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Ruthenium(II)-Catalyzed Hydration of Terminal Alkynes in PEG-400

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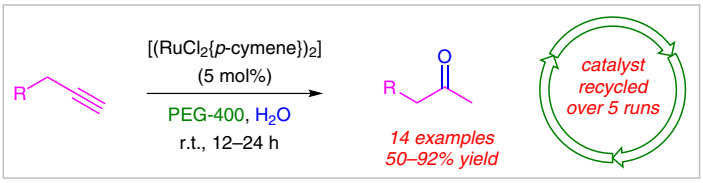

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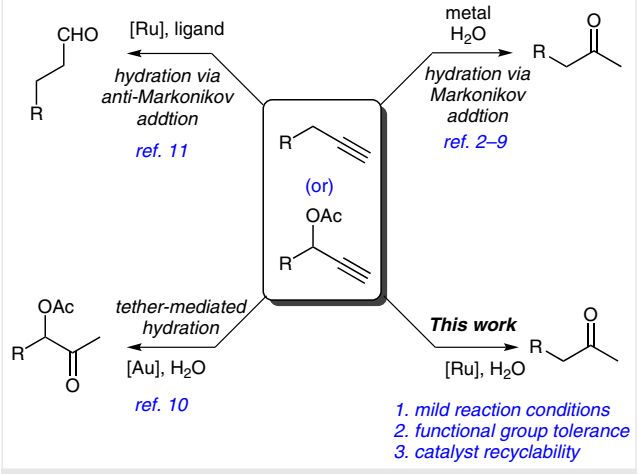
Abstract The ruthenium(II)-catalyzed hydration of terminal alkynes in PEG-400 to yield methyl ketones through Markovnikov addition of water across alkyne is reported.

Key words PEG-400, ruthenium, methyl ketones, terminal alkynes

Synthesis of methyl ketones from terminal alkynes is a well studied reaction.[1] As summarized in Scheme 1, the addition of water to alkynes has been reported using metal catalysts such as gold,[2] silver,[3] indium,[4] platinum,[5] rhodium,[6] cobalt,[7] mercury,[8] and iridium.[9] Addition of ligands such as porphyrins[7] or trisubstituted phosphines[9] to the catalytic system helps to improve the yield of the methyl ketone. The presence of a directing group such as a proximal hydroxyl or acetoxy substituent leads to conversion into the ketone in higher yields.[10] Addition of water in the presence of alcohol as solvent helps in selective formation of the ketone over aldehyde through the formation of a ketal, in accordance with Markovnikov's rule. Special catalysts, such as Ru,[11] have been developed for the formation of aldehydes, which are the disfavored anti-Markovnikov product. Ru(II) catalysts, in the presence of alcohols, have been used to synthesize keto esters and this approach avoids the additional step of ester formation.

These reports describe formation of carbonyl compounds from terminal alkynes but, in many cases, require strong acids as additives, which limits their application to a wider variety of substrates. The cost of the metal catalysts may also be a consideration. Other catalysts use ligands such as triphenylphosphine, trialkoxy phosphite, porphyrin or NHC. We wished to carry out the reaction in PEG-400, which has the advantages that the reagent can be recycled,



Scheme 1 Hydration of terminal alkynes

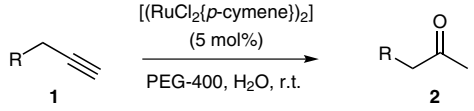
ligands are not required to carry out the reaction, and the use of other solvents can be avoided.

We have used PEG extensively as an environmentally benign solvent for reactions involving metal catalysts such as Heck[12] and Sharpless dihydroxylation reactions.[13] The total synthesis of centrilobine[14] has been achieved in PEG-400 and methodologies have been developed for the synthesis of pyrrole[15] and 3-indole derivatives.[16] In a continuation of our work towards reactions in PEG-400, we decided to explore the hydration of terminal alkynes using dichloro(*p*-cymene)ruthenium(II) dimer.

As a first step, to explore the reaction of terminal alkyne with dichloro(*p*-cymene)ruthenium(II) dimer in PEG-400, 3-butynol benzyl ether (**1a**) was used as substrate (Scheme 2). The reaction led to the formation of 4-*O*-benzyl-2-butanone (**2a**) in 63% yield. Analytical data confirmed the formation of **2a** (Table 1).[17] With this unusual result, given that Ru (II) was expected to yield the aldehyde, we explored

more scaffolds to determine whether there would be consistent ketone formation. Thus, diketone **1b**, *O*-benzoyl-3-butynol (**1c**), *N*-propynyl phthalimide (**1d**), aryl alcohol **1e**, and cyclohexanedione **1f** were reacted using dichloro(*p*-cymene)ruthenium(II) dimer in PEG-400 and the resulting methyl ketones **2b**–**f** were obtained in yields of 58 to 89%. To expand the substrate scope, alkynoic acids **1g**, **1h**, and **1i** were reacted to isolate the keto acids **2g**–**i** directly in 86–92% yields, unlike previous reports where acids were converted into esters. Substrates **1j**, **1k**, and **1l** also gave the corresponding methyl ketones **2j**–**l** in good yields. Cholesterol alkyne ester **1m** was converted into **2m** in 58% yield and sugar ether **1n** gave **2n** in 50% yield. Thus, we have developed mild conditions for the synthesis of methyl ketones for a variety of substrates without affecting other functionalities present in the molecule, by using Ru(II) catalyst. The only substrates that failed to generate the methyl ketones were arylalkynes.

Table 1 Ru(II)-Catalyzed Hydration of Terminal Alkynes[a,b]



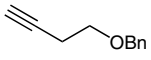
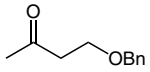
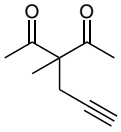
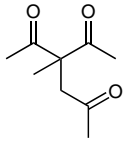
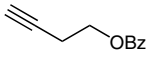
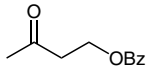
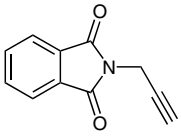
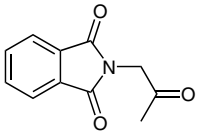
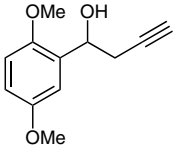
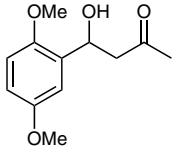
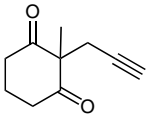
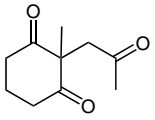
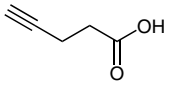
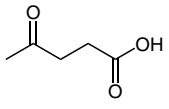
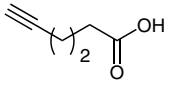
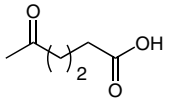
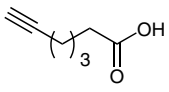
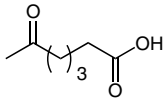
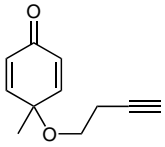
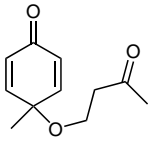
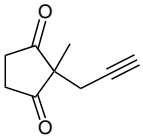
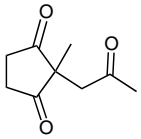
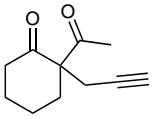
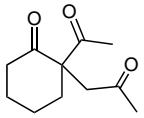
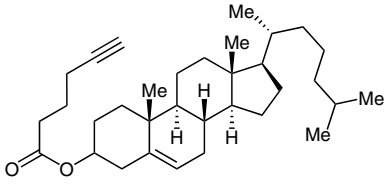
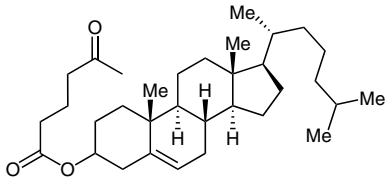
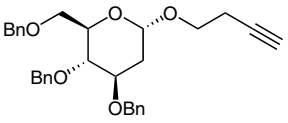
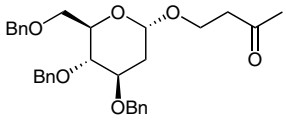
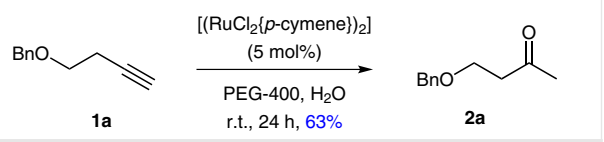
Entry	Alkyne		Time (h)	Product		Yield (%)
1	**1a**		24	**2a**		63
2	**1b**		12	**2b**		78
3	**1c**		24	**2c**		58
4	**1d**		24	**2d**		88
5	**1e**		24	**2e**		73
6	**1f**		12	**2f**		89
7	**1g**		12	**2g**		92
8	**1h**		12	**2h**		86

Table 1 (continued)

Entry	Alkyne	Time (h)	Product	Yield (%)
9	**1i** 	12	**2i** 	88
10	**1j** 	12	**2j** 	78
11	**1k** 	12	**2k** 	81
12	**1l** 	12	**2l** 	80
13	**1m** 	48	**2m** 	58
14	**1n** 	48	**2n** 	50

[a] Reactions were carried out with **1** (1 mmol) in 4:1 mixture of PEG 400/H_2O (0.5 M).
[b] Isolated yield after column chromatography.

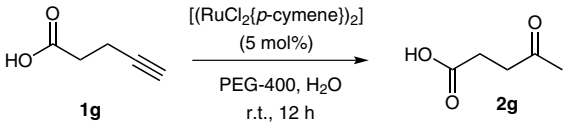


1a **2a**

Scheme 2 Initial attempts

After studying various scaffolds for substrate specificity, we investigated the activity of the catalyst for recyclability (Table 2). Thus, 4-pentynoic acid was used as a substrate and the catalyst was recycled, the second run gave good yield (83%) and the third gave a reasonable yield (70%); however, the yields continued to drop subsequently, possibly due to loss of the catalyst during workup. The product obtained in the repeated runs was identical in all respects with the first run product. Thus, modification of the Ru catalyst to make it less soluble in organic solvents, so that recyclability is efficient, is of possible interest.

Table 2 Recyclability of Ruthenium(II) Catalyst in PEG-400



1g **2g**

Run	1st	2nd	3rd	4th	5th
Yield (%)[a]	92	83	70	65	52

[a]Isolated yield after column chromatography.

In conclusion, a novel, mild and high yielding methodology for conversion of alkyne acids into keto acids has been developed. The methodology can be extended to ethers, esters, and carbonyl containing compounds and to scaffolds

such as steroidal and carbohydrate derivatives. This methodology avoids the use of strong acids or ligands.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561864.

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(16) Chandrasekhar, S.; Patro, V.; Reddy, G. P. K.; Gree, R. *Tetrahedron Lett.* **2012**, *53*, 6223.
(17) **General Procedure for Hydration of Terminal Alkynes in PEG-400:** To a solution of alkyne (1.0 mmol) in PEG-400/H_2O (4:1) was added [Ru(*p*-cymene)Cl_2]$_2$ (0.01 mmol), and the mixture stirred at room temperature. Upon completion of the reaction (monitoring by TLC), the reaction mixture was diluted with Et_2O (10 mL), stirred for 10 min, and allowed to stand in an ice-salt bath to solidify the PEG-400. The organic layer was decanted, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by silica gel flash column chromatography (ethyl acetate–petroleum ether) to give the pure product.
4-(Benzyloxy)butan-2-one (2a): Prepared according to the general procedure and purified by flash chromatography (EtOAc–hexanes, 10%). Yield: 63%; green liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.02 (m, 5 H), 4.51 (s, 2 H), 3.73 (t, *J* = 6.3 Hz, 2 H), 2.71 (t, *J* = 6.3 Hz, 2 H), 2.17 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 207.2, 138.1, 128.4, 127.7, 73.3, 65.3, 43.8, 30.5. IR (neat): 2925, 2855, 1721, 1458, 1275, 1110, 707 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}O_2$: 179.1066; found: 179.1065.
4-Oxopentanoic Acid (2g): Prepared according to the general procedure and purified by flash chromatography (EtOAc–hexanes, 10%). Yield: 92%; colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.25 (s, 1 H), 2.75 (t, *J* = 6.4 Hz, 2 H), 2.61 (t, *J* = 6.4 Hz, 2 H), 2.19 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 207.1, 178.5, 37.7, 29.8, 27.8. IR (neat): 2923, 2854, 1708, 1404, 1367, 1165, 555 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_5H_9O_3$: 117.0546; found: 117.0557.
4-Methyl-4-(3-oxobutoxy)cyclohexa-2,5-dienone (2j): Prepared according to the general procedure and purified by flash chromatography (EtOAc–hexanes, 50%). Yield: 78%; dark-green oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.72 (d, *J* = 10.2 Hz, 2 H), 6.23 (d, *J* = 10.2 Hz, 2 H), 3.50 (t, *J* = 6.0 Hz, 2 H), 2.57 (t, *J* = 6.0 Hz, 2 H), 2.11 (s, 3 H), 1.33 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.4, 184.1, 150.8, 129.2, 71.5, 59.5, 42.8, 29.6, 25.4. IR (neat): 2927, 1712, 1669, 1389, 1176, 1087, 863, 701 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}O_3$: 195.1015; found: 195.1019.
2-Methyl-2-(2-oxopropyl)cyclopentane-1,3-dione (2k): Prepared according to the general procedure and purified by flash chromatography (EtOAc–hexanes, 50%). Yield: 81%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.10 (s, 2 H), 2.92–2.71 (m, 4 H), 2.00 (s, 3 H), 0.98 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 216.4, 206.3, 52.4, 51.7, 34.7, 28.2, 19.3. IR (neat): 2926, 2856, 1718, 1455, 1390, 1183, 1074, 802, 548 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{13}O_3$: 169.0859; found: 169.0855.