JOC*Note*

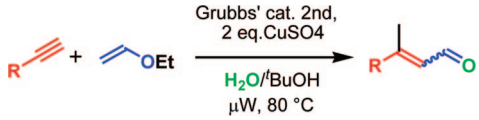
Alkyne-Enol Ether Cross-Metathesis in the Presence of $CuSO_4$: Direct Formation of 3-Substituted Crotonaldehydes in Aqueous Medium

Daniele Castagnolo, Lorenzo Botta, and Maurizio Botta*

Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, Via A. de Gasperi 2, 53100 Siena, Italy

botta@unisi.it

Received February 02, 2009



An efficient synthesis of 3-substituted crotonaldehydes via alkyne-enol ether cross-metathesis in the presence of $CuSO_4$ and in aqueous medium was developed. Crotonaldehydes were obtained in good yields from terminal aryl-alkynes as well as from terminal alkyl-alkynes. All of the reactions were carried out under microwave irradiation and were completed in a few minutes. Water was used as the cosolvent, making this approach safer, economic, and desiderable from an enviromental point of view.

Crotonaldehydes, and more generally α,β-unsaturated carbonyl compounds, are versatile organic molecules that may be used in synthetic applications such as carbonyl addition, conjugate addition, and as a prochiral dienophile.[1] Commercially available crotonaldehyde **1** is often employed in the synthesis of tocopherol (vitamin E), the food preservative sorbic acid, and the solvent 3-methylbutanol as well as many natural products.[2] Moreover, crotonaldehyde and crotyl structural motifs are also present in many natural compounds such as polyketides, retinoids, and carotenoids (Figure 1).[3] Surprisingly, a few direct approaches for the synthesis of crotonaldehydes are known, and they generally require several steps.[4,5]

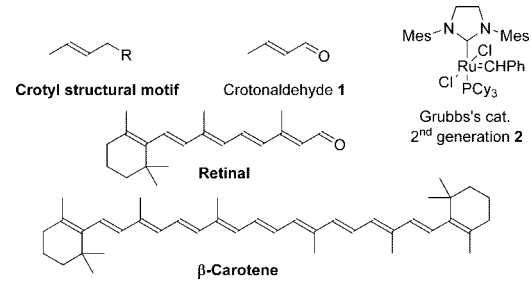


FIGURE 1. Grubbs' catalyst and crotyl systems.

Consequently, due to their versatility and use in organic synthesis, attempts in the development of new syntheses of crotonaldehydes and crotyl-related compounds are of high interest. Herein a rapid and efficient synthesis of 3-aryl/alkyl-crotonaldehydes through an enyne cross-metathesis reaction in aqueous medium and in the presence of copper was reported. Enyne metathesis constitutes an important and largely used method for 1,3-diene synthesis.[6] The most synthetically useful version of catalytic enyne metathesis is the intermolecular (cross) reaction which involves the addition of an alkene across the triple bond of an alkyne producing conjugated dienes with a high degree of regiocontrol. The synthetic appeal of cross-metathesis is that it offers direct and catalytic access to conjugated dienes, which have broad utility in synthesis. In the course of our work on the synthesis of enantiopure antifungal agents via enyne cross-metathesis,[7] we were attracted by the possibility of performing metathetic reactions in water since it offers several advantages such safety, economics, and environmental compatibility. Despite the fact that the aqueous olefin metathesis has been documented,[8] only a few studies on alkene-alkyne metathesis reactions carried out in aqueous medium have been reported so far.[9] During our metathetic studies in water, we were surprised to find that reaction of alkyne **3a** with ethylvinyl ether (EVE) in the presence of Grubbs' second generation catalyst **2** (Figure 1) in 1:1 *tert*-butanol/water led to the expected diene **4a** together with a small amount of the side compound 3-phenyl-crotonaldehyde **5a** (Scheme 1 and Table

(1) For reviews, see: (a) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Elsevier: Oxford, 1991; Vol. *4*, p 1. (b) LeeV. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Elsevier: Oxford, 1991; Vol. 4, pp 69 and 139. (c) Kozlowski, J. A. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I. M., Semmelhack, M. F., Eds.; Pergamon Elsevier: Oxford, 1991; Vol. 4, p 169. (d) Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001. (e) Ciganek, E. *Org. React.* **1997**, *51*, 201. (f) Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(2) (a) Smith, A. B., III; Simov, V. *Org. Lett.* **2006**, *8*, 3315–3318. (b) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao, J.-H. *Org. Lett.* **2006**, *8*, 2217–2220. (c) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274–9283.

(3) Krinsky, N. I. *Pure Appl. Chem.* **1994**, *66*, 1003–1010.

(4) Fischer, R.; Weitz, H. U.S. Patent 4284796.

(5) Hibst, H.; Storck, S.; Demuth, D.; Stichert, W.; Klein, J.; Schunk, S.; Sundermann, A. U.S. Patent 7071363.

(6) For review, see: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382. (b) Mori, M. *J. Mol. Catal. A* **2004**, *213*, 73–79. (c) Mori, M. In *Enyne Metathesis in Top. Organomet. Chem.*; Furstner, A., Ed.; Springer: Berlin Heidelberg, 1998; Vol. 1, p 133. (d) Mori, M. In *Enyne Metathesis in Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, p 176.

(7) (a) Castagnolo, D.; Giorgi, G.; Spinosa, R.; Corelli, F.; Botta, M. *Eur. J. Org. Chem.* **2007**, 3676–3686. (b) Castagnolo, D.; Renzulli, M. L.; Galletti, E.; Corelli, F.; Botta, M. *Tetrahedron: Asymmetry* **2005**, *16*, 2893–2896. (c) Giessert, A. J.; Snyder, L.; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793–1796.

(8) (a) Lipshutz, B. H.; Aguinaldo, G. T.; Ghorai, S.; Voigtritter, K. *Org. Lett.* **2008**, *10*, 1325–1328. (b) Gallivan, J. P.; Jordan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **2005**, *46*, 2577–2580. (c) Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904–9909. (d) Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508–3509. (e) Binder, J. B.; Blank, J. J.; Raines, R. T. *Org. Lett.* **2007**, *9*, 4885–4888. (f) Polshettiwar, V.; Varma, R. S. *J. Org. Chem.* **2008**, *73*, 7417–7419.

(9) (a) Gułajski, Ł.; Michrowska, A.; Naroznik, J.; Kaczmarska, Z.; Rupnicki, L.; Grela, K. *ChemSusChem* **2008**, *1*, 103–109. (b) Binder, J. B.; Guzei, I. A.; Raines, R. T. *Adv. Synth. Catal.* **2007**, *349*, 395. (c) Gułajski, Ł.; Sledz, P.; Lupa, A.; Grela, K. *Green Chem.* **2008**, *10*, 271. (d) Michrowska, A.; Gułajski, Ł.; Kaczmarska, Z.; Mennecke, K.; Kirschning, A.; Grela, K. *Green Chem.* **2006**, *8*, 685.

10.1021/jo900205x CCC: $40.75
Published on Web 03/18/2009

SCHEME 1. Enyne Cross-Metathesis in the Presence of $CuSO_4$

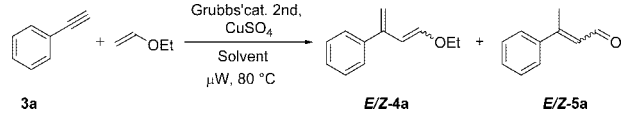
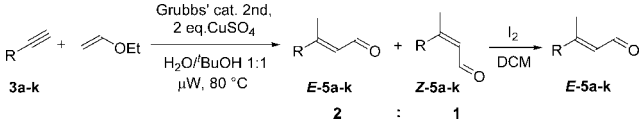


TABLE 1. Optimization of the Copper-Mediated Enyne Cross-Metathesis

entry	solvent[a]	$CuSO_4$ (equiv)	dienes *E/Z* **4a** (conv %)[b]	aldehyde *E/Z* **5a** (conv %)[b]
1	toluene		>95	ND
2	toluene	2	>95	ND
3	H_2O/^{t}BuOH 1:1		83	17
4	H_2O/^{t}BuOH 1:1	0.5	traces	85
5	H_2O/^{t}BuOH 1:1	1.0	traces	88
6	H_2O/^{t}BuOH 1:1	2.0	traces	>90

[a] All of the reactions were carried out at 80 °C under microwave irradiation. [b] Conversion was calculated by ^{1}H NMR.

SCHEME 2. Synthesis of Crotonaldehydes 5a−k

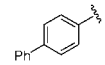
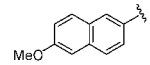


1, entry 3).[10] On the other hand, the standard metathetic reaction[7] of **3a** with EVE in toluene led only to **4a** and no traces of aldehyde **5a** were detected (entry 1).

Since the enol ether **4a** can be considered as the protected equivalent of aldehyde **5a**, the formation of this latter compound could be explained through the hydrolysis of the enol ether **4a** itself. Hence, on the basis of literature data on the cleavage of acetals,[11] it was reasoned that performing the same reaction in aqueous medium and in the presence of the weak acidic salt $CuSO_4$ could lead to the complete conversion of **4a** into **5a**. Experiments using different solvents and amounts of $CuSO_4$ were performed, and results are shown in Table 1. When 2.0 equiv of $CuSO_4$ was used (entry 6), the highest conversion of **4a** into **5a** was achieved. The use of catalytic or stoichiometric amount of $CuSO_4$ (entries 4 and 5) led to slightly lower conversion values. Finally, when **3a** and EVE were reacted in the presence of 2 equiv of $CuSO_4$ in toluene (entry 2), no traces of aldehydes **5a** were detected and only dienes **4a** were obtained.[12] In all of the cases, reactions were carried out under microwave irradiation and were completed in 30 min (3 runs × 10 min).[7a,b] Hence, in order to generalize these results, a series of alkynes **3a−k** were reacted with EVE in a mixture of 1:1 H_2O/^{t}BuOH and in the presence of $CuSO_4$ (Scheme 2). Results are summarized in Table 2. In all of the cases, aldehydes **5a−k** were obtained as a 2/1 mixture of *E/Z* isomers that were separated by chromatography on silica gel.

When the aromatic alkynes **3a−c** were reacted with EVE, the desired aldehydes **5a−c** were obtained in good yields (entries 1−3). Only traces of dienes **4a−c** were detected by ^{1}H NMR analysis. Reaction of aromatic alkyne **3d** led to desired aldehydes **5d** in low yields (entry 4), maybe due to the electron-withdrawing effect of the *p*-methoxy moiety on the naphthyl ring, which makes alkyne **3d** less reactive toward metathesis reaction. However, as shown by conversion values in Table 2, only a small amount of dienes **4d** was detected from the reaction mixture. When propargylic alcohols **3e−g** were reacted with EVE, the desired compounds **5e−g** were obtained together with dienes **4e−g** in an almost 2:1 ratio (entries 5−7). Attempts to obtain full conversion of these alkynes into aldehydes was unsuccessful. However, dienes **4e−g** could be recycled and converted into desired aldehydes **5e−g** (in a 2:1 *E/Z* ratio) in 45% yield after treatment with $CuSO_4$ (2 equiv) in 1:1 H_2O/^{t}BuOH. The lower yields of aldehydes **5e−g** compared to those of **5a−c** could be due to the steric hindrance of substituents on the propargylic alcohols, which makes these substrates less reactive. This latter hypothesis was confirmed by the behavior of the less hindered alkyl-alkynes **3h**,**i**, which were converted into **5h**,**i** in good yields (entries 8 and 9). Only a small amount of the dienes **4h**,**i** was detected. On the other hand, when the bulky triisopropylsilylacetylene **3j** was subjected to the copper-mediated enyne cross-metathesis, only traces of the dienes **4j** were detected by HPLC-MS analysis and no aldehydes **5j** were formed (entry 10). This result confirms the poor reactivity of bulky alkynes toward the enyne cross-metathesis reaction. Finally, alkyne **3k** was reacted with EVE, affording aldehyde

TABLE 2. Conversions and Yields of 5

entry	alkyne 3	R	conv. (%)[a],[b] dienes 4/ aldehydes 5	yields aldehydes 5 (%)[b],[c] E / Z	yield *E*-5 (%)[d] after reaction with I_2
1	**a**		traces / 95	36 / 18	51
2	**b**		traces / 92	40 / 18	55
3	**c**		16 / 84	48 / 22	68
4	**d**		14 / 86	29 / 12	40
5	**e**		35 / 65	29 / 14	39
6	**f**		33 / 67	31 / 15	43
7	**g**		35 / 65	24 / 12	35
8	**h**		11 / 89	41 / 19	60
9	**i**		8 / 92	41 / 21	63
10	**j**		traces / 0	0 / 0	0
11	**k**		11 / 89	48 / 0	48

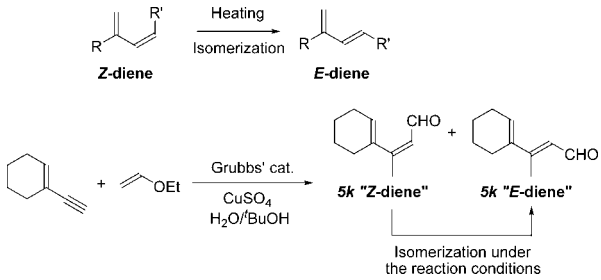
[a] All of the reactions were performed at 80 °C with 2 equiv of $CuSO_4$ under microwave irradiation for 3 × 10 min. [b] Conversion of alkynes into dienes and aldehydes was calculated by ^{1}H NMR. [c] Isolated yields are reported. [d] Isolated yields of *E* isomers after equilibration of the *E/Z* mixture with I_2 were reported.

(10) Compounds **4a** and **5a** were always isolated as a 2/1 mixture of *E*/Zisomers.

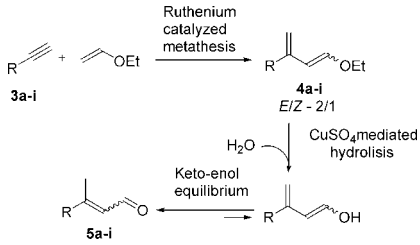
(11) (a) Caballero, G. M.; Gros, E. G. *Synth. Commun.* **1995**, *25*, 395–404. (b) Tokunaga, M.; Aoyama, H.; Kiyosu, J.; Shirogane, Y.; Iwasawa, T.; Obora, Y.; Tsuji, Y. *J. Organomet. Chem.* **2007**, *692*, 472. (c) Aoyama, H.; Tokunaga, M.; Hiraiwa, S.; Shirogane, Y.; Obora, Y.; Tsuji, Y. *Org. Lett.* **2004**, *6*, 509.

(12) Experiments in the presence of different acids (namely, 0.1 N HCl, 60 mol % of TsOH, 100 mol % of BF_3·Et_2O, 80 mol % of $Cu(OTf)_2$) were attempted. In all of the cases, conversion values were lower. When 150 mol % of $Cu(OTf)_2$ was used, a coversion value (<90%) comparable to that achieved in the presence of $CuSO_4$ was obtained.

SCHEME 3. Isomerization of (*Z*)-5k to (*E*)-5k



SCHEME 4. Proposed Mechanism of Formation of Crotonaldehydes 5



5k in good yield (entry 11). Surprisingly, only (*E*)-**5k** aldehyde was isolated, and no traces of (*Z*)-**5k** were detected. The compounds (*E*/*Z*)-**5k** are dienes due to the conjugation of the formed crotyl system with the cyclohexene double bond.

It is documented that (*Z*)-dienes could be converted into the corresponding (*E*)-dienes by simple heating in toluene.[13] As a consequence, it has been hypothesized that in the course of the copper-mediated metathetic reaction a *Z* to *E* equilibration of "diene (*Z*)-**5k**" could occur, leading to the formation of the thermodynamically stable (*E*)-**5k** as the only reaction product, as illustrated in Scheme 3. The high yield of **5k** could also confirm this assumption.

In all of the other cases, aldehydes **5a**−**i** were obtained in a 2:1 *E*/*Z* isomeric ratio as observed by ^{1}H NMR. This result might be explained by assuming that the reaction proceeds first through the formation of dienes **4a**−**i** in a 2:1 ratio[7] via ruthenium-catalyzed metathesis followed by $CuSO_4$-mediated hydrolysis and subsequent keto-enolic equilibration to afford crotonaldehydes **5a**−**i**, as proposed in Scheme 4.

Finally *E*/*Z* aldehyde isomers were equilibrated through reaction with I_2.[14,15] Treatment of pure *Z* aldehydes **5a**−**i** with a catalytic amount of I_2 in DCM (Scheme 2) led in all cases after 7 h to the formation in quantitative yields of the *E* isomer as the only product, confirming that *E* isomers are the thermodynamically stable compounds. The structure of the *E*/*Z* isomers was assigned by NOESY experiments.

In summary, an efficient and rapid synthesis of 3-substituted crotonaldehydes **5** in aqueous medium has been developed. In this work, we have discovered that 3-substituted crotonaldehydes **5** could be synthesized directly from aryl/alkyl-alkynes through an alkyne-enol ether cross-metathesis reaction when water was used as cosolvent. The presence of $CuSO_4$ proved to be fundamental for achieving high conversion of alkynes **3** into desired aldehydes **5**. All of the reactions were carried out in aqueous medium, making this approach an easy and green method for the transformation of terminal alkynes into crotyl systems.

Experimental Section

Synthesis of Crotonaldehydes (*E*)-5a and (*Z*)-5a. Alkyne **3a** (1.0 mmol), ethylvinyl ether (9.0 mmol), $CuSO_4$ (2.0 mmol), and Grubbs' catalyst (0.1 mmol) were suspended in a 1:1 mixture of water and *tert*-BuOH (2.0 mL each) in a 10 mL glass vial equipped with a small magnetic stirring bar. The mixture was heated at 80 °C under microwave irradiation for 3 × 10 min, using an irradiation power of 300 W. The mixture was then poured into a solution of NH_4Cl (20 mL), NH_4OH (0.5 mL), and Et_2O (10 mL), stirred for an additional 10 min, and then extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2) using 1:4 Et_2O/hexanes as the eluent to yield the crotonaldehydes (*E*)-**5a** and (*Z*)-**5a** as single isomers, as tan oils.

(*E*)-5a: Yield 36%; R_f = 0.38 Et_2O/hexanes 1:4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (d, J = 7.7 Hz, 1H), 7.48−7.47 (m, 2H), 7.35−7.31 (m, 3H), 6.33 (d, J = 7.7 Hz, 1H), 2.50 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 157.6, 140.5, 130.1, 128.7, 128.4, 127.2, 126.3, 126.2, 16.4 ppm; IR ($CHCl_3$) ν 1660 cm^{-1}; MS (ESI) m/z = 147.1 [M + H], 169.0 [M + Na$^+$]. Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.20; H, 7.03.

(*Z*)-5a: Yield 18%; R_f = 0.47 Et_2O/hexanes 1:4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (d, J = 8.0 Hz, 1H), 7.34−7.24 (m, 5H), 6.07 (d, J = 8.0 Hz, 1H), 2.25 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 162.1, 138.4, 129.2, 129.1, 128.4, 128.3, 26.4 ppm; IR ($CHCl_3$) ν 1660 cm^{-1}; MS (ESI) m/z = 147.1 [M + H], 169.0 [M + Na$^+$]. Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.19; H, 6.98.

Acknowledgment. We are grateful to Italian Ministero dell'Istruzione, dell'Università e della Ricerca (PRIN Anno 2006 prot.-2006030948_002).

Supporting Information Available: General methods, characterization data, and ^{1}H NMR and ^{13}C NMR spectra of aldehydes **5a**−**k** are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900205X

(13) Barluenga, J. *Synthesis* **1997**, 968–974.
(14) (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1. (c) Saltiel, J.; Ganapathy, S.; Werking, C. *J. Phys. Chem.* **1987**, *91*, 2755.
(15) Hanessian, S.; Botta, M. *Tetrahedron Lett.* **1987**, *28*, 1151–1154.