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Microwave-assisted direct addition of cycloethers to alkynes

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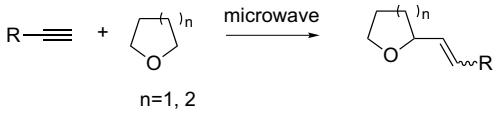
Abstract—Under microwave conditions, tetrahydrofuran (THF), tetrahydropyran and 1,4-dioxane are added directly onto alkynes and generated various vinyl cycloethers.

2-Vinyl substituted heterocycles are the key structural features of a large number of natural products that show a wide range of biological activities.[1] Therefore there has been a sustained interest in developing methods for forming such structures. Traditionally, 2-vinyl substituted heterocycles can be prepared by methods such as the Horner–Emmons approach reacting alkyl(diphenyl)phosphine oxide with a carbonyl compound,[2] intermolecular hydroalkoxylation of alkynes catalyzed by palladium/benzoic acid,[3] and direct synthesis via zinc chloride.[4] Recently, it has been reported that the addition of α-heterosubstituted radicals to styryl sulfimides, styryl triflone and β-nitrostyrenes can give such compounds in good yields at the presence of AIBN or benzoyl peroxide.[5] However, all these methods require the preparation of starting materials and involve an addition–elimination procedure, producing an equivalent of side product at the same time.

On the other hand, an overall addition reaction is an atom economical and efficient way to construct more complex structures from simpler units.[6] As a general effort in developing 'greener synthetic methods', we have been interested in the direct functionalization of various C–H bonds through various catalytic methods within the last few years.[7] One of these efforts is the development of methods for synthesizing tetrahydrofuran and tetrahydropyran derivatives.[8] Conceivably, an efficient method for forming such structures is the direct addition of cyclic ether such as tetrahydrofuran and tetrahydropyran to alkynes. Herein, we wish to report a direct addition of cycloethers to various terminal alkynes under microwave conditions (Scheme 1).



Scheme 1.

Within the last several years, microwave has become a powerful method in organic synthesis. Many elegant

Table 1. Optimization of the product formation

Entry	Molar ratio (alkyne/THF)	Temperature (°C)	Time (min)	Yield (%)[a]
1	1:15	165	10	5/6/89
2	1:20	180	10	6/7/87
3	1:10	180	10	<1%
4	1:25	200	30	6/7/87
5	1:40	110[b]	72 h	<10%
6	1:40	110[c]	72 h	35/28/37
7	1:40	200[d]	20	9/10/81
8	1:100	200	20	37/44/18
9	1:200	200	20	39/50/11
10	1:200	200	40	39/50/11
11	1:200	200	60	60%[e]

[a] Yields and ratios were based on ^{1}H NMR of crude reaction mixtures (for the ratio of *trans*-isomer:*cis*-isomer:unreacted material).
[b] Refluxing under oil bath.
[c] Refluxing under oil bath with AIBN added.
[d] AIBN was added.
[e] Isolated yield after chromatography.

Keywords: Alkyne–THF coupling; Atom-economy; Microwave; C–C bond formation.
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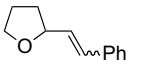
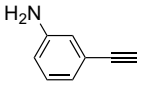
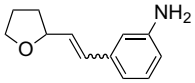
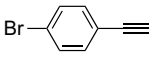
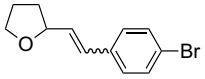
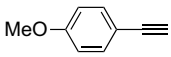
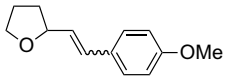
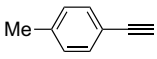
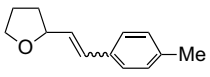
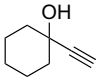
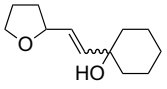
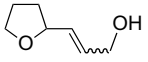
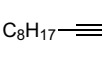
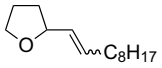
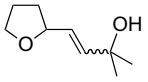
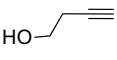
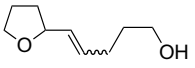
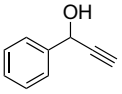
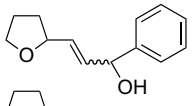
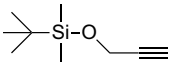
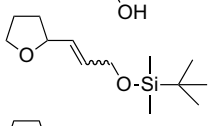
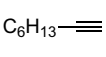
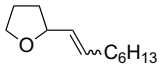
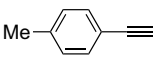
studies have been reported in the literature.[9] In particular, Leadbeater and Marco reported an efficient Suzuki-type coupling without transition-metal catalyst under microwave conditions.[10]

At the beginning of our investigation, we dissolved phenylacetylene in tetrahydrofuran (THF) together with various transition-metal catalysts. After subjected to microwave irradiation, we were surprised to find that the corresponding addition product was produced in almost all cases together with various by-products.[11] Subsequently, optimizing of the product was performed by varying the amount of catalysts. It was found that the best results were obtained without using any catalyst. Then, the product formation was optimized in terms of the microwave power, the reaction time and temper-

Table 2. Microwave-assisted direct addition of cycloethers to alkynes

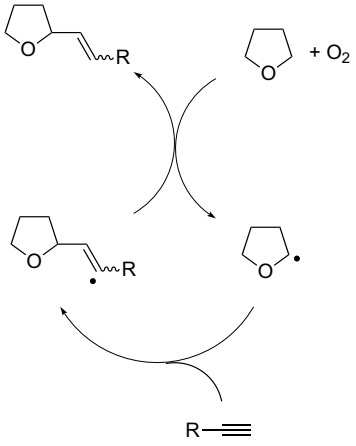
Entry	Alkyne	Cycloether	Conditions (W/temp (°C)/time)	Product	*cis*/*trans*-Ratio[a]	Total yield (%)[b]
1			300/200/40 min		53:47	60
2			300/200/120 min		58:42	52
3			300/200/60 min		55:45	71
4			300/200/80 min		56:44	58
5			300/200/80 min		57:43	68
6			300/200/120 min		26:74	42[c]
7			300/200/130 min		31:69	56
8			300/200/120 min		38:62	47
9			300/200/180 min		21:79	38
10			300/200/180 min		40:60	37
11			300/200/180 min		21:79	38
12			300/200/120 min		44:56	43
13			300/200/60 min		37:63	26
14			300/200/120 min		58:42	22
15			300/200/40 min		50:50	34
16			300/200/40 min		55:45	57

[a] *cis*/*trans* were determined by ^{1}H NMR based on Ref. 5c.
[b] Isolated yields were reported.
[c] Only *trans*-isomer was isolated.

ature and the conditions were summarized in Table 1. As shown in Table 1, a 5 mmol concentration of alkyne in THF microwaved at 200 °C in 60 min produced the desired addition product in good isolated yield as a mixture of *cis*/*trans* geometrical isomers. The addition of various additives, such as radical initiators (AIBN) or Lewis acids and transition-metal catalysts, to the reaction mixture decreased the yield of the product. Subsequently, the reaction of tetrahydrofuran with various terminal alkynes were examined under similar conditions (Table 2).

As shown in Table 2, aromatic alkynes appeared more reactive than aliphatic alkynes under the same reaction conditions. The presence of electron-withdrawing groups on the aryl group of aromatic alkyne further improved the reaction (entries 2, 3, 4 and 5). Alkynes bearing hydroxyl groups and an amine can be used directly without the need of protection groups (entries 6, 7, 9, 10 and 11); and no significant reactivity difference was observed between protected and unprotected propargyl alcohol under the reaction conditions (compare entries 7 and 12). The reaction also proceeded well with tetrahydropyran and 1,4-dioxane. However, the yields were lower with these compounds than those with THF; and the required reaction temperatures were also higher.

In conclusion, a direct addition of cycloethers to alkynes was developed under microwave conditions to generate various 2-vinyl substituted cyclic ether derivatives. A tentative mechanism (Scheme 2) for the reaction was proposed to involve the abstraction of the 2-hydrogen of tetrahydrofuran by oxygen molecule to generate tetrahydrofuran radicals. Then, a direct radical addition to the terminal alkynes forms a C–C bond and a vinyl radical, which undergoes subsequent radical abstract and regenerate new tetrahydrofuran radicals for further reactions. Previously, tetrahydrofuran radical addition to alkyne has been observed in the study of Bergman cyclization reaction.[12] This radical mechanism was also confirmed by our using a deuterated phenylacetylene (entry 16). Currently, efforts were made to control the stereochemistry of the reaction. The scope, mechanism and synthetic application of this direct addition reaction are under investigation.



Scheme 2. Tentative mechanism for the direct addition of tetrahydrofuran and tetrahydropyran to alkynes.

The following procedure is representative: a mixture of phenylacetylene (20.4 mg, 0.2 mmol) and THF (3.25 mL. 40 mmol) in a sealed tube was placed in a CEM microwave oven. The mixture was heated while stirring under microwave (at 200 °C with 300 W operating power) for 40 min. Upon cooling to room temperature, the reaction vial was taken out. After removal of the solvent, the residue was separated by column chromatography on silica gel eluting with hexane/ethyl acetate (20:1) to give the desired compound (21 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.19 (m, 10H), 6.59–6.55 (t, 2H, J = 11.6, 6.4 Hz), 6.22–6.14 (q, 1H, J = 6.8, 9.2, 6.8 Hz), 5.17–5.67 (t, 1H, J = 8.8, 11.6 Hz), 4.68–4.62 (q, 1H, J = 7.6, 8, 7.6 Hz), 4.48–4.43 (q, 1H, J = 6.4, 6.8, 7.6 Hz), 3.96–3.92 (m, 2H), 3.85–3.74 (m, 2H), 2.17–2.07 (m, 2H), 2.04–1.86 (m, 4H), 1.74–1.63 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 137.05, 136.90, 133.05, 131.72, 130.71, 130.67, 129.05, 128.73, 128.38, 127.72, 127.34, 126.67, 79.90, 75.27, 68.41, 68.31, 33.15, 32.61, 26.62, 26.14; MS: *m*/*z* (%): 174 (100) [M^+], 157 (25), 131 (53), 115 (26), 104 (33); *m*/*z* (%): 174 (100) [M^+], 157 (25), 131 (50), 115 (22), 104 (31).

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11. The following catalysts were used under microwave at 180 °C for 10 min: $Ru(C_6H_6)_2Cl_2$, $(CH_3CN)_2PdCl_2$, $[Rh(COD)Cl]_2$, $RhCl(PPh_3)_3$, $Ru(H)(CO)(Cl)(PPh_3)$, $Pt(bipy)_2Cl_2$, $Ni(PPh_3)_2Br_2$, $RuCl_2(PPh_3)_3$, $Ru(C_5H_5)(Cl)(PPh_3)_2$. They all produced the target product, sometimes phenylacetylene dimers were yielded together.
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