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Indium Triflate-Catalyzed Vinylation of *β*-Ketoesters with Acetylene Gas

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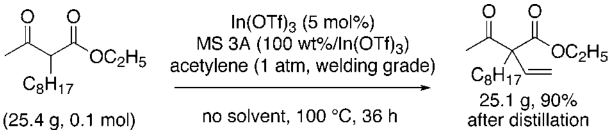
ABSTRACT



An In(OTf)$_3$-catalyzed addition of a *β*-ketoester to acetylene in the presence of molecular sieves produces a α-vinylated ketoester in good to excellent yield. The vinylation reaction proceeds without any loss of elements in starting molecules under solvent-free conditions and allows the use of welding-grade acetylene, providing a practical method for synthetic utilization of acetylene gas.

Acetylene gas is a useful carbon resource in industry and laboratory synthesis and is used as a building block for the synthesis of either alkynes through substitution of the hydrogen atoms or alkenes through addition across the unsaturated bond.[1] Addition of enolate anions to acetylene may produce α-vinyl carbonyl compounds that are useful for further synthetic elaboration. Some progress has been reported for the α-alkenylation of carbonyl compounds, making it possible to achieve intermolecular addition to substituted acetylenes[2,3] or its intramolecular variants.[4] The use of the parent acetylene in these transformations has, however, been difficult[5] because of the gaseous nature as well as the base and acid sensitivity of acetylene. We report herein a simple and effective procedure of the vinylation of *β*-ketoesters by using 1 atm welding-grade acetylene gas under catalysis by indium triflate [In(OTf)$_3$] in the presence of molecular sieves (MS).

The acetylenic triple bond is not polarized and hence is intrinsically not an ideal acceptor of nucleophiles. In addition, it has acidic protons, and reacts with Brønstead acids (e.g., TfOH). The conditions that we developed for addition of enolates to unactivated C−C multiple bonds[6] failed for the reaction with acetylene gas. We noticed a few synthetic problems specific to gaseous acetylene: Acetylene supplied as the cheap welding grade contains acetone and water; purified acetylene tends to be destroyed by Lewis acid under the reaction conditions (i.e., at 100 °C), and acetylene is not

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[1] (a) Friedrich, K. *Chemistry of Functional Groups*, *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983; Suppl. C, part 2, p 1380. (b) Brandsma, L. *Preparative Acetylene Chemistry*, 3rd ed.; Elsevier: Amsterdam, 1988. (c) Ben-Efraim, D. A. *The Chemistry of the Carbon−Carbon Triple Bond*; Patai, S., Ed.; Wiley: New York, 1978; pp 790−800.

[2] (a) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002−13003. (b) Nakamura, M.; Fujimoto, T.; Endo, K.; Nakamura, E.; *Org. Lett.* **2004**, *6*, 4837−4840.

[3] (a) Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *J. Am. Chem. Soc.* **1999**, *121*, 4074−4075. (b) Arisawa, M.; Akamatsu, K.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 789−790 and references therein.

[4] (a) Quian, H.; Pei, T.; Widenhoefer, R. A. *Organometallics* **2005**, *24*, 287−301 and references therein. (b) Liu, G.; Lu, X. *Tetrahedron Lett.* **2002**, *43*, 6791−6794. (c) Renaud, J.-L.; Aubert, C.; Malacria, M. *Tetrahedron* **1999**, *55*, 5113−5128. (d) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526−4528. (e) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350−5353. (f) Yao, X.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 6884−6885. (g) Nguyen, R.-V.; Yao, X.; Bohle, D. S.; Li, C.-J. *Org. Lett.* **2005**, *7*, 673−675.

[5] In a single example that we found thus far in the literature for the α-vinylation reaction of *β*-ketoester, 25 atm of acetylene was used together with a zinc carboxylate: Seefelder, M. *Liebigs Ann. Chem.* **1962**, *652*, 107−114.

[6] (a) Nakamura, M.; Hatakeyama, T.; Hara, K.; Fukudome, H.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 14344−14345. (b) Nakamura, M.; Hatakeyama, T.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 11820−11825. (c) Nakamura, M.; Hatakeyama, T.; Hara, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 6362−6363. (d) Nakamura, M.; Kubota, K.; Sakata, G.; Nakamura, E. *Org. Lett.* **1999**, *1*, 1505−1507. (e) Nakamura, E.; Kubota, K.; Sakata, G. *J. Am. Chem. Soc.* **1997**, *119*, 5457−5458. (f) Kubota, K.; Nakamura, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2491−2493. (g) Nakamura, E.; Kubota, K. *Tetrahedron Lett.* **1997**, *38*, 7099−7102.

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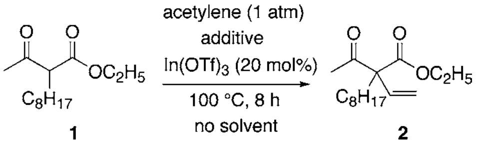
to be used under high pressure for safety and practical considerations.

We first examined the addition of β-ketoester **1** to acetylene under the conditions shown in Table 1. When the reaction was performed with purified or welding-grade acetylene together with 20 mol % $\mathrm{In(OTf)_3}$, **1** was consumed quickly but gave the desired adduct **2** in only 25 and 15% yield, respectively (entries 1 and 2), together with a large amount of high molecular weight byproducts. Because we suspected the occurrence of acid-catalyzed side reactions, we used diazabicycloundecene (DBU) as a basic additive. The yield was much improved to 94% for purified acetylene (entry 3), but only to 28% for the welding grade (entry 4). After considerable experimentation, the reaction in the presence of 3 Å molecular sieves (MS) [100 wt % with respect to $\mathrm{In(OTf)_3}$] consistently afforded 95% yield for both purified and welding-grade acetylene (entries 5 and 6). Molecular sieves of different pore sizes (3 Å, 4 Å, 5 Å, and 13X) exerted an equally favorable effect (entries 5−9). We speculate that MS act as an acid and water scavenger.

Table 1. Indium-Catalyzed Addition of β-Ketoester **1** to Acetylene[a]

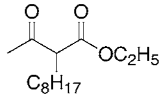
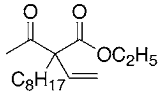
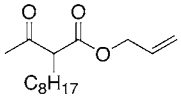
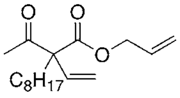
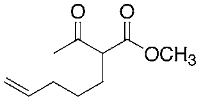
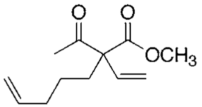
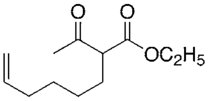
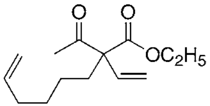
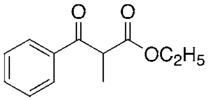
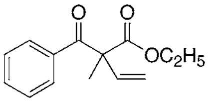
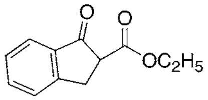
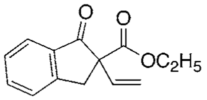
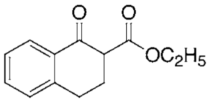
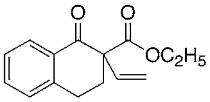
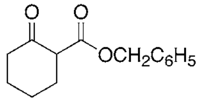
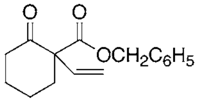
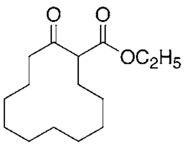
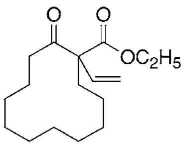


entry	acetylene	additive	yield (%)[b]
1	purified[c]	none	25
2	welding grade	none	15[g]
3	purified	DBU[e] (20 mol %)	94
4	welding grade[d]	DBU (20 mol %)	28
5	purified	3 Å MS (100 wt %/$\mathrm{In(OTf)_3}$)[f]	95
6	welding grade	3 Å MS (100 wt %/$\mathrm{In(OTf)_3}$)[f]	95
7	welding grade	4 Å MS (100 wt %/$\mathrm{In(OTf)_3}$)[f]	95
8	welding grade	5 Å MS (100 wt %/$\mathrm{In(OTf)_3}$)[f]	93
9	welding grade	13X MS (100 wt %/$\mathrm{In(OTf)_3}$)[f]	89

[a] All reactions were conducted under a 1 atm acetylene atmosphere (balloon) at 100 °C unless otherwise noted. [b] ^{1}H NMR yield with dibromomethane as an internal standard. [c] Commercially available 100% acetylene gas. [d] Commercially available acetylene gas from an acetone solution. [e] DBU; 1,8-diazabicyclo[5.4.0]undec-7-ene. [f] Molecular sieves were used as received. [g] Starting material **1** was recovered (34%), and 2-undecanone was obtained in 18% yield, in addition to several unidentified side products.

With the optimal conditions in hand, we studied the vinylation reaction of a variety of β-ketoesters shown in Table 2. The reaction was performed without solvent (condition A), unless the substrate was too volatile or too viscous (or solid), thereby necessitating the use of a solvent (toluene: condition B). When the substrate (and the product) was acid-sensitive, both MS and DBU were added to the reaction mixture (condition C). A representative experimental procedure is given for condition A: A mixture of β-ketoester **1** (25.4 g, 105 mmol), $\mathrm{In(OTf)_3}$ (2.95 g, 5.25 mmol, 5 mol %), and 3 Å MS (2.95 g) was heated at 100 °C for 36 h under an acetylene atmosphere (welding grade). Filtration through a pad of silica gel and distillation of the crude mixture at 96 °C/9.3 Pa gave the α-vinylated β-ketoester **2** in 90% yield (25.1 g, >96% GC area ratio, entry 1). The same reaction on a 1 mmol scale gave adduct **2** in 95% yield after purification by column chromatography.

Table 2. $\mathrm{In(OTf)_3}$/MS-Catalyzed Vinylation of β-Ketoesters

entry	β-ketoester	condition[a,b]	product, yield[c]
1	 **1**	**A**	 **2**, 86% (95%) 90% (>96% purity)[d]
2	 **3**	**B**	 **4**, 74%
3	 **5**	**B**	 **6**, 82%
4	 **7**	**A**	 **8**, 93%
5	 **9**	**B**	 **10**, 70% (82%)
6	 **11**	**C**	 **12**, 75%
7	 **13**	**C**	 **14**, 100%
8	 **15**	**C**	 **16**, 89%
9	 **17**	**A**	 **18**, 98%

[a] Condition A: $\mathrm{In(OTf)_3}$ (20 mol %) and 3 Å MS (100 wt %/ $\mathrm{In(OTf)_3}$) at 100 °C. Condition B: $\mathrm{In(OTf)_3}$ (20 mol %) and 3 Å MS (100 wt %/ $\mathrm{In(OTf)_3}$) in toluene at 100 °C. Condition C: $\mathrm{In(OTf)_3}$ (20 mol %), 3 Å MS (100 wt %/ $\mathrm{In(OTf)_3}$), and DBU (20 mol %) in toluene at 100 °C. [b] Under an atmosphere of welding-grade acetylene (balloon). [c] Isolated yield. The yield in parentheses was determined by ^{1}H NMR with dibromomethane as an internal standard. [d] A 25 g scale experiment described in the text. Purity was determined according to the noncalibrated GC area ratio.

An acid-sensitive allyl acetoacetate **3** (entry 2) underwent α-vinylation in toluene to give the corresponding product **4** in a slightly diminished yield of 74%. Similarly, ω-alkenyl-β-ketoesters **5** and **7** reacted with acetylene either with or without solvent to give the vinyl products **6** and **8**, respectively, without any trace of intramolecular cyclization reaction (entries 3 and 4). The olefinic moieties in these products may be used for further synthetic transformations. Aromatic substrates can also participate in the vinylation reaction (entries 5−7). 2-Benzoylpropionate **9** reacted with acetylene in toluene to give adduct **10** in 70% isolated yield. Bicyclic aromatic β-ketoesters **11** and **13** can also be readily vinylated in 75 and 100% yield, respectively. No Friedel−Crafts reaction took place on the aromatic moiety under the reaction conditions.[7] A cyclic ketoester, benzyl 2-oxocyclohexanecarboxylate **15** was found to be relatively unstable under the reaction conditions, but the reaction under condition C (DBU added) afforded the product **16** in 89% yield (entry 8). Similarly, a 12-membered cycloalkanone **17** afforded adduct **18** quantitatively (entry 9).

In summary, we found that the In(OTf)$_3$/MS/DBU conditions effect the addition of β-ketoesters to acetylene in good to excellent yields, which almost fails under our previous additive-free In(OTf)$_3$ conditions developed for substituted acetylenes.[2] The new conditions that tolerate acid-sensitive groups are also applicable to the reaction of substituted acetylenes at the expense of reaction rate.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2000**, 1573−1574. (b) Tsuchimoto, T.; Hatanaka, K.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2003**, 2454−2455. (c) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Shirakawa, E.; Kawakami, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 1360−1364.