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# MICROWAVE-ACCELERATED RUTHENIUM-CATALYZED $[2\pi + 2\pi]$ CYCLOADDITIONS OF DIMETHYLACETYLENE DICARBOXYLATE WITH NORBORNENES

# Davor Margetić,<sup>1</sup> Pavle Trošelj,<sup>1</sup> and Yasujiro Murata<sup>2</sup>

<sup>1</sup>Laboratory for Physical–Organic Chemistry, Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Zagreb, Croatia <sup>2</sup>Institute for Chemical Research, Kyoto University, Uji, Kyoto, Japan

## **GRAPHICAL ABSTRACT**



**Abstract** An efficient and convenient procedure has been developed for the rutheniumcatalyzed  $[2\pi + 2\pi]$  cycloadditions of dimethylacetylene dicarboxylate with norbornenes. Reaction is significantly accelerated in microwave conditions, while the commonly used benzene solvent was replaced by environmentally benign tetrahydrofuran.

Keywords Acetylenes; [2+2] cycloadditions; microwave reaction; norbornene derivatives

#### INTRODUCTION

Much effort by organic chemists has been devoted to the preparation of complex polycyclic rigid compounds that possess functionalities at the desired distance and spatial orientation. In this respect, synthesis of a polynorbornane skeleton functionalized at both ends<sup>[1,2]</sup> has been achieved, utilizing several synthetic strategies, and cycloaddition reactions were shown to be the most effective. In particular, acetylene cyclobutene epoxide (ACE) coupling protocol,<sup>[3]</sup> its aza-ACE variant,<sup>[4]</sup> and photochemical  $[2\pi + 2\pi]$  dimerisation<sup>[5]</sup> were employed by Warrener et al. These methods were based on cyclobutene diester functionalization, where the Mitsudo reaction has been the cornerstone in the preparation of ester functionalized norbornene cyclobutenes of type **2** (Scheme 1). The Mitsudo reaction is a thermal reaction of norbornenes **1** with dimethylacetylene dicarboxylate (DMAD) in the

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Address correspondence to Davor Margetić, Laboratory for Physical–Organic Chemistry, Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, 10001 Zagreb, Croatia. E-mail: margetid@emma.irb.hr



Scheme 1. Mitsudo reaction.

presence of ruthenium catalyst,  $\text{RuH}_2\text{CO}(\text{PPh}_3)_{3,}^{[6]}$  with high  $\pi$ -facial selectivity, taking place specifically at the *exo*-face exclusively. Double C-C bond formation between alkynes and acetylenes by ruthenium(0)-catalyzed [2+2] cycloaddition of strained cycloalkene with highly electron-deficient DMAD afford cyclobutene.<sup>[7]</sup> This reaction protocol has several drawbacks—it is limited to the norbornenes (strained olefins), while cyclohexenes or bicyclo[2.2.2]oct-2-enes do not react. Also, the number of acetylenes that may be employed is limited.<sup>[8]</sup> From the practical point of view, the impractibility of this method lies in the fact that these cycloadditions are usually carried out in benzene by heating at 60–80 °C for 2–3 days, and some substrates require up to 7 days. The aim of this study is to address this issue and improve the synthetic protocol.

The most important improvement of the Mitsudo reaction would be significant shortening of reaction time; therefore, we looked at microwave conditions as the most promising option. Many reactions can be carried out in microwave conditions to shorten the reaction time, increase the efficiency, or initiate the formation of new products compared with conventional heating methods.<sup>[9]</sup> As far as we know, results presented in this article are the first account of the use of microwaves to enhance ruthenium-catalyzed  $[2\pi + 2\pi]$  alkene/alkyne cycloaddition. Ruthenium-catalyzed reactions of olefins in microwave conditions are reported for olefin metathesis, [2+2+2] cyclotrimerization, and 1,6-diene and 1,6-enyne cycloisomerizations.<sup>[10]</sup> On the other hand, just a few examples exist of transition metal–catalyzed addition of various reagents to norbornenes (chromium complexes in C-C bond–forming [2+2+1]/[2+1] addition),<sup>[11]</sup> Pauson–Khand reaction (with cobalt reagents),<sup>[12]</sup> and ring-opening methathesis of norbornenes employing Grubb's Ru catalysts.<sup>[13]</sup> These literature examples indicate the stability and suitability of various ruthenium catalysts to be used in microwave conditions.

#### **RESULTS AND DISCUSSION**

As a model norbornene system, diester **3** was used for optimization of the Mitsudo reaction under microwave conditions, where tetracyclic tetraester **4** is obtained as the product. A systematic study on variation of catalyst and DMAD amounts, solvent, and temperature was carried out, and the results are collected in Table 1. As a major result, dramatic reduction of reaction time with moderate to good yields was obtained. Inspection of results showed that the toxic benzene solvent could be replaced by less toxic tetrahydrofuran (THF), dimethylformamide (DMF), or toluene (entries 1, 6, and 7). The best results were obtained in dry

Entry	Substrate	Product	Conditions <sup>b</sup>	Solvent <sup>b</sup>	Yield (%)
1					83
2			30 min		58
3	Λ -	E A F	10 min		25
4			30 min	Wet THF	50
5	L	E	2 h		86
6				DMF	23
7				Toluene	53
8				DMAD	50
9			90 °C		78
10			60 ° C		10
11			2.4 eq DMAD		98
12			0.05 eq Ru		46
13			0.2 eq Ru		41
14			0.2 eq Ru	THF 1 mL	42

**Table 1.** Optimization of Mitsudo reaction with diester **3** under microwave conditions<sup>*a*</sup>

<sup>*a*</sup>Standard reaction conditions: DMAD (1.2 equiv), Ru catalyst (0.1 equiv), dry THF (0.5 mL), 80 °C, 1 h. Literature procedure: DMAD (2–5 equiv), Ru catalyst (0.2–0.5 equiv), dry benzene, 80 °C, 24 h, 67%. <sup>*b*</sup>Variation of standard conditions.

THF (83%) without loss of efficiency as compared to benzene. On the other hand, the use of wet THF, toluene, and DMF resulted in decreased yields. When the microwave reaction was conducted without a solvent, in neat DMAD (excess), reduction of yield to 50% was observed (entry 8). However, the use of excess DMAD (2.4 equivalents, entry 11) in THF obtained full conversion of 3 to product 4 within just 1 h (98%). Reaction times from 3-7 days in thermal reactions could be reduced to 1 h (entry 1) with 83% yield, while a 2-h reaction gave a slightly better vield (86%, entry 5). Further shortening of reaction time to 30 and 10 min leaves much of substrate unreacted (58% and 25%, entries 2 and 3). Temperature variations from standard 80 °C to 60 °C or 90 °C decreased yields to 10% and 78%, respectively (entries 10 and 9). Furthermore, the influence of amount of catalyst on the reaction outcome is analyzed. It was found that reduction of catalyst to 5% diminishes the reaction yield to 46% (entry 12). Surprisingly, when the amount of catalyst was doubled to 20%, almost identical yield was obtained (41%, entry 13). This result could be explained by the presence of an insufficient amount of solvent and therefore an increase in viscosity of reaction media. When more solvent was added, a similar result was obtained (entry 14).

Optimized reaction conditions were used in subsequent experiments, and results are presented in Table 2. Versatility of the new reaction protocol was tested for a series of substrates 5–13. Excellent results were obtained for norbornene 5 and benzonorbornadienes 6 and 7 (96%, 95%, and 79% yields, respectively, entries 15, 16, and 17), which are superior to the literature reaction conditions. Substrate compatibility was investigated in the case of substrates where the norbornene methylene bridge (CH<sub>2</sub>) of the norbornene moiety was replaced with oxygen or nitrogen (molecules 8 and 9). In these cases, good yield was obtained for 7-azabenzonorbornadiene 9 (88%, entry 19), while the 7-oxabenzonorbornadiene reaction yieleded less

Entry	Substrate	Product	Conditions <sup>b</sup>	Lit. <sup>c</sup>	Yield (%)
15	5	E 14		24 h, 65%	96
16	6	E 15		20 h 50 °C 65%	95
17	OMe 7 OMe	OMe H <sub>b</sub> E 16		3 d, 75%	79
18	8			6 h, 100 °C 39%	38
19	CO <sub>2</sub> Bn N 9	CO <sub>2</sub> Bn N E 18		4 d, 70 °C, 95%	88
20	0 NMe 10	E NMe 19		3 d, 66%	75
21			2.4 eq DMAD	_	
22	0 0 12 0 NHBoc	E O O E 21 O N NHBoc	2.4 eq DMAD	_	5
23 24 25	13	3+4+ E 22	2.4 eq DMAD 3 h	1d, 37% <sup>e</sup>	$5/10/20^{d}$ 5/15/40 20/5/50

 Table 2. Mitsudo reaction with norbornenes under microwave conditions<sup>a</sup>

 $^a$  Standard reaction conditions: DMAD (1.2 equiv), Ru catalyst (0.1 equiv), dry THF (0.5 mL), 80 °C, 1 h.  $^b$  Variation of standard conditions.

 $^c\text{Literature}$  procedure: dry benzene, 80  $^\circ\text{C},$  1–4 days.

<sup>*d*</sup>Yields for products 3/4/22.

<sup>e</sup>Only product **3** was obtained.



Figure 1. Molecular structure of product 16.

product (38%, entry 18). The Mitsudo reaction with another 7-oxanorbornene substrate, **10**, was much more efficient, furnishing 75% yield (entry 20).

The *exo*-cyclobutene structure of all Mitsudo products was fully supported by correlation spectroscopy (COSY) NMR spectra (W coupling of methylene H<sub>a</sub> protons and *endo*-protons H<sub>b</sub>) and unequivocally proven by the single-crystal x-ray structure analysis of representative product **10** presented in Fig. 1.

In principle, double  $[2\pi + 2\pi]$  cycloaddition could be also achieved in the case of substrates possessing two double bonds, such as **11**, **12**, and norbornadiene **13**. However, it was found that the introduction of the second double bond significantly affects reaction yields. In the case of **11** and **12**, just 5% of product was detected (entries 21 and 22). Even the addition of a larger amount of DMAD (4.8 equiv.) does not improve reaction efficiency. This unreactivity may be the result of the steric hindrance caused by the *endo*-positioned imide functionalities (as opposed to *exo*-placed imide in substrate **10**).

Transformation of norbornadiene to product **4** in a one-pot reaction would represent an improvement over the classical three-step synthesis.<sup>[6,14]</sup> While the literature has shown that microwave heating in general significantly reduces unwanted side reactions compared with conventional heating methods, this is not true for norbornadiene. In the case of norbornadiene (entries 23–25), a complex product mixture was obtained, consisting mainly of three components, **4**, **5**, and **22**, where the bishomo  $[2\pi + 2\pi + 2\pi]$  cycloaddition product **22** dominates. Variation of reaction conditions gives essentially the same outcome.

#### EXPERIMENTAL

Mixture of DMAD (44 mg, 0.31 mmol),  $RuH_2CO(PPh_3)_3$  catalyst (24 mg, 0.025 mmol), and substrate **3** (60 mg, 0.25 mmol) in dry THF (0.5 mL) was subjected to microwave reaction. Reactions were conducted in a CEM Discover LabmateTH/ ExplorerPLS single-mode microwave reactor using the closed reaction vessel technique (power = 125 W). Excess of solvent was removed in vacuo and products were analyzed by thin-layer chromatography (TLC), gas chromatography (GC), or <sup>1</sup>H NMR spectroscopy. Radial chromatography (with petroleum ether–ethyl acetate)

was used for product isolation. All new compounds gave <sup>1</sup>H and <sup>13</sup>C NMR spectra and high-resolution mass spectra (HRMS) corresponding to their assigned structures.

#### **Data on Selected Compounds**

**Compound 3.** Oil. <sup>1</sup>H (CDCl<sub>3</sub>),  $\delta$ /ppm: 1.36 (1H, d, J = 9.6 Hz), 1.42 (1H, d, J = 9.6 Hz), 2.53 (2H, s), 2.63 (2H, s), 3.79 (12H, s), 6.20 (2H, t J = 1.45 Hz).

**Compound 4.** Mp 141–143 °C. <sup>1</sup>H (CDCl<sub>3</sub>), δ/ppm: 1.39 (2H, s), 2.43 (2H, s), 2.58 (4H, s), 3.81 (12H, s).

**Compound 14.** Oil. <sup>1</sup>H (CDCl<sub>3</sub>),  $\delta$ /ppm: 1.03 (1H, d, J = 11.1 Hz), 1.08 (2H, d, J = 8.4 Hz), 1.24 (1H, d, J = 11.1 Hz), 1.57 (2H, d, J = 8.4 Hz), 2.24 (2H, s); 2.64 (2H, s), 3.73 (6H, s).

**Compound 15.** Mp 81–82 °C. <sup>1</sup>H (CDCl<sub>3</sub>),  $\delta$ /ppm: 1.76 (2H, s), 2.73 (2H, s), 3.26 (2H, s), 3.82 (6H, s).

**Compound 16.** Mp 120–123 °C. <sup>1</sup>H (CDCl<sub>3</sub>),  $\delta$ /ppm: 1.82 (1H, d, J = 5.2 Hz), 1.90 (1H, d, J = 5.2 Hz), 2.94 (2H, s), 3.88 (6H, s), 4.03 (6H, s), 7.44 (2H, dd, J = 6.6 Hz, J = 3.2 Hz), 8.07 (2H, dd, J = 6.6 Hz, J = 3.2 Hz); <sup>13</sup>C (CDCl<sub>3</sub>),  $\delta$ /ppm: 37.6, 39.3, 46.2, 52.0, 61.9, 122.1, 125.5, 128.3, 132.9, 142.9, 145.6, 161.5. HRMS (m/z): calcd. for C<sub>23</sub>H<sub>22</sub>O<sub>6</sub>: 394.1416; found: 394.1420.

**Compound 17.** Mp 150–152 °C. <sup>1</sup>H (CDCl<sub>3</sub>),  $\delta$ /ppm: 1.92 (2H, s), 3.87 (6H, s), 5.21 (2H, s), 7.20 (2H, dd, J=7.5 Hz, J=1.5 Hz), 7.34 (2H, dd, J=7.5 Hz, J=1.5 Hz).

**Compound 18.** Mp 96–97 °C. <sup>1</sup>H (CDCl<sub>3</sub>), δ/ppm: 2.86 (1H, brs), 2.88 (1H, brs), 3.66 (3H, s), 3.87 (3H, s), 4.95 (1H, brs), 5.05 (1H, brs), 5.21 (1H, brs), 5.26 (1H, brs), 7.18–7.24 (9H, m).

**Compound 19.** Mp 91–94 °C. <sup>1</sup>H (CDCl<sub>3</sub>),  $\delta$ /ppm: 2.91 (2H, s), 2.97 (3H, s), 3.11 (2H, s), 3.80 (6H, s), 4.77 (2H, s).

### **Crystallographic Data**

CCDC 741971 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/cif. Crystal data:  $C_{23}H_{22}O_6$ ,  $M_r = 394.41$ , monoclinic, P2(1)/c, a = 7.7234(7) Å, b = 27.719(2) Å, c = 9.3834(8) Å,  $\beta = 109.7520(10)^\circ$ , V = 1890.7(3) Å<sup>3</sup>, Z = 4, T = 100(2) K, density = 1.386 Mg/m<sup>3</sup>, crystal size =  $0.23 \times 0.18 \times 0.15$  mm<sup>3</sup>. Final R indices I > 2sigma(I), R1 = 0.0389, wR2 = 0.0999. R indices (all data), R1 = 0.0472, wR2 = 0.1042. Data/restraints/parameters, 3318/0/266. Goodness of fit on F<sup>2</sup>, 1.041.

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