Three-Component Cycloadditions: The First Transition Metal-Catalyzed [5+2+1] Cycloaddition Reactions

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Received November 28, 2001

Previous studies in our laboratory aimed at catalyzing forbidden or difficult to achieve reactions[1] have resulted in the first [4+4] cycloadditions of bis-dienes,[2] [4+2] cycloadditions of diene-ynes (and allenes),[3] [5+2] cycloadditions of vinylcyclopropanes (VCPs) and π-systems (**1**→**3**),[4] and [6+2] cycloadditions of vinylcyclobutanones and π-systems (**4**→**6**).[5] The present study was prompted by the view that these two-component [*m*+*n*] reactions could be intercepted by a third component [*o*] of one or more atoms to produce new families of three-component [*m*+*n*+*o*] cycloadditions. Illustrative of this view, inspection of plausible mechanisms for the [5+2] and [6+2] cycloadditions suggests a crossover point at which the putative intermediate **2** of a [5+2] cycloaddition could be intercepted by CO[6] to produce intermediate **5** of a [6+2] cycloaddition, from which cycloadduct **6** would be produced by an overall [5+2+1] cycloaddition (**1**→**6**). Support for the feasibility of this process is suggested by the observation of the reverse crossover (**5**→**2**) as a minor [6+2−1] side reaction in some [6+2] cycloadditions.[5] Herein we report the first examples of [5+2+1] cycloadditions of VCPs, alkynes, and CO, leading to eight-membered rings, from which bicyclo[3.3.0]octenone derivatives are obtained, often in excellent yields.
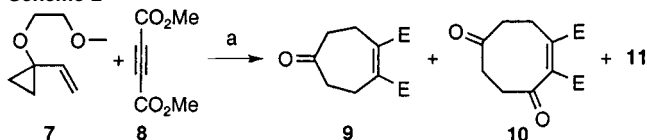
Scheme 1
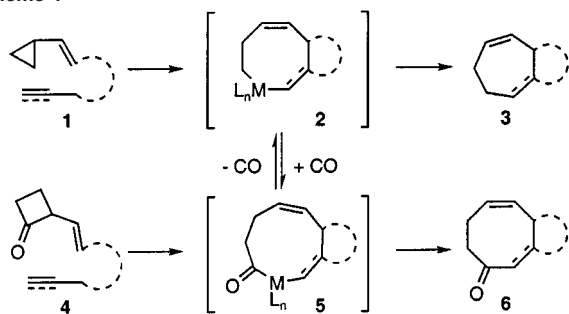
Initial attempts to effect the [5+2+1] cycloaddition with VCP **7**[4g] and alkyne **8** in the presence of rhodium(I) catalyst were marginally encouraging, providing only minor amounts of an eight-membered-ring product **10** (18%) along with the [5+2] cycloadduct **9** (13%) and a third component **11** (32%), which was isomeric with **10** (Scheme 2). Extensive spectroscopic analysis[7] of **11** led to the realization that it was a bicyclo[3.3.0]octenone, arising from transannular closure of intermediate **12** (Scheme 3). As such, the major course of this original test reaction did indeed follow a [5+2+1] path.

Due to the complexity of the reaction with **8**, further optimization studies were conducted with hexynone **14** (Table 1). Significantly, under optimized conditions, VCP **7** and hexynone **14** (1.2 equiv) in the presence of CO (2 atm) and with [Rh(CO)$_2$Cl]$_2$ catalyst (2.5 mol %) in 1,4-dioxane[8] gave, after hydrolytic workup, the bicyclo-

Scheme 2 [a]

[a] Key: (a) CO (1 atm), [Rh(CO)$_2$Cl]$_2$ (5 mol %), 1,2-dichloroethane (0.1M, **7**), 60 °C; H$_3$O$^+$.

Scheme 3
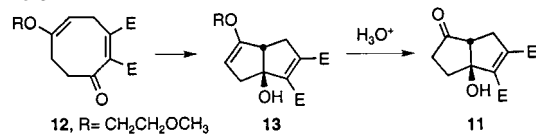
[3.3.0]octenone product **15** *in >99% yield by GC and in 97% isolated yield*.

The effects of concentration, temperature, pressure, and catalyst loading on the efficiency of the reaction are summarized in Table 1. These studies reveal that the preferred temperature for the reaction is 60 °C, with higher temperatures leading to lower yields of the [5+2+1] cycloadduct, and lower temperatures leading to long reaction times and lower yields (cf. entries 3, 4, and 5). At 1 atm CO pressure the optimal concentration of VCP **7** was 0.1 M (cf. entries 1, 2, 4, and 7). However, raising the pressure of the reaction provided higher yields and allowed for more concentrated reactions (cf. entries 7, 8, and 9), culminating in a >99% GC yield and 98% isolated yield of **15** at 0.5 M (entry 9). The reaction could be performed at higher concentrations (1 M) with some loss in efficiency (entry 10), although further optimization at this concentration was not pursued. Interestingly, although lowering the catalyst load resulted in longer reaction times, it also led to higher yields (entries 11−14). For example, when the catalyst load was reduced to 2.5 mol %, the reaction proceeded under reduced CO pressure (2 atm) with a yield comparable to that of the reaction conducted with 5 mol % catalyst and 4 atm CO (cf. entries 9 and 14).

With use of these preferred conditions, the propensity of other alkynes to undergo the [5+2+1] reaction with VCP **7** was examined (Table 2). Our studies indicate that carbonyl activated alkynes,[9] including alkynyl ketones, esters, amides, and even aldehydes, work well in this new process. The non-carbonyl subunit can be alkyl, aryl, TMS, or ester. The X-ray structures of **17**, **18**, **21**, and the eight-membered ring product **23**, along with 1D-nOe analysis of **15**, serve to indicate that CO insertion occurs distal to the carbonyl functionality of the alkyne. The regiochemistry of the other products was assigned by analogy and supported by NMR analyses. In all cases, with the exception of ethyl butynoate (Table 2, entry 8), only one regioisomer was observed.

In conclusion, a new transition metal-catalyzed three-component [5+2+1] cycloaddition is described. It proceeds in good to excellent yield and with high or complete regioselectivity with a variety of

Table 1. [5+2+1] Optimization Studies

entry	conc [M]	T [°C]	CO [atm]	loading [mol %]	t [h]	yield[a] [%]
1	0.01	60	1	5.0	72	87
2	0.05	60	1	5.0	36	88
3	0.10	40	1	5.0	72	77[b]
4	0.10	60	1	5.0	15	92 (90)
5	0.10	80	1	5.0	5	59
6	0.10	60	2	5.0	26	>99 (97)
7	0.50	60	1	5.0	7	62
8	0.50	60	2	5.0	10	79
9	0.50	60	4	5.0	14	>99 (98)
10	1.00	60	4	5.0	7	82
11	0.10	60	1	2.5	25	(92)
12	0.10	60	1	1.0	65	(99)
13	0.50	60	1	2.5	15	(86)
14	0.50	60	2	2.5	20	(97)

[a] GC yield (isolated yield). [b] At 90% conversion.

Table 2. Alkyne Substrates in the [5+2+1] Cycloaddition Reaction

entry	R₁	R₂	CO [atm]	t [h]	product	yield[a] [%]
1	−COCH₃	−Et	2	20	**15**	97
2	−COCH₃	−TMS	1	42	**16**	54
3	−COCH₃	−Ph	1	26	**17**	88
4	−CONH₂	−Ph	1	40	**18**	96
5	−CHO	−Ph	2	26	**19**	69[b]
6	−CO₂Et	−Ph	1	24	**20**	79
7	−CO₂Et	−TMS	1	26	**21**	67[c]
8	−CO₂Et	−Me	1	20	**22**	85[d]
9	−CO₂Me	−CO₂Me	1	30	**11**	48[e]

[a] Isolated yield. [b] Also 14% yield of [5+2] product. [c] Also 11% yield of eight-membered-ring product **23**. [d] 6:1 ratio of regioisomers by ¹H NMR. [e] Also 30% yield of [5+2] product and 8% yield of eight-membered-ring product.

carbonyl-substituted alkynes to give bicyclo[3.3.0]octenone adducts resulting from transannular closure of the intermediate eight-membered rings. The process provides access to complex building blocks for synthesis based on simple, commercially available components.[10] Further studies on the scope and limitations of this new process and related [m+n+o] processes, including substrate and catalyst variations, are in progress.

Supporting Information Available: Representative procedure and tabulated spectral data for compounds **10**, **11**, and **15**−**23** (PDF) and a CIF file containing X-ray information on compounds **17**, **18**, **21**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The assignment was made on the basis of ¹H NMR, ¹³C NMR, and MS analysis, as well as IR and deuterium exchange experiments (¹H NMR) indicating the presence of hydroxyl functionality, ¹³C NMR (gated mode) showing the presence of a methine carbon, and ¹H-COSY showing the presence of methylene−methine and methylene−methylene spin systems. Details can be found in the Supporting Information.

(8) Other solvents screened include: toluene, 1,2-dichloroethane, tetrahydropyran, acetone, ethanol, 1,2-dimethoxyethane, ethyl acetate, tetrahydrofuran, and 2,2,2-trifluoroethanol.

(9) Simple terminal and non-carbonyl-substituted alkynes react inefficiently under the above conditions. Further studies on these simple alkynes are in progress.

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JA0176301