aniline in THF (20 ml) with stirring for 1 hr at 0°C. The reaction mixture was diluted with

ethyl acetate (50 ml) and extracted with 0.25 N NaOH (100 ml). The aqueous phase was titrated with 2 N HCl to pH 4-5 and then extracted with ethyl acetate (100 ml x2). The organic phase was dried (sodium sulfate) and evaporated to give almost pure products. These compounds could be further purified by chromatography on silica gel using acetone-chloroform (0-10%) as eluent.

1. N-Phenylmalonamic acid; 32% yield; mp 123-124°C (lit.[4] 134-135°C, lit.[5] 137 °C); IR (KBr) 3320, 3200-2500, 1710, 1660, 1600; ^{1}H NMR (Aceton-d_6), 3.47 (s, 2H, CH_2), 7.1 (t, 1H, C_4H, J=7.8Hz), 7.31 (t, 2H, C_3H & C_5H, J=7.8Hz), 7.64 (d, 2H, C_2H & C_6H, J=8.2Hz), 9.5 (s, 1H, NH). Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found C, 60.08; H, 5.12; N, 7.73

2 . N-(3-Chlorophenyl)malonamic acid, 31.5% yield; mp 123-124°C (lit.[1] 127°C); IR(KBr) 3320, 3280-2500, 1730, 1620, 1590; ^{1}H NMR (Acetone-d_6) 3.84 (s, 2H, CH_2), 7.15 (d, 1H,, C_4H), 7.32 (t, 1H, C_5H, J=8.4Hz), 7.89 (s, 1H, C_2H), 9.7 (s, 1H, NH). Anal. Calcd for $C_9H_8ClNO_3$: C, 50.73; H, 3.77; N, 6.56. Found C, 50 73; H, 3.77; N, 6.55

3. N-(4-Chlorophenyl)malonamic acid, 50% yield; mp 137-139°C (Lit. [1] 168°C); IR (KBr) 3330, 3300-2500, 1720, 1650, 1605; ^{1}H NMR (acetone-d_6) 3.47 (s, 2H, CH_2), 7.33 (d, 2H, C_3H & C_5H), 7.67 (d, 2H, C_2H & C_6H, J=8.4Hz), 9.5 (s, 1H, NH). Anal. Calcd for $C_9H_8ClNO_3$: C, 50.73; H, 3.77; Cl, 16.60. Found C, 50.73; H, 3.80; Cl, 16.50

4. N-(2,3-Dichlorophenyl)malonamic acid, 56% yield; mp 133-135°C; IR (KBr) 3240, 3140-2500, 1730, 1670, 1580; ^{1}H NMR (Acetone-d_6) 3.64 (s, 2H, CH_2), 7.34 (d, 2H, C_4H & C_6H, J=5.6Hz), 8.29 (t, 1H, C_5H, J=5.6Hz), 9.84 (s, 1H, NH). Anal. Calcd for $C_9H_7Cl_2NO_2$: C, 43.57; H, 2.80; N, 5.65. Found C, 43.65; H, 2.86; N, 5.49

5. N-(2,6-Dichlorophenyl)malonamic acid, 34.9% yield; mp 146-148°C; IR (KBr) 3240, 3140-2500, 1720, 1605, 1570; ^{1}H NMR (Acetone-d_6) 3.58 (s, 2H, CH_2), 7.38 (m, 1H, C_4H), 7.49 (d, 2H, C_3H & C_5H, J=7.4Hz), 9.35 (s,1H, NH). Anal. Calcd for $C_9H_7Cl_2NO_3$: C, 43.57; H, 2.80; N, 5.65. Found C, 43.76; H, 2.84; N, 5.47

6. N-(3,4-Dichlorophenyl)malonamic acid, 39% yield; mp129-130°C (Lit.[1]

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131°C): IR (KBr) 3500-2500, 1710, 1620, 1580; ^{1}H NMR (acetone-d_6) 3.48 (s, 2H, CH_2), 7.35 (s, 1H, C_5H), 7.51 (s, 1H, C_6H), 8.04 (s, 1H, C_2H), 9.7 (s, 1H, NH).

7. N-(2,4-Dichlorophenyl)malonamic acid, 27% yield; mp 142-144°C (Lit. [1] 164°C); IR (KBr) 3250, 3180-2500, 1710, 1650, 1580. Anal. Calcd for $C_9H_7Cl_2NO_3$: C, 43.57; H, 2.80; N, 5.65. Found: C, 43.59; H, 2.86; N, 5.60

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