Ultrasound-Assisted Synthesis of Highly Functionalized Cyclopentadienes *via* an Isocyanide-Based Three-Component Reaction

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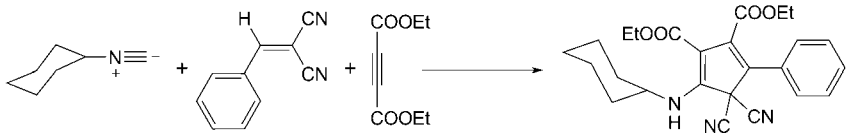
This report provides a description of an efficient and simple procedure for the synthesis of substituted cyclopentadienes *via* a one-pot three-component reaction of cyclohexyl isocyanide, diethyl acetylenedicarboxylate and (arylmethylidene)malononitriles in H_2O under ultrasonic irradiation. The remarkable advantages are the simplicity of the experimental procedures, high yields, short reaction times, and avoidance of organic solvents.

Introduction. – Ultrasound irradiation is a powerful technique in synthetic organic chemistry. The influence of sonic waves traveling through liquids was first reported by *Robert Williams Wood* (1868–1955) and *Alfred Lee Loomis* (1887–1975) in 1927 [1]. It has favorable effects, especially in cases where traditional methods require harsh reaction conditions or prolonged reaction times [2]. Enhanced reaction rates, simple experimental procedure, and high yields are the notable features of the ultrasound approach as compared to established methods [3–5]. The synthesis of cyclopentadienes under sonication conditions has not been reported before. Herein, we describe a convenient, practical, and efficient reaction for the synthesis of highly substituted cyclopentadienes *via* a one-pot three-component reaction of cyclohexyl isocyanide, diethyl acetylenedicarboxylate and (arylmethylidene)malononitriles (=2-(arylmethylidene)propanedinitriles) in H_2O under ultrasonic irradiation.

Results and Discussions. – The cyclopentadienes were synthesized by the cyclocondensation of isocyanide, dialkyl acetylenedicarboxylate, and various (arylmethylidene)malononitriles under both established and ultrasonic irradiation conditions. For optimizing the experimental conditions, the reaction between cyclohexyl isocyanide, diethyl acetylenedicarboxylate and 2-benzylidenemalononitrile was considered as a model reaction. To find the best solvent, several solvents such as CH_2Cl_2, EtOH, MeCN, and H_2O were employed as media (*Table 1*). However, it was noticed that the highest yield was achieved with CH_2Cl_2, when the reaction was performed in an established manner, while the formation of the product was more facile and proceeded in shorter time and with high yield under ultrasonic irradiation conditions in H_2O (*Table 1*, *Entry 4*).

The effect of temperature on the reaction was also studied. We found that the best results were obtained in H_2O at 30° under ultrasound irradiations (*Table 1*, *Entry 5*).

Table 1. *Optimization of the Reaction Conditions for One-Pot Synthesis of Substituted Cyclopentadienes*

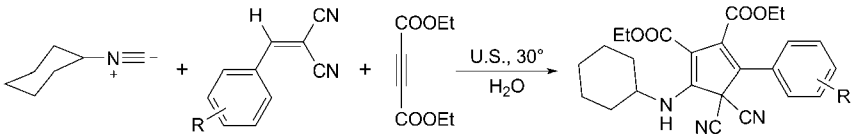


Entry	Solvent	Temp. [°] Normal/Sonication[a])	Time Normal/Sonication[a])	Yield [%] Normal/Sonication[a])
1	CH_2Cl_2	r.t./45	3.5 h/15 min	80/83
2	MeCN	r.t./45	3.5 h/15 min	66/70
3	EtOH	r.t./45	3.5 h/15 min	60/68
4	H_2O	r.t./45	3.5 h/10 min	70/84
5	H_2O	–/30	3.5 h/12 min	–/82

[a]) Constant frequency: 60 W.

Using the optimized reaction conditions, we extended our study to different (arylmethylidene)malononitriles to prepare a series of substituted cyclopentadienes (*Table 2*). To study the effect of ultrasound, the reactions were carried out under silent and ultrasonic irradiation conditions. Ultrasound irradiation accelerated such reactions.

Table 2. *Synthesis of Cyclopentadienes under Normal and Ultrasonic (U.S.) Conditions*

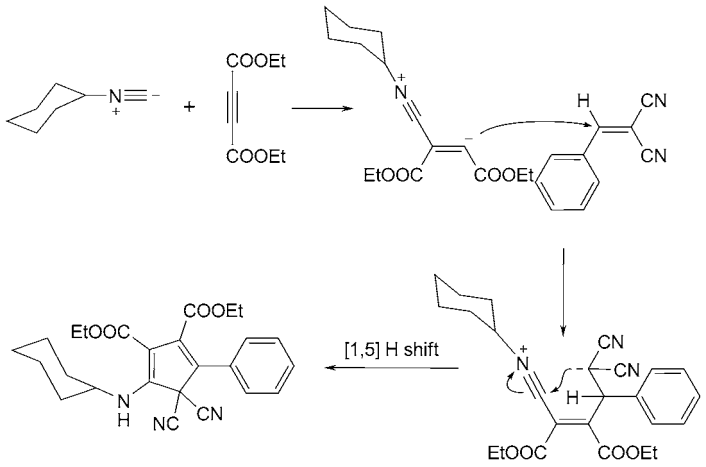


Entry	R	Time Normal/Sonication	Yield [%] Normal/Sonication	M.p. [°]
1	H	3.5 h/12 min	82/80	114–115
2	3-NO_2	3.5 h/10 min	83/85	147–149
3	4-F	3.5 h/8 min	85/82	96–98
4	4-Cl	3.5 h/10 min	83/78	102–103
5	4-Me	3.5 h/15 min	82/85	99–101
6	2-F	3.5 h/10 min	70/75	99–101
7	2-Cl	3.5 h/13 min	70/73	110–112
8	4-MeO	3.5 h/15 min	86/80	103–104
9	4-NO_2	3.5 h/8 min	84/85	107–109
10	3-Br	3.5 h/8 min	90/90	124–126

Sonication can produce very fine emulsions from immiscible phases which also cause the reaction to take place rapidly [6][7].

Although the mechanism of the reaction has not yet been established experimentally, the formation of the product can be rationalized as outlined in the *Scheme*.

Scheme



In summary, we have developed an improved and convenient procedure for the synthesis of substituted cyclopentadienes under ultrasonic irradiations at 30°. The remarkable advantages of this method are simple experimental procedure, avoidance of organic solvents, short reaction times, high yields, and the ease of product isolation.

Experimental Part

Materials and Instruments. The products were characterized by IR, ^{1}H-, and ^{13}C-NMR spectra and elemental analysis. M.p.: *Büchi* melting point *B-540 B.V.CHI* apparatus. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance 500* MHz spectrometers (*DRX*). Elemental analyses: *Costech ECS 4010 CHN* analyzer.

General Procedure for the Synthesis of the Cyclopentadiene Derivatives. Normal Conditions. A soln. of cyclohexyl isocyanide (1 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise to a magnetically stirred soln. of (arylmethylidene)malononitrile (1 mmol) and dimethyl acetylenedicarboxylate (1 mmol) in dry CH_2Cl_2 (3 ml) at r.t. for over 10 min. The mixture was then stirred at r.t. for 3.5 h. The solvent was removed under reduced pressure, and the residue was separated by CC (SiO_2; hexane/AcOEt 7:3).

Ultrasound Irradiation. A soln. of appropriate (arylmethylidene)malononitrile (1 mmol), dimethyl acetylenedicarboxylate (1 mmol), and cyclohexyl isocyanide (1 mmol) in H_2O (6 ml) was sonicated in a sonic bath working at 60 W (constant frequency) maintained at 30° (temp. of ultrasonic bath) for the appropriate period of time, until the initial materials were no longer detectable (TLC). The mixture was extracted with $CHCl_3$ (3 × 10 ml). The org. layer was dried (Na_2SO_4), concentrated, and purified by CC (SiO_2 (100–200 mesh); with hexane/AcOEt 7:3).

Selected Data. Diethyl 4,4-Dicyano-3-(cyclohexylamino)-5-(4-fluorophenyl)cyclopenta-2,5-diene-1,2-dicarboxylate (*Table 2*, *Entry 3*): IR: 3345, 2985, 2944, 2853, 2231, 1734, 1700, 1614, 1595, 1577, 1445, 1341, 1247. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.33 (*t*, *J* = 7.0, 3 H); 1.35 (*t*, *J* = 7.0, 3 H); 1.42–1.51 (*m*, 5 H); 1.72 (*m*, 1 H); 1.85 (*m*, 2 H); 2.19 (*m*, 2 H); 3.93 (*m*, 1 H); 4.22 (*q*, *J* = 7.0, 2 H); 4.33 (*q*, *J* = 7.0, 2 H); 7.08 (*d*, *J* = 8.5, 2 H); 7.21 (*d*, *J* = 8.5, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 13.9; 14.2; 24.5; 24.9; 31.0; 34.1; 56.0; 60.6; 61.9; 110.1; 116.1; 117.1; 125.8; 130.1; 133.5; 158.3; 16.3; 164.4. Anal. calc. for $C_{25}H_{26}FN_3O_4$ (451.49): C 66.51, H 5.80, N 9.31; found: C 65.9, H 6.0, N 9.6.

Diethyl 3-(4-Chlorophenyl)-4,4-dicyano-5-(cyclohexylamino)cyclopenta-2,5-diene-1,2-dicarboxylate (*Table 2*, *Entry 4*). IR: 3340, 3263, 2941, 2858, 2202, 1738, 1668, 1600, 1452, 1373, 1215. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.31 (*t*, *J* = 7.2, 3 H); 1.33 (*t*, *J* = 7.2, 3 H); 1.45–1.56 (*m*, 5 H); 1.73 (*m*, 1 H); 1.87 (*m*,

2 H); 2.20 (*m*, 2 H); 3.87 (*m*, 1 H); 4.24–4.32 (*m*, 4 H); 7.42 (*d*, *J* = 6.0, 2 H); 7.5 (*d*, *J* = 6, 2 H); 8.36 (*d*, *J* = 11.5, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 13.9; 14.2; 24.5; 24.9; 31.0; 34.1; 56.1; 60.6; 62.0; 110.1; 116.5; 128.9; 129.4; 135.1; 140.0; 156.8; 164.4; 164.6. Anal. calc. for $C_{25}H_{26}ClN_3O_4$ (467.94): C 64.17, H 5.60, N 8.98; found: C 64.5, H 6.0, N 9.0.

Diethyl 4,4-Dicyano-3-(cyclohexylamino)-5-(2-fluorophenyl)cyclopenta-2,5-diene-1,2-dicarboxylate (*Table 2*, *Entry 6*). IR: 3267, 2940, 2859, 1742, 1672, 1606, 1454, 1375, 1349, 1269, 1252, 1106. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.20 (*t*, *J* = 7.0, 3 H); 1.32 (*t*, *J* = 7.0, 3 H); 1.50 (*m*, 5 H); 1.70 (*d*, *J* = 12.0, 1 H); 1.85 (br. *s*, 2 H); 2.20 (br. *s*, 2 H); 3.87 (br. *s*, 1 H); 4.20 (*q*, *J* = 7.0, 2 H); 4.26 (*q*, *J* = 7.0, 2 H); 7.20 (*t*, *J* = 8.9, 1 H); 7.44 (*d*, *J* = 6.0, 1 H); 7.55 (*t*, *J* = 7.3, 1 H); 8.38 (*d*, *J* = 10.5, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.2; 14.6; 24.8; 25.4; 34.6; 43.9; 56.3; 60.9; 62.0; 100.4; 110.1; 116.5; 116.7; 124.9; 132.0; 157.7; 164.2; 164.9. Anal. calc. for $C_{25}H_{26}FN_3O_4$ (451.49): C 66.51, H 5.80, N 9.31; found: C 65.5, H 5.8, N 9.5.

Diethyl 3-(3-Bromophenyl)-4,4-dicyano-5-(cyclohexylamino)cyclopenta-2,5-diene-1,2-dicarboxylate (*Table 2*, *Entry 10*). IR: 3258, 2986, 2937, 2855, 2233, 1743, 1672, 1602, 1580, 1451, 1346, 1215. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.33 (*m*, 6 H); 1.47–1.58 (*m*, 5 H); 1.72 (*m*, 1 H); 1.87 (*m*, 2 H); 2.20 (*m*, 2 H); 3.89 (*m*, 1 H); 4.27 (*q*, *J* = 7.0, 2 H); 4.32 (*q*, *J* = 7.0, 2 H); 7.32 (*t*, *J* = 7.5, 1 H); 7.53 (*d*, *J* = 7.0, 1 H); 7.56 (*d*, *J* = 7.0, 1 H); 7.71 (*t*, *J* = 2.0, 1 H); 8.39 (*d*, *J* = 11.0, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.0; 14.2; 24.5; 24.9; 34.1; 42.2; 56.1; 60.6; 62.1; 110.0; 115.8; 123.1; 125.8; 130.6; 132.0; 140.6; 157.0; 164.36; 164.42. Anal. calc. for $C_{25}H_{26}BrN_3O_4$ (512.40): C 58.60, H 5.11, N 8.20; found: C 58.1, H 5.6, N 8.0.

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