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ScienceDirect
Ultrasonics Sonochemistry 15 (2008) 265–268
Ultrasonics SONOCHEMISTRY
www.elsevier.com/locate/ultsonch

Short Communication

An efficient and practical synthesis of 2-((1*H*-indol-3-yl)(aryl)methyl)malononitriles under ultrasound irradiation

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Received 15 May 2007; received in revised form 29 July 2007; accepted 3 August 2007
Available online 1 September 2007

Abstract

Synthesis of 2-((1*H*-indol-3-yl)(aryl)methyl)malononitrile *via* the Michael addition of indole with various arylmethylenemalononitriles was carried out in good yields using anhydrous zinc chloride as the catalyst under ultrasound irradiation.

PACS: 43.35.Vz; 81.20.Ka

Keywords: 2-((1*H*-Indol-3-yl)(aryl)methyl)malononitrile; Synthesis; Indole; Michael addition; Ultrasound irradiation

1. Introduction

Indole frameworks have been widely known as prominent agents in compounds of high biological, agrochemical and pharmacological relevance [1]. Furthermore, 3-substituted indoles are components of drugs and are commonly found in molecules of pharmaceutical interest in a variety of the therapeutic areas [2].

Ultrasound has increasingly been used in organic synthesis in recent years. Compared with traditional methods, this method is more convenient and reactions can be carried out in higher yield, shorter reaction time and milder conditions under ultrasound irradiation [3]. Recently, we reported ultrasound promoted the preparation of β-indolylketones catalyzed by silica sulfuric acid and the synthesis of bis(indolyl)methanes catalyzed by aminosulfonic acid in anhydrous ethanol [4]. Continuing our investigations in this area [5], we herein report the preparation of 2-((1*H*-indol-3-yl)(aryl)methyl)malononitriles *via* Michael addition of indole with arylmethylenemalononitriles catalyzed by zinc chloride in ethyl acetate under ultrasound irradiation (Scheme 1).

2. Method

2.1. Apparatus and analysis

Melting points were uncorrected. ^{1}H NMR spectra were measured on a Bruker AVANCE 400 (400 MHz) spectrometer using TMS as the internal standard and $CDCl_3$ as a solvent. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). Elemental analyses were measured on a HERAEUS (CHNO, Rapid) analyzer. Sonication was performed in Shanghai Branson-CQX ultrasonic cleaner (with a frequency of 25 kHz and a nominal power 250 W). The reaction flask was located in the ultrasonic bath, where the surface of reactants is slightly lower than the level of the water. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

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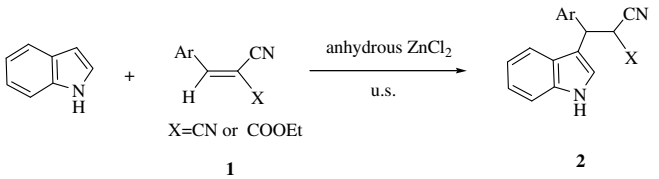
1350-4177/$ - see front matter
doi:10.1016/j.ultsonch.2007.08.005



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Scheme 1.

2.2. General procedure for the Michael additions

The preparation of arylmethylenemalononitriles was referred to Ref. [6]. The preparation of ethyl α-cyanocinnamates was referred to Ref. [7].

Indole (70.2 mg, 0.6 mmol), arylmethylenemalononitriles or ethyl α-cyanocinnamates (0.5 mmol), anhydrous $ZnCl_2$ (136 mg, 1.0 mmol), ethyl acetate (3 mL), were mixed in a 50 mL Pyrex flask. The mixture was irradiated in the water bath of the ultrasonic cleaner for a period as indicated in Table 1 (the reaction was followed by TLC). After the completion of the reaction, the resulting suspension was quenched with 10 mL water. The reaction mixture was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate for 12 h and filtered. Ethyl acetate was evaporated under reduced pressure to give the crude product, which was separated by column chromatography on silica (200–300 mesh), eluted with petroleum ether or a mixture of petroleum ether and diethyl ether. The authenticity of the products was established by the data of ^1H NMR, IR and elemental analyses.

Table 1
Synthesis of 2-((1*H*-indol-3-yl)(aryl)methyl)malononitriles catalyzed by anhydrous $ZnCl_2$ at rt under ultrasound irradiation

Entry	1		Time (h)	2
	Ar	X		Yield (%)
a	3-ClC_6H_4	CN	1.5	95[a]
			1.5	73[b]
			1.5	78[c]
			1.5	64[d]
			1.5	42[e]
b	2-ClC_6H_4	CN	1.5	97
			1.5	34[e]
c	4-ClC_6H_4	CN	1.5	96
			1.5	42[e]
d	4-ClC_6H_4	CO_2Et	6.0	94
e	2,4-$Cl_2C_6H_3$	CN	1.5	95
f	3-BrC_6H_4	CN	1.5	95
g	C_6H_5	CN	1.5	88
			1.5	28[e]
h	2-$NO_2C_6H_4$	CN	1.5	76
			2.0	0[e]
i	3-$NO_2C_6H_4$	CN	1.5	60
			2.0	0[e]
j	4-$NO_2C_6H_4$	CN	1.5	57
k	2,4-$(NO_2)_2C_6H_3$	CN	3.0	34
l	4-$CH_3OC_6H_4$	CN	3.0	0
m	4-$CH_3OC_6H_4$	CO_2Et	3.0	51
n	4-$CH_3C_6H_4$	CN	3.0	trace
o	4-$CH_3C_6H_4$	CO_2Et	3.0	19

The amount of $ZnCl_2$: [a]1.0 mmol; [b]0.5 mmol; [c]0.75 mmol; [d]2.0 mmol; [e]1.0 mmol and stirred without ultrasound.

2.2.1. 2-((3-Chlorophenyl)(1H-indol-3-yl)methyl) malononitrile (**2a**)

Solid, m.p.: 179–181 °C. ^1H NMR ($CDCl_3$): δ 4.47 (d, $J = 6.4$ Hz, 1H, CH), 4.94 (d, $J = 6.4$ Hz, 1H, CH), 7.12 (t, $J = 7.2$ Hz, 1H), 7.25–7.46 (m, 8H, ArH), 8.34 (s, 1H, NH) ppm. IR (KBr) *v*: 3386, 3059, 2879, 2258, 2220 cm^{-1}. Anal. calcd. for $C_{18}H_{12}N_3Cl$: C 70.82, H 3.93, N 13.77; found C 70.79, H 3.90, N 13.75.

2.2.2. 2-((2-Chlorophenyl)(1H-indol-3-yl)methyl) malononitrile (**2b**)

Solid, m.p.: 66–68 °C. ^1H NMR ($CDCl_3$): δ 4.48 (d, $J = 6.4$ Hz, 1H, CH), 4.96 (d, $J = 6.4$ Hz, 1H, CH), 7.12 (t, $J = 7.2$ Hz, 1H), 7.26–7.50 (m, 8H, ArH), 8.34 (s, 1H, NH) ppm. IR (KBr) *v*: 3384, 3059, 2878, 2258, 2220 cm^{-1}. Anal. calcd. for $C_{18}H_{12}N_3Cl$: C 70.82, H 3.93, N 13.77; found C 70.81, H 3.98, N 13.74.

2.2.3. 2-((4-Chlorophenyl)(1H-indol-3-yl)methyl) malononitrile (**2c**)

Solid, m.p.: 70–72 °C. ^1H NMR ($CDCl_3$): δ 4.47 (d, $J = 6.4$ Hz, 1H, CH), 4.93 (d, $J = 6.4$ Hz, 1H, CH), 7.12 (t, $J = 7.2$ Hz, 1H), 7.25–7.47 (m, 8H, ArH), 8.34 (s, 1H, NH) ppm. IR (KBr) ν_{max}: 3385, 3058, 2880, 2259, 2220 cm^{-1}. Anal. calcd. for $C_{18}H_{12}N_3Cl$: C 70.82, H 3.93, N 13.77; found C 70.84, H 3.96, N 13.73.

2.2.4. Ethyl 3-(4-chlorophenyl)-2-cyano-3-(1H-indol-3-yl) propanoate (**2d**)

Viscous liquid. ^1H NMR ($CDCl_3$): δ 1.13 (t, $J = 8.0$ Hz, 3H, CH_3), 1.18 (t, $J = 8.0$ Hz, 3H, CH_3), 4.10–4.22 (m, 4H, CH_2), 4.36 (d, $J = 8.0$ Hz, 2H, CH), 5.10 (dd, $J = 8.0$, 20.0 Hz, 2H, CH), 7.05–7.51 (m, 18H, ArH), 8.40 (d, $J = 8.0$ Hz, 2H, NH) ppm. IR (KBr) ν_{max}: 3408, 3053, 2981, 2933, 2251 cm^{-1}. Anal. calcd. for $C_{20}H_{17}N_2O_2Cl$: C 68.18, H 4.83, N 7.95; found C 68.24, H 4.88, N 7.98.

2.2.5. 2-((2,4-Dichlorophenyl)(1H-indol-3-yl)methyl) malononitrile (**2e**)

Solid, m.p.: 162–164 °C. ^1H NMR ($CDCl_3$): δ 4.53 (d, $J = 6.0$ Hz, 1H, CH), 5.51 (d, $J = 5.6$ Hz, 1H, CH), 7.10 (t, $J = 7.2$ Hz, 1H), 7.20–7.62 (m, 7H, ArH), 8.38 (s, 1H, NH) ppm. IR (KBr) ν_{max}: 3411, 3059, 2899, 2256, 2219 cm^{-1}. Anal. calcd. for $C_{18}H_{11}N_3Cl_2$: C 63.72, H 3.24, N 12.39; found C 63.74, H 3.25, N 12.39.

2.2.6. 2-((3-Bromophenyl)(1H-indol-3-yl)methyl) malononitrile (**2f**)

Solid, m.p.: 82–84 °C. ^1H NMR ($CDCl_3$): δ 4.46 (d, $J = 6.4$ Hz, 1H, CH), 4.93 (d, $J = 6.4$ Hz, 1H, CH), 7.12