Trimethylsilylethynyl Ketones as Surrogates for Ethynyl Ketones in the Double Michael Reaction

Derrick S. Holeman, Ravindra M. Rasne, and Robert B. Grossman*

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506-0055

rbgros1@uky.edu

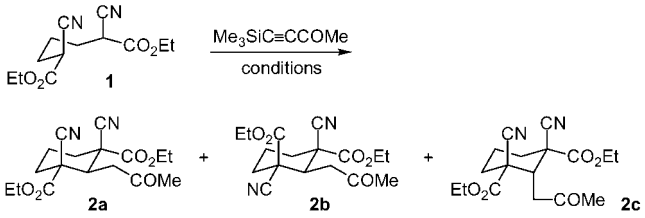
Received November 21, 2001

Abstract: Trimethylsilylethynyl ketones can be desilylated in the presence of a tethered carbon diacid and induced to undergo a double Michael reaction in situ. The trimethylsilylethynyl ketones can serve as surrogates of ethynyl ketones that are difficult to prepare or isolate.

Our group has been exploring the double Michael reactions of "tethered diacids" (consisting of two carbon acids connected by a tether) and 3-butyn-2-one, and we have demonstrated the utility of these reactions for the synthesis of densely functionalized and architecturally complex compounds.[1] A significant limitation to scale-up of our methodology has been the limited availability and high cost of 3-butyn-2-one (currently more than \$8 g^{-1}) from commercial sources. However, preparation of this material ourselves is not an attractive prospect. The method most widely used for its synthesis is Jones oxidation of the alcohol, but this method is quite capricious, with the original 1946 preparation reporting only 5% yield.[2] The compound has also been prepared by borax-catalyzed desilylation of 4-trimethylsilyl-3-butyn-2-one in aqueous methanol[3] or water,[4] hydrolysis of 2-methoxy-1-buten-3-yne,[5] by addition of $NaAl(C{\equiv}CH)_4$ to acetic anhydride,[6] and by ozonolysis of 2-methyl-2-buten-3-yne.[7] All of these methods (including the Jones oxidation) require a careful distillation of 3-butyn-2-one at the end of the synthesis to separate it from solvent (aqueous or organic) or unreacted 3-butyn-2-ol, and this distillation presents a serious explosion hazard.

We reasoned that we might be able to avoid the difficulty and hazard of distilling 3-butyn-2-one if we could prepare it in situ from 4-trimethylsilyl-3-butyn-2-one in the course of a double Michael reaction. The latter compound is easily prepared in one step from acetic anhydride and trimethylsilylacetylene (which can currently be purchased for as little as \$0.79 g^{-1}), and its isolation and purification does not present any special difficulties or hazards.[8,9] This paper describes our experiments in this area.

Scheme 1



For our exploratory studies of the in situ desilylation−double Michael reaction, we decided to use diethyl 2,6-dicyanopimelate[10] (**1**) as the tethered diacid (Scheme 1), for several reasons. First, **1** was known to undergo a clean and high-yielding double Michael reaction with 3-butyn-2-one, and depending on the reaction conditions, either kinetic or thermodynamic ratios of the three diastereomeric products, **2a**−**c**, were obtained.[1] We wanted to see whether we could find comparable kinetic and thermodynamic conditions for the in situ desilylation−double Michael reaction. Second, **1** was very easily prepared.[10] Third, the three diastereomeric double Michael adducts **2a**−**c** were separated very well by GC.

We surveyed a wide variety of catalysts and solvents for the in situ desilylation−double Michael reaction of **1** and 4-trimethylsilyl-3-butyn-2-one (Table 1). We found that fluoride ion (either $Bu_4N^+F^-$ or $KF{\cdot}2H_2O$) doubled as a convenient base and desilylating agent. In most cases, the products **2a**−**c** were obtained quite cleanly, with no byproducts visible by GC−MS unless the reaction mixture was allowed to stir long past completion. The diastereomeric ratios (dr's) varied from as low as 4:4:1 (Table 1, entry 1) to as high as 15:6:1 **2a**:**2b**:**2c** (Table 1, entry 5). By comparison, the double Michael reaction of **1** with 3-butyn-2-one gave dr's that ranged from 4:4:1 (kinetic conditions: K_2CO_3, acetone, rt) to 5:1:0 (kinetic conditions: NaH, THF, −78 °C to rt) up to 30:1:0 (thermodynamic conditions: *t*-BuOK, CH_2Cl_2, 0 °C).[1,11] The in situ desilylation−double Michael reaction did not proceed in the absence of any base (Table 1, entry 14) or protic solvent (Table 1, entry 15); however, polar solvents such as acetone contained enough water to allow the reaction to proceed (Table 1, entries 11 and 12). Curiously, under some conditions, the in situ desilylation−double Michael reaction favored the asymmetric isomer **2b** over the lower energy C_s-symmetric isomer **2a** (Table 1, entries 2 and 4). In these cases, the dr's may have reflected the inherent energies of the TS−solvent complexes under these (and not other) conditions or they may have resulted from selective removal of **2a** by a further reaction. The dr's sometimes changed upon extended stirring of the reaction mixture (Table 1, entries 7 and 8), which may reflect equilibration of the isomers by a

* To whom correspondence should be addressed. E-mail: rbgros1@uky.edu.

(1) Grossman, R. B. *Synlett* **2001**, 13.
(2) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39. Nemirovskii, V. D.; Chelpanova, L. F.; Petrov, A. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1961**, *31*, 2380. Landor, S. R.; Miller, B. J.; Tatchell, A. R. *J. Chem. Soc. C* **1971**, 2339. Reimann, E.; Reitz, R. *Justus Liebigs Ann. Chem.* **1976**, 610.
(3) Bradshaw, C. W.; Fu, H.; Shen, G.-J.; Wong, C.-H. *J. Org. Chem.* **1992**, *57*, 1526.
(4) Hirao, K.; Yamashita, A.; Ando, A.; Hamada, T.; Yonemitsu, O. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2913. An experimental procedure was not provided.
(5) Petrov, A. A. *J. Gen. Chem. USSR* **1940**, *10*, 1682.
(6) Gawrilenko, V. V.; Ivanov, L. L.; Zakharkin, L. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1965**, *35*, 638.
(7) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.
(8) Komarov, N. V.; Yarosh, O. G. *J. Gen. Chem. USSR (Engl. Transl.)* **1967**, *37*, 247.
(9) Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45.
(10) Grossman, R. B.; Varner, M. A. *J. Org. Chem.* **1997**, *62*, 5235.
(11) Grossman, R. B.; Varner, M. A.; Skaggs, A. J. *J. Org. Chem.* **1999**, *64*, 340.

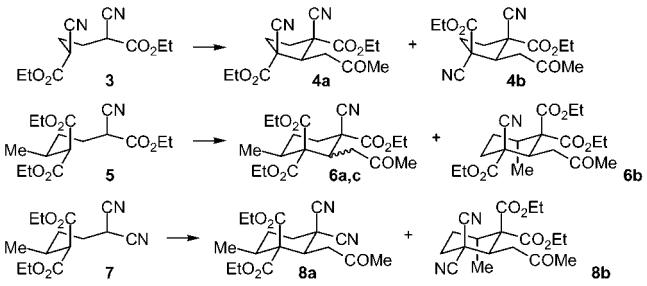
10.1021/jo0163086 CCC: \$22.00
Published on Web 04/05/2002

Table 1. Diastereoselectivity of the Double Michael Reaction Depicted in Scheme 1

entry	catalyst, solvent	*T* (°C), time	**2a**/**2b**/**2c**[a]
1	TBAF, THF	0 °C to rt, 1 h	4:4:1
2	TBAF, THF	−78 °C to rt, 1 h	7:11:1
3	TBAF, CH_2Cl_2	−78 °C to rt, 1 h	9.0:3.5:1
4	TBAF, DMF	0 °C to rt, 1 h	3.5:5.5:1
5	TBAF (10 mol %), $KF{\cdot}2H_2O$, EtOH	−78 to 0 to −78 °C, 1 h[b]	15:6:1
6	TBAF (10 mol %), $KF{\cdot}2H_2O$, EtOH	−78 °C to rt, 1 h	7:3:1
7	TBAF (10 mol %), CH_2Cl_2	rt, 1 h	5.4:3.7:1
8	TBAF (10 mol %), CH_2Cl_2	rt, 1 d	8:5:1
9	$Bu_4N^+ Br^-$ (10 mol %), $KF{\cdot}2H_2O$ (solid), CH_2Cl_2	rt, 1 h	5.8:3.5:1
10	$Bu_4N^+ Br^-$ (10 mol %), $KF{\cdot}2H_2O$, H_2O and CH_2Cl_2[c]	0 °C, 1 h	NR[d]
11	K_2CO_3, acetone	rt, 1 h	5:5:1
12	K_2CO_3, acetone	rt, overnight	3:6:1
13	K_2CO_3, EtOH	rt, 1 h	4:3:1
14	EtOH	rt, 2 d	NR[d]
15	*t*-BuOK, CH_2Cl_2	−78 to 0 °C, 1 h	NR[d]

[a] Determined by GC−MS. [b] The alkynone and the salts were combined at −78 °C, allowed to warm to 0 °C, and cooled to −78 °C, and then **1** was added. [c] A two-phase mixture was used. [d] No reaction.

Scheme 2



retro-Michael−Michael reaction or selective removal of **2b** and **2c** by a further reaction.

We then executed the in situ desilylation−double Michael reaction of both **1** and other tethered diacids on a preparatory scale (Scheme 2). In most cases, we used the conditions that gave the best dr of **2** on a small scale: 10% TBAF and 1 equiv of $KF{\cdot}2H_2O$ in THF. The results were compared with the results obtained from the conventional double Michael reaction with 3-butyn-2-one (Table 2). The new method usually gave comparable but slightly lower yields and dr's, perhaps because it was restricted to protic solvents and because it proceeded at higher temperatures.

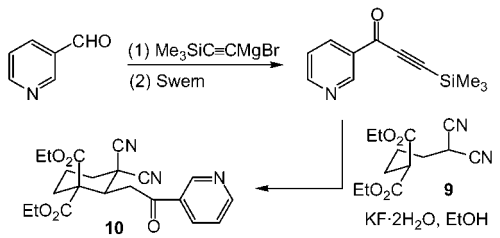
We had already been interested in extending the double Michael reaction to substrates such as aryl ethynyl ketones, but our progress had been hampered by the instability of ethynyl ketones that contained electron-poor aryl groups. In light of the above results, we hypothesized that we might be able to use a trimethylsilylethynyl ketone as a surrogate for an unisolable ethynyl ketone in the double Michael reaction. In the event, we were unable to prepare ethynyl 3-pyridyl ketone, but trimethylsilylethynyl 3-pyridyl ketone (prepared from nicotinaldehyde in two high-yielding steps) reacted with dicyano diester **9**[10] in the presence of $KF{\cdot}2H_2O$ in EtOH to afford double Michael adduct **10** in 71% isolated yield (Scheme 3). Double Michael adducts such as **10** might be used to prepare rigid and functionalized bicyclic nicotine analogues.

Table 2. Comparison of Double Michael Reactions of 4-Trimethylsilyl-3-butyn-2-one and 3-Butyn-2-one

tethered diacid	double Michael adducts	yield, dr of isolated material[a] (conditions) from 4-trimethylsilyl-3-butynone	yield, dr of isolated material[a] (conditions) from 3-butyn-2-one[11,12]
1	**2a**−**c**	68%, 7:3:1;[b] 36% **2a**,[c] 20% **2b**[b] (10% TBAF, $KF{\cdot}2H_2O$, EtOH, 0 °C to rt)	52% **2a**,[b] 11% **2b**[b] (NaH, THF, −78 °C)
3	**4a**,**b**	55% **4a**[c] (10% TBAF, $KF{\cdot}2H_2O$, EtOH, rt, 14 d)	72%, 8:1[b] (NaH, THF, rt)
5	**6a**−**c**	57%, 4:4:1[b] (TBAF, THF, rt)	63%, 1:1:0[b] (*t*-BuOK, CH_2Cl_2, 0 °C)
7	**8a**,**b**	66%, 60:1[c] ($KF{\cdot}2H_2O$, *t*-BuOH, rt)	

[a] Determined by GC−MS. [b] Chromatographed material. [c] Recrystallized material.

Scheme 3



In conclusion, we have discovered that easily prepared and purified trimethylsilylethynyl ketones can be substituted for ethynyl ketones as substrates for the double Michael reaction. The yields and diastereoselectivities are slightly lower when trimethylsilylethynyl ketones are used, but this disadvantage must be balanced against the loss of time and material sustained upon preparation and purification of the corresponding ethynyl ketones. The in situ desilylation−double Michael reaction is safe and convenient, requires inexpensive and innocuous catalysts, and proceeds under a wide variety of conditions. It will not completely replace the standard double Michael reaction, but it is a useful alternative when the ethynyl ketone is not readily available or is prohibitively expensive. Trimethylsilylethynyl ketones may also prove to be useful surrogates for inaccessible ethynyl ketones in other applications such as cycloadditions.

Experimental Section

The syntheses and characterization of **1**−**9** have been reported elsewhere.[10−12]

4-Trimethylsilyl-3-butyn-2-one. This procedure was modified from the literature.[8] A 2.0 M solution of ethylmagnesium chloride in THF (0.30 L, 0.60 mol) under N_2 was diluted with THF (300 mL). The solution was cooled to 0 °C, and trimethylsilylacetylene (85 mL, 0.60 mol) was added slowly to the THF solution (**CAUTION**: evolution of ethane gas). After the mixture was stirred at 0 °C for a further 20 min, a solution of acetic anhydride (113 mL, 1.20 mol) in dry THF (200 mL) was added via cannula. The resulting reaction mixture was allowed to warm to room temperature and allowed to stir overnight. The reaction was quenched with water (100 mL), neutralized with 5% aqueous

(12) Grossman, R. B.; Rasne, R. M. *Org. Lett.* **2001**, *3*, 4027.

hydrochloric acid (100 mL), and allowed to stir for 3 h. The organic layer was washed three times with saturated aqueous $NaHCO_3$ solution (75 mL each), three times with water (75 mL each), and twice with brine (50 mL each), dried over $MgSO_4$, filtered, and evaporated. The remaining material was distilled through a twelve-inch Vigreux column under reduced pressure (aspirator), and the product was collected at 45−50 °C as a colorless liquid (63.12 g, 450.0 mmol, 75% yield).

Typical Procedure for Preparatory-Scale in Situ Double Michael Reaction. A solution of tethered diacid (10 mmol), TBAF (1 mmol), and $KF{\cdot}2H_2O$ (10 mmol) in EtOH (150 mL) was cooled to 0 °C. A solution of 4-trimethylsilyl-3-butyn-2-one (15 mmol) in THF (10 mL) was added slowly by addition funnel. After 1 h, all solvent was evaporated, and water (50 mL) was added to the reaction mixture. The solution was extracted three times with EtOAc (50 mL), and the organic layer was washed three times with water (50 mL). All organic fractions were combined, dried with brine and $MgSO_4$, and concentrated to yield a yellow oil. The products were purified by flash chromatography and by recrystallization from hot ethanol.

Trimethylsilylethynyl 3-Pyridyl Carbinol. A solution of ethylmagnesium chloride in THF (24 mL, 2.0 M, 48 mmol) was diluted with THF (50 mL), and trimethylsilylacetylene (6.75 mL, 43.8 mmol) was slowly added (**CAUTION:** evolution of ethane gas). The flask was covered to exclude light, nicotinaldehyde (4.50 mL, 47.7 mmol) was added, and the solution was allowed to stir overnight. The reaction was quenched with saturated aqueous NH_4Cl (100 mL). Ether (100 mL) was added to the organic layer. The organic layer was washed three times with water (75 mL each) and twice with brine (50 mL each), dried over $MgSO_4$, and filtered and the solvent evaporated. The product was collected as a brown solid (8.79 g, 43.0 mmol, 98% yield): mp 71−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, 2.2 Hz, 1H), 8.51 (dd, 1.5 Hz, 4.8 Hz, 1H), 7.91 (dddd, 0.7 Hz, 1.8 Hz, 2.4 Hz, 7.6 Hz, 1H), 7.32 (ddd, 0.7 Hz, 4.8 Hz, 7.9 Hz, 1H), 5.45 (s, 1H), 3.95 (broad, 1H), 0.21 (s, 9H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 149.0, 148.0, 136.4, 134.8, 123.5, 103.9, 92.4, 62.5, −0.3; IR (KBr) 3144, 2164, 1594, 1581 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NOSi$: C, 64.34; H, 7.36. Found: C, 64.19; H, 7.49.

Trimethylsilylethynyl 3-Pyridyl Ketone. A solution of DMSO (1.70 mL, 24.0 mmol) in CH_2Cl_2 (3 mL) was added to a solution of oxalyl chloride (1.00 mL, 5.41 mmol) in CH_2Cl_2 (25 mL) at −78 °C. A solution of trimethylsilylethynyl 3-pyridyl carbinol (2.05 g, 10.13 mmol) in CH_2Cl_2 (5 mL) was then added. After 15 min, triethylamine (7.00 mL, 50.2 mmol) was added, and the reaction was allowed to stir for 5 min. The ice bath was removed, and the reaction was allowed to reach room temperature. Saturated aqueous NH_4Cl (75 mL) was added to quench the reaction, and the organic layer was washed three times with water (75 mL) and twice with brine (50 mL each), dried over $MgSO_4$, filtered, and evaporated to give the ketone (1.94 g, 9.69 mmol, 96% yield) as a light brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (dd, 0.9 Hz, 2.2 Hz, 1H), 8.81 (dd, 1.7 Hz, 4.8 Hz, 1H), 8.34 (ddd, 1.8 Hz, 2.2 Hz, 8.1 Hz, 1H), 7.44 (ddd, 0.9 Hz, 4.9 Hz, 8.1 Hz, 1H), 0.35 (s, 9H); ^{13}C{H} NMR (50 MHz, $CDCl_3$) δ 176.0, 154.2, 151.5, 136.1, 131.7, 123.4, 102.5, 99.9, −0.9; IR (neat) 2154, 1653, 1585, 1570 cm^{-1}. $C_{11}H_{13}NOSi$.

Diethyl 3,3-Dicyano-2-(nicotinoylmethyl)-1,1-cyclohexanedicarboxylate (10). A solution of trimethylsilylethynyl 3-pyridyl ketone (1.05 g, 5.19 mmol) and diethyl (4,4-dicyanobutyl)malonate (1.06 g, 3.98 mmol) in EtOH (120 mL) was treated with a catalytic amount of $KF{\cdot}2H_2O$ and allowed to react overnight. The solvent was evaporated, and EtOAc (100 mL) was added. The organic layer was washed three times with water (50 mL) and twice with brine (50 mL), dried over $MgSO_4$, and filtered and the solvent evaporated. The resulting solid was purified by flash chromatography (eluant: 50% EtOAc in petroleum ether) to give **10** (1.12 g, 2.82 mmol, 71% yield) as a light yellow solid: mp 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, 1.6 Hz, 1H), 8.83 (dd, 1.6 Hz, 4.8 Hz, 1H), 8.31 (dt, J_t = 1.8 Hz, J_d = 8.1 Hz, 1H), 7.48 (ddd, 0.7 Hz, 5.0 Hz, 8.1 Hz, 1H), 4.34 (∼q, 7.1 Hz, 2H), 4.16 (dq, J_q = 7.1 Hz, J_d = 12.0 Hz, 1H), 4.11 (dq, J_q = 7.1 Hz, J_d = 12.0 Hz, 1H), 3.89 (dd, 2.4 Hz, 19.4 Hz, 1H), 3.81 (dd, 2.4 Hz, 6.6 Hz, 1H), 3.48 (dd, 6.6 Hz, 19.2 Hz, 1H), 2.62 (dm, J_d = 13.7 Hz, 1H), 2.52 (dm, J_d = 13.0 Hz, 1H), 2.20 (dt, J_d = 3.8 Hz, J_t = 13.4 Hz, 1H), 2.09 (qm, J_q = 13.7 Hz, 1H), 1.96 (dm, J_d = 14.6 Hz, 1H), 1.75 (dt, J_d = 4.0 Hz, J_t = 13.2 Hz, 1H), 1.40 (t, 7.4 Hz, 3H), 1.18 (t, 7.2 Hz, 3H); ^{13}C{H} NMR (50 MHz, $CDCl_3$) δ 194.0, 169.6, 168.0, 153.9, 149.5, 135.6, 131.4, 123.8, 115.0, 113.9, 62.6, 62.4, 56.5, 40.5, 39.6, 37.6, 35.5, 31.9, 19.0, 13.8, 13.8; IR (KBr) 2164, 1748, 1721, 1692, 1587 cm^{-1}. Anal. Calcd for $C_{21}H_{23}N_3O_3$: C, 63.46; H, 5.83. Found: C, 63.43; H, 5.97.

Acknowledgment. We thank the National Science Foundation (CAREER award to R.B.G., Grant No. CHE-9733201) and the National Institutes of Health (GM61002-02) for their generous support of this work. NMR instruments used in this research were obtained with funds from the CRIF program of the National Science Foundation (CHE-997841) and the Research Challenge Trust Fund of the University of Kentucky. D.S.H. thanks the University of Kentucky for a Lyman T. Johnson Fellowship.

JO0163086