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Microwave-Mediated Nickel-Catalyzed Cyclotrimerization Reactions: Total Synthesis of Illudinine

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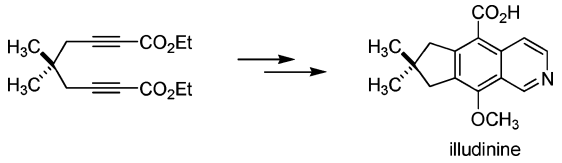


illudinine

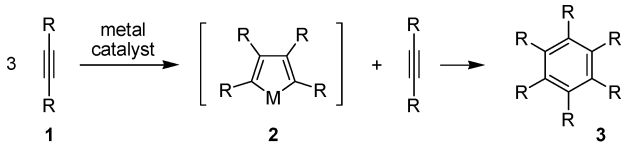
Rapid and efficient [2 + 2 + 2] cyclotrimerization reactions were discovered through the application of microwave irradiation in conjunction with a $Ni(CO)_2(PPh_3)_2$ catalyst. This enables the facile construction of highly substituted indane, isoindoline, and tetraline core structures. The developed microwave-mediated Ni-catalyzed cyclotrimerization reaction was employed as the key step in a concise synthesis of the isoquinoline natural product illudinine. This represents the first example of a Ni-catalyzed cyclotrimerization reaction in total synthesis.

[2 + 2 + 2] Cyclotrimerization reactions are excellent tools for the highly convergent assembly of aromatic rings,[1] and several elegant examples of their application to the synthesis of benzene containing natural products have been reported.[2]

In a classical cyclotrimerization reaction, three alkynes (e.g., **1**) react in presence of a metal catalyst to form a benzene **3** via a metallacyclopentadiene **2** (Scheme 1). Since this type of reaction is difficult to perform in a selective fashion, most alkyne cyclotrimerizations use tethered alkynes (diynes or triynes) as substrates.

Applications of [2 + 2 + 2] cyclotrimerization reactions in total synthesis involve the utilization of catalyst systems based on cobalt,[2e,f] rhodium,[2b,d] ruthenium,[2a] or palladium.[2c] In contrast, nickel-catalyzed [2 + 2 + 2] cyclotrimerizations have not been applied to total synthesis, despite the fact that the first

SCHEME 1. General [2 + 2 + 2] Cyclotrimerization Reaction



M = metal center; potential ligands are omitted for clarity.

"cyclic polymerization of acetylene" conducted under homogeneous catalysis was reported by Reppe in 1948 using an in situ formed Ni catalyst.[3] In 1961, Meriwether reported the utilization of $Ni(CO)_2(PPh_3)_2$ in the homogeneous catalysis of [2 + 2 + 2] cyclotrimerization reactions.[4] Typically, reactions were performed in refluxing benzene or cyclohexane for up to 24 h to give mixtures of aromatized products and linear polymers. The authors noted a general order of reactivity where acetylenic esters and ketones were more reactive than arylalkynes, and alkylalkynes were the least reactive. Disubstituted alkynes were typically inert. Cyclotrimerization reactions involving alkylalkynes were hindered by high levels of linear polymer formation. Later, Smith and co-workers used stoichiometric amounts of Ni(0) and achieved cyclotrimerizations of diynes with an average yield of 50% (rt, 17 h),[5] which was subsequently optimized by Mori (up to 97% yield, 8−20 mol % of catalyst) although extended reaction times were still necessary (40 h on average).[6] Recently, binary Ni/Zn and Ni/Al metal systems have been reported which induce cyclotrimerization reactions with mixed efficiencies.[7] Louie et al. tuned the activity of Ni-based catalysts through the application of specifically designed carbene ligands, enabling facile reactions with nitriles, isocyanates, and CO_2.[8] Recently, we[9] and others[10] observed dramatic effects of microwave irradiation[11] on Co- and Ru-catalyzed cyclotrimerization reactions to benzenes and pyridines.

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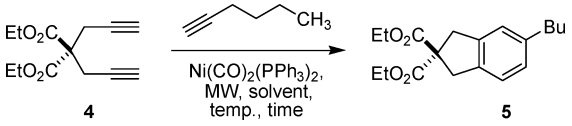
TABLE 1. Optimization of the Microwave-Mediated [2 + 2 + 2] Cyclotrimerization Reaction under $Ni(CO)_2(PPh_3)_2$ Catalysis



entry	**5** (%)	MW (W)	temp (°C)	solvent	time (min)
1	75	300	117	toluene	10
2	**78**	**300**	**82**	**toluene**	**2**
3			82[a]	toluene	2
4	70	300	105	THF	2
5	63	300	133	$C_2H_4Cl_2$	2
6	47	300	117	CH_3CN	2

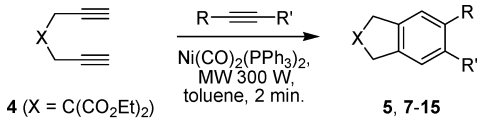
[a] The temperature profile inside the reaction vessel was identical to the microwave reaction with a final temperature of 82 °C. The oil bath temperature was 92 °C.

Here, we are reporting the application of microwave irradiation to overcome the limitations of the $Ni(CO)_2(PPh_3)_2$ catalyst system, enhancing its reactivity, and enabling its application in alkaloid total synthesis. In order to find optimal reaction conditions, we conducted [2 + 2 + 2] cyclotrimerization reactions of a classical substrate for this reaction type, diethyl dipropargyl malonate[12] (**4**), with 1-hexyne leading to the benzene **5**[13] (Table 1).

Conditions previously found to be optimal for microwave-assisted solid-supported cyclotrimerization reactions (10 mol % of catalyst, $PhCH_3$, 10 min)[9] served as a reference point for these investigations and gave the aromatic product **5** in 75% yield (entry 1). Interestingly, in case of the $Ni(CO)_2(PPh_3)_2$ catalyst, decreasing the reaction time to 5 min (data not shown) and 2 min (entry 2) still led to complete reaction of **4** and furnished **5** in 78% yield, with a final reaction temperature of 82 °C (see Supporting Information). Conducting the identical reaction without microwave irradiation (82 °C final reaction temperature, 92 °C oil bath temperature, 2 min; entry 3) did not yield any cyclotrimerization product **5**, thus demonstrating the enhancing effects[14] of microwave irradiation on the Ni-catalyzed reaction. Potential solvent effects on the cyclotrimerization reaction were then explored by using THF, 1,2-dichloroethane, and acetonitrile (entries 4−6). In these cases, the reaction temperatures were raised above the 82 °C observed in the case of toluene, and generally lower yields (47−70%) were observed. No pyridine product was observed in the case of acetonitrile. Thus, all subsequent [2 + 2 + 2] cyclotrimerization reactions were performed by microwave irradiation (300 W) of a solution of the diyne, monoyne (10 equiv), and $Ni(CO)_2(PPh_3)_2$ (10 mol %; lower catalyst loadings led to greatly diminished yields) in $PhCH_3$ for 2−5 min.

We subsequently investigated the functional group compatibility of this reaction with several different substrates (Scheme 2), including 1-hexyne, phenylacetylene, benzylated propargyl alcohol,[15a] Boc-protected propargyl amine,[15b] and an internal alkyne, 3-hexyne. The reaction of the diyne **4** proceeded smoothly, delivering the indanes **7**−**10** in 50−82% yield. Surprisingly, benzylated propargyl alcohol failed to cyclotrimerize with **4**, and phenylacetylene furnished **7**[16] in only 50% yield. However, both alkynes produced cyclotrimerization products in high yield with the other diynes investigated (see below). In contrast, the much less reactive internal 3-hexyne delivered **10** in 63%, which has previously failed to react under Meriwether's conditions.[4] In order to investigate the synthesis of isoindolines and the effect of a ring nitrogen center on the cyclotrimerization reaction, we synthesized the Boc-protected dipropargylamine[17] **6** and subjected it to the same [2 + 2 + 2] cyclotrimerization conditions. The isoindolines **11**−**15** were obtained in good yields (55−80%). Here, all terminal alkynes display comparable levels of reactivity.

SCHEME 2. Microwave-Mediated $Ni(CO)_2(PPh_3)_2$-Catalyzed Cyclotrimerization Reactions toward Indanes and Isoindolines



Cmpd.	X	R	R'	Yield
5	$C(CO_2Et)_2$	Bu	H	78%
7	$C(CO_2Et)_2$	Ph	H	50%
8	$C(CO_2Et)_2$	CH_2OBn	H	-
9	$C(CO_2Et)_2$	CH_2NHBoc	H	82%
10	$C(CO_2Et)_2$	Et	Et	63%
11	NBoc	Bu	H	80%
12	NBoc	Ph	H	75%
13	NBoc	CH_2OBn	H	76%
14	NBoc	CH_2NHBoc	H	80%
15	NBoc	Et	Et	55%

Toward the synthesis of illudinine (see below), we envisioned the use of an electron-deficient diyne cyclotrimerization precursor bearing carboxylates on both triple bonds. Moreover, Meriwether reported high reactivity of the $Ni(CO)_2(PPh_3)_2$ catalyst in the case of electron-poor triple bonds.[4] Thus, the compound **16** was synthesized[18] and subjected to the microwave-mediated Ni-catalyzed cyclotrimerization reactions with the same alkynes as before delivering penta- to hexa-substituted benzenes **18**−**22** in good to excellent yields (61−98%, Scheme 3). These yields were generally higher than in case of the electron-neutral diynes **4** and **6**. Moreover, we were able to construct tetralines **23**−**27** using the homologous precursor[18] **17**. The tetralin [2 + 2 + 2] cyclotrimerization yields (58−70%) were slightly lower compared to the those of the indane synthesis, and the reaction time needed to be extended to 5 min, due to the higher activation barrier when forming six-membered rings.[19]

The facile reaction of **16** set the stage to showcase the applicability of the developed nickel-catalyzed microwave-mediated [2 + 2 + 2] cyclotrimerization reaction in total synthesis (Scheme 4). The sesquiterpene alkaloid illudinine (**36**) was isolated as a fungal metabolite from the basidiomycete *Clitocybe illudens* (also known as *Omphalotus olearius* or Jack-

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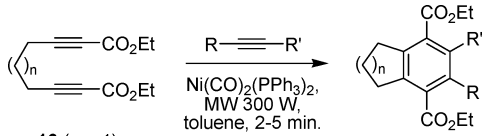
SCHEME 3. Microwave-Mediated $Ni(CO)_2(PPh_3)_2$-Catalyzed Cyclotrimerization Reactions of Electron-Deficient Diynes



16 (n = 1)
17 (n = 2)

18-27

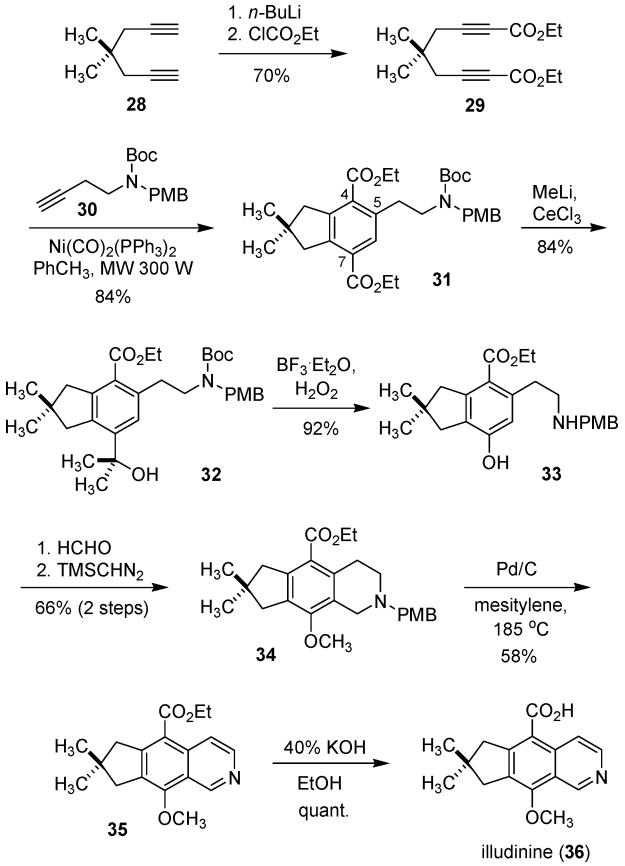
Cmpd.	n	R	R'	Yield
18	1	Bu	H	79%
19	1	Ph	H	93%
20	1	CH_2OBn	H	98%
21	1	CH_2NHBoc	H	90%
22	1	Et	Et	61%
23	2	Bu	H	70%
24	2	Ph	H	64%
25	2	CH_2OBn	H	60%
26	2	CH_2NHBoc	H	61%
27	2	Et	Et	58%

O-Lantern mushroom), and a biogenetic relationship to illudalic acid was suggested.[20] Only two total syntheses of illudinine are known: one by Woodward and Hoye,[21] requiring 15 steps from indane (including a necessary separation of regioisomers), and one by Rao and co-workers, requiring 14 steps from 6-methoxy-1,2,3,4-tetrahydronaphthalene.[22]

Our synthesis commences with the known diyne **28**[23] (synthesized in five steps) which is lithiated at both terminal triple bonds and then carboxylated to form the diester **29** (70% yield). As in case of the model studies with **16**, this molecule underwent a smooth reaction with the alkyne **30**[24] via a Ni-$(CO)_2(PPh_3)_2$-catalyzed [2 + 2 + 2] cyclotrimerization reaction under microwave irradiation in toluene for 2 min at 300 W. The alkyne **30** was selected since previous experiments demonstrated the incompatibility of basic nitrogen centers with the Ni-catalyzed cyclotrimerization (data not shown) and because the PMB group can be efficiently removed in an oxidation step toward the completion of the total synthesis. The cyclotrimerization product **31** was isolated in 84% yield.

The next steps involved the selective introduction of the phenolic OH group at C-7. On the basis of model studies with the previously synthesized indane **18**, a benzylic hydroperoxide rearrangement was discovered as a potential route (data not shown).[25] Gratifyingly, treatment of **31** with an excess of CH_3-Li in the presence of $CeCl_3$ delivered the tertiary alcohol **32** as the only product in 84% yield. We speculate that the observed exclusive regioselectivity is a result of the steric hindrance of a nucleophilic addition into the carboxy group at C-4 due to the alkyl substituent located in close proximity at C-5. This selective addition will most likely find application in other syntheses. The subsequent carbenium ion rearrangement of **32**

SCHEME 4. Total Synthesis of Illudinine (36) via a Microwave-Mediated $Ni(CO)_2(PPh_3)_2$-Catalyzed Cyclotrimerization Reaction



to **33** is mediated by treatment with $BF_3{\cdot}OEt_2/H_2O_2$ in DCM at 0 °C.[25] Simultaneous removal of the Boc group delivers the phenol **33** in 92% yield and sets the stage for the assembly of the tricyclic skeleton via a classical Pictet−Spengler reaction.[26] Thus, treatment of **33** with formaldehyde in the presence of a sodium acetate buffer furnishes the corresponding tetrahydroisoquinoline, which is directly converted into the methyl ether **34** through exposure to trimethylsilyldiazomethane (66% over two steps).[27] The oxidation of **34** to the isoquinoline was conducted with Pd/C in mesitylene at 185 °C. These conditions lead to a concomitant removal of the PMB protecting group in a combined yield of 58%. Quantitative saponification of the ester with 40% aqueous KOH in EtOH/H_2O (95:5) completes this convergent and highly selective total synthesis of illudinine (**36**).

In summary, we discovered mild and fast [2 + 2 + 2] cyclotrimerization reactions by employing the commercially available $Ni(CO)_2(PPh_3)_2$ catalyst in conjunction with the enhancing effects of microwave irradiation. Several diynes were reacted with a range of alkynes delivering fused bicyclic systems in good to excellent yields. Subsequently, we employed these reaction conditions in the first example of a Ni-catalyzed cyclotrimerization reaction in total synthesis. The sesquiterpene alkaloid illudinine was assembled in eight steps from known material. We are currently extending this technology to the construction of other natural product targets.

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Experimental Section

The following general protocol for Ni-catalyzed cyclotrimerization reactions toward **5**, **7**−**15**, and **18**−**27** was used: To a flame-dried microwave vial equipped with a stir bar were added the diyne (0.085 mmol), the monoalkyne (0.85 mmol), $Ni(CO)_2(PPh_3)_2$ (5.4 mg, 0.0085 mmol), and dry toluene (2.8 mL). The vial was flushed with nitrogen, capped with a microwave vial septum, and irradiated for 2−5 min in a CEM Discover microwave synthesizer at 300 W. After cooling to room temperature, the reaction mixture was concentrated, and the residue was purified by silica gel chromatography, eluting with hexanes/EtOAc to give the pure cyclotrimerization product.

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Supporting Information Available: All experimental protocols of the illudinine synthesis, representative microwave temperature−time profiles, and analytical data, as well as ^{1}H NMR spectra for compounds **9**−**15**, **18**−**27**, **29**, and **31**−**36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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