ELSEVIER

Silylformylation–desilylation of propargyl amides: synthesis of α,β-unsaturated aldehydes

Laura Antonella Aronica, Patrizio Raffa, Giulia Valentini,
Anna Maria Caporusso* and Piero Salvadori

Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento, 35–56126 Pisa, Italy

Abstract—α,β-Unsaturated aldehydes are prepared from easily available propargyl amides through a two-step sequence of silyl-formylation–desilylation reactions. The substituent on the nitrogen atom markedly influences both reactions, β-silylalkenals being formed in the presence of tosyl or *tert*-butoxycarbonyl protected amines. TBAF is employed to induce the desilylation process that is performed under very mild experimental conditions. A contemporary elimination step occurs when tosylamido aldehydes are reacted affording 2-methylaryl-2-alkenals, while this process can be suppressed changing the functional group to NBOC, thus allowing the formation of β-amino carbonyl compounds.
© 2005 Elsevier Ltd. All rights reserved.

Transition metal catalyzed carbonylation of unsaturated compounds with carbon monoxide is one of the most important reactions in synthetic organic chemistry.[1] In particular treatment of terminal acetylenes with CO and a hydrosilane (silylformylation process) usually results in the formylation of the internal sp carbon of the triple bond affording (Z)-β-silylalkenals in high yields and with high degree of regio and stereochemical control. The silylformylation reaction has been studied extensively in the past few years[2] due to its wide applicability to unsaturated compounds bearing several functional groups such as alcohols, ethers, esters, ketones, aldehydes, halogens and double bonds. In 1992,[3] Matsuda et al. reported that propargyl amine derivatives reacted under CO pressure with two equivalents of hydrosilane to generate 2-silylmethyl-2-alkenals **5**, while the expected β-silylalkenals (Z)-**3** could not be isolated in good yields (Scheme 1).

A following deep analysis of the mechanistic aspects[4] of this process revealed that the β-silylalkenal **3** was probably the unstable intermediate that was converted into the double silylated product **4**, susceptible to an elimination step to form **5** in the presence of heat or acid. The
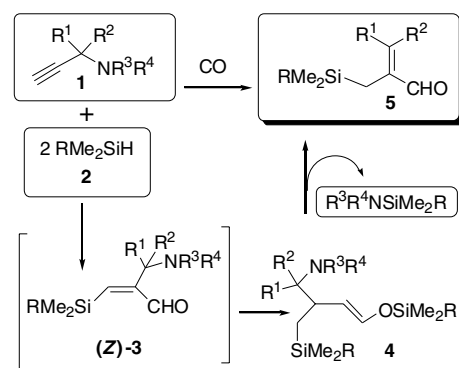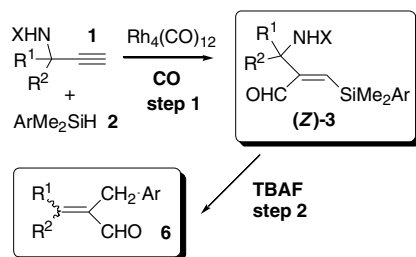

Scheme 1.

nature of the substituents on the nitrogen atom highly affected the reaction, the benzyl groups providing clear results with high yields.

In this letter, we report that suitable propargyl amides react with one equivalent of ArMe$_2$SiH affording the corresponding β-silylalkenals (Z)-**3** that are stable and can be isolated in good yields (Scheme 2, step 1). The protection of nitrogen atom is a fundamental step, since free amino moieties are responsible for the formation of uncharacterized material. Aldehydes (Z)-**3** can be submitted to a desilylation process by treatment with tetrabutylammonium fluoride (TBAF)[5] that is able to induce a 1,2-migration of the aryl group of the silyl

Scheme 2.

moiety with a contemporary elimination step that yields 2-methylaryl-2-alkenals **6** (Scheme 2, step 2). This result is particularly interesting since only a few methods of preparation of such molecules are described.[6]

Initially the silylformylation reaction of propargyl amides **1** was investigated and the principal results are summarized in Table 1. The reactions were performed in a stainless steel autoclave, under 30 atm of CO, in the presence of catalytic amounts of $Rh_4(CO)_{12}$ (0.1–0.5 mol % respect to the acetylene). In agreement with the data reported by Matsuda and co-workers,[3,4] monobenzylamine **1a** reacted with two equivalents of Me_2PhSiH to generate the allylsilylalkenal **7aa** exclusively. Under the same experimental conditions, the *para*-tosyl derivative **1b** yielded (*Z*)-**3ba** as major product with concomitant formation of considerable quantities of **7ba** (Table 1, entry 2). These preliminary data confirmed that the nature of the substituent on the nitrogen atom was a key element of the reaction. Indeed, the chemoselectivity towards the β-silylalkenals could be improved by reacting the tosyl amides **1** with 1 equiv of hydrosilane at 100 °C. The reaction temperature

played an important role since at 25 °C the formation rate of (*Z*)-**3** was too low and the generated β-silylalkenals were smoothly converted into the elimination product **7** (Table 1, entry 4). In order to reach a good to complete conversion of the reagents, 24 h was necessary (Table 1, entries 6–9).

The silylformylation of propargyl amides was appreciably affected by the structure of the acetylenic reagents, in agreement with the results we previously observed studying the reaction of nonfunctionalized 1-alkynes.[7] Indeed, the less hindered tosyl amides reacted rapidly with almost total selectivity towards the corresponding β-silylalkenals (*Z*)-**3** (Table 1, entries 3, 8 and 9). On the other hand, decreases on both the reaction rate and selectivity were detected when the silylformylation was carried out with acetylenes characterized by a bulky propargyl carbon (Table 1, entries 6 and 7). In particular, in the case of propargyl amide **1e**, the conversion after 24 h was 53% and the hydrosilylation reaction resulted highly competitive with the formylation one.

An analogous reaction trend was observed when substituted arylsilanes were employed: the use of *ortho*-tolyldimethylsilane involved a significant lowering of the reaction rate with respect to Me_2PhSiH (Table 1, entry 10 vs 9). In any cases, the chemoselectivity of the process resulted quite good if not complete, thus allowing the extension of the silylformylation of propargyl amides to functionalized hydrosilanes.

With the easy access to tosylamido aldehydes (*Z*)-**3** in hand, we turned to the desilylation step promoted by tetrabutylammonium fluoride (Table 2).[6] The reactions

Table 1. Silylformylation of propargyl amides **1** with aryldimethylsilanes[a]

Entry	1	X	R^1/R^2	*t* (h)	2	Ar	Conv.[b] (%)	Yield[b] (%)			
								(*Z*)-3		7[c]	
1[d]	a	CH$_2$Ph	Et/Me	4	a	Ph	76	/	/	aa	100
2[d]	b	*p*-Ts	Me/Me	4	a	Ph	100	ba	67	ba	33
3	c	*p*-Ts	Me/Me	24	a	Ph	100	ca	87 (42)	ca	13
4[e]	d	*p*-Ts	Me/Et	24	a	Ph	32	da	47	da	53
5	d	*p*-Ts	Me/Et	6	a	Ph	54	da	82	da	18
6	d	*p*-Ts	Me/Et	24	a	Ph	79	da	80 (44)	da	20
7	e	*p*-Ts	Me/*t*-Bu	24	a	Ph	53	ea	38	/	[f]
8[g]	f	*p*-Ts	H/*t*-Bu	24	a	Ph	73	fa	95 (49)	/	/
9[g]	g	*p*-Ts	H/Me	24	a	Ph	100	ga	91 (71)	/	/
10	g	*p*-Ts	H/Me	24	b	*o*-MePh	65	gb	100 (38)	/	/
11	c	*p*-Ts	Me/Me	24	c	*p*-MePh	82	cc	86 (51)	cc	14
12	c	*p*-Ts	Me/Me	24	d	*p*-OMePh	68	cd	87	cd	13

[a] Reactions were performed with 2 mmol of silane, 2 mmol of amide, 2×10^{-3}–10^{-2} mmol of $Rh_4(CO)_{12}$, 3 mL of CH_2Cl_2, in a stainless steel autoclave, under 30 atm of CO, at 100 °C, unless otherwise specified.
[b] Determined by GLC of the reaction mixture after work up. All new compounds were identified and characterized by FT-IR, NMR (^{1}H and ^{13}C), GC–MS and elemental analysis. In parentheses the isolated yields of pure compounds are reported.
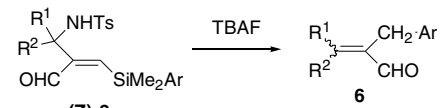[c] A *E/Z* mixture was always observed.
[d] Reactions run with 2 equiv of Me_2PhSiH.
[e] The reaction was performed at room temperature.
[f] 62% of hydrosilylated products were detected by ^{1}H NMR analysis.
[g] Small amounts of isomerisation byproducts were observed.

Table 2. TBAF induced desilylation of β-silylalkenals (*Z*)-3[a]

Entry	(*Z*)-3	Ar	R^1	R^2	6	Yield[b] (%) (*E*/*Z*)[c]
1	ga	Ph	H	Me	ga	52 (100/0)
2	fa	Ph	H	*t*-Bu	fa	45 (100/0)
3	ca	Ph	Me	Me	ca	75
4	da	Ph	Me	Et	da	59 (65/35)
5	gb	*o*-Tol	Me	H	gb	67 (100/0)
6	cd	*p*-MeO	Me	Me	cd	55

[a] Reactions were performed adding 1 mmol of β-silylalkenals to a THF solution (10 mL) of TBAF (2.5 mmol) at room temperature.

[b] Yields of pure compounds (not optimized). All new molecules were identified and characterized by FT-IR, NMR (^{1}H and ^{13}C), GC–MS and elemental analysis.

[c] Diasteromeric ratio was obtained by ^{1}H NMR analysis. *E* and *Z* configurations of the products were determined by NOE experiments.

were performed under very mild experimental conditions, adding 1 mmol of aldehydes to a THF solution of TBAF (2.5 mmol) and hydrolyzing immediately afterwards with water. A complete consumption of the reagents was observed and the obtained products were recovered in good yields (not optimized). The fluoride source induced a 1,2-anionotropic rearrangement of the aryl substituent from silicon to carbon with subsequent desilylation.[5] Unexpectedly, a contemporary elimination of the tosyl amide moiety was detected and 2-methylaryl-2-alkenals **6** were generated. The reaction resulted totally stereoselective when a secondary allylic carbon was present on the (*Z*)-3 precursors, the more stable isomer (*E*) being formed exclusively (Table 2, entries 1 and 2). The 1,2-rearrangement of the aromatic ring occurred with complete retention of the original configuration of the Ar, as observed in the cases of *ortho*- and *para*-functionalized groups (Table 2, entries 5 and 6).

The obtained data indicated that it was not possible to maintain the amide moiety in the TBAF promoted desilylation process, probably due to the good leaving group properties of *para*-toluenesulfonamide. This result was achieved by the two-step sequence of silylformylation–desilylation of the BOC protected substrate **1h** (Scheme 3).

Both reactions afforded the corresponding products in good yield. The silylformylation of the *tert*-butoxycarbonyl protected amine **1h** with Me$_2$PhSiH generated the expected β-silylalkenal (*Z*)-3ha exclusively. The TBAF promoted phenyl migration resulted in being totally chemoselective towards the formation of the β-amino aldehyde **8**. It is noteworthy that β-amino carbonyl moieties are found not only as structural units of natural products,[8] but are potentially useful building blocks for Wittig type condensations[9] and for the synthesis of natural molecules,[10] β-amino acids and 1,3-amino alcohols.[11]

All the reported data were in agreement with the mechanism hypothesized for the TBAF induced rearrangement of non functionalized β-silylalkenals[6] as depicted in Scheme 4. The proposed mechanism involves the
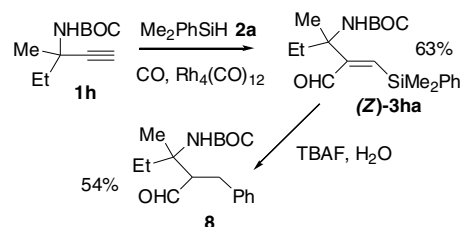
Scheme 3.
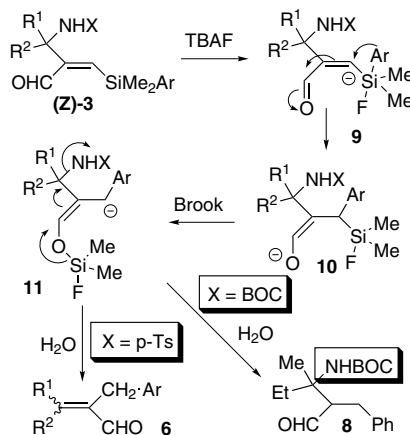
Scheme 4.

addition of fluoride to silicon yielding a pentacoordinate Si atom **9**, aryl-1,2-anionotropic migration to the adjacent carbon atom with the formation of enolate **10** and its possible Brook rearrangement. Hydrolysis of **11** generates the Boc protected amide **8**, while contemporary elimination of the tosyl group affords the observed 2-methylaryl-2-alkenals **6**.

In conclusion, we have shown that it is possible to perform the silylformylation of acetylenes functionalized by a propargyl amide group with aryldimethylsilanes, providing that the reaction is carried out with equivalent amounts of the reagents. The obtained β-silylalkenals are stable and can be submitted to a desilylation process by treatment with TBAF.[†] Different functionalized alde-

---

[†] 2-Benzyl-3-methyl-2-pentenal (representative procedure): 2 mmol of Me$_2$PhSiH, 2 mmol of (*R*)(*S*)-*N*-(1-methyl-1-ethyl-2-propinyl)-*p*-toluenesulfonamide **1d**, 0.0016 g (2×10^{-3} mmol) of Rh$_4$(CO)$_{12}$ and 3 mL of CH$_2$Cl$_2$ were put, in a Pyrex 'Schlenk' tube, under CO atmosphere. This solution was introduced in a 25 mL stainless steel autoclave fitted with a Teflon inner crucible and a stirring bar, previously placed under vacuum (0.1 mmHg), by a steel siphon. The reactor was pressurized with 30 atm of carbon monoxide and the mixture was stirred at 100 °C for 24 h. After removal of excess CO (fume hood), the reaction mixture was diluted with CH$_2$Cl$_2$, filtered (Celite) and concentrated under vacuum. The residue was purified by column chromatography on silica gel using CH$_2$Cl$_2$ as eluent affording 0.37 g (44%) of the pure aldehyde (*Z*)-3da. To a solution of 2.5 mmol of TBAF in 10 mL of THF was added, at room temperature, 1 mmol of (*Z*)-3d. The reaction mixture was hydrolyzed with water, extracted with Et$_2$O and the organic layers were dried over Na$_2$SO$_4$. After concentration under vacuum, the crude product was purified by column chromatography on silica gel using CH$_2$Cl$_2$ as eluent affording 0.11 g (59%) of a (*E*/*Z*) mixture of 2-benzyl-3-methyl-2-pentenal **6**.

hydes are obtained according to the nature of the protecting group on the nitrogen atom, enhancing the versatility of this two-step protocol.

References and notes

1. Tsuji, J. *New J. Chem.* **2000**, *24*, 127–135; Vizer, S. A.; Yerzhanov, K. B.; Al Quntar, A. A.; Dembitsky, V. M. *Tetrahedron* **2004**, *60*, 5499–5538; Ungvary, F. *Coord. Chem. Rev.* **2004**, *248*, 867–880; Twigg, M. V.; Colquhoun, H. M.; Thompson, D. J. In *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum: New York, 1991.

2. Matsuda, I.; Ogiso, A.; Sato, S.; Izumi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2332–2333; Ojima, I.; Ingallina, P.; Donovan, R. J.; Clos, N. *Organometallics* **1991**, *10*, 38–41; Ojima, I.; Donovan, R. J.; Eguchi, M.; Shay, W. R.; Ingallina, P.; Korda, A.; Zeng, Q. *Tetrahedron* **1993**, *49*, 5431–5444; Doyle, M. P.; Shanklin, M. S. *Organometallics* **1994**, *13*, 1081–1088; Zhou, J.; Alper, H. *Organometallics* **1994**, *13*, 1586–1591; Jain, N. F.; Cirillo, P. F.; Schaus, J. V.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8723–8726; Chatani, N.; Murai, S. *Synlett* **1996**, 414–424; Matsuda, I.; Fukuta, Y.; Tsuchihashi, T.; Nagashima, H.; Itoh, K. *Organometallics* **1997**, *16*, 4327–4345; Matsuda, I.; Niikawa, N.; Kuwabara, R.; Inoue, H.; Nagashima, H.; Itoh, K. *J. Organomet. Chem.* **1999**, *574*, 133–141; Eilbracht, P.; Hollmann, C.; Schmidt, A. M.; Barfacker, L. *Eur. J. Org. Chem.* **2000**, *10*, 38–41, pp 1131–1135; Marciniec, B. *Appl. Organomet. Chem.* **2000**, *14*, 527–538; Okazaki, H.; Kawanami, Y.; Yamamoto, K. *Chem. Lett.* **2001**, 650–651; Alonso, M. A.; Casares, J. A.; Espinet, P.; Vallés, E.; Soulantica, K. *Tetrahedron Lett.* **2001**, *42*, 5697–6700; Ojima, I.; Moralee, C. M.; Vassar, V. C. *Topics in Catalysis* **2002**, *19*, 89–99; Denmark, S. E.; Kobayashi, T. *J. Org. Chem.* **2003**, *68*, 5153–5159; Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *Tetrahedron* **2003**, *59*, 8889–8900.

3. Matsuda, I.; Sakakibara, J.; Inoue, H.; Nagashima, H. *Tetrahedron Lett.* **1992**, *33*, 5799–5802.

4. Matsuda, I.; Fukuta, Y.; Itoh, Kenji *Inorg. Chim. Acta* **1999**, *296*, 72–79.

5. Aronica, L. A.; Morini, F.; Caporosso, A. M.; Salvatori, P. *Tetrahedron Lett.* **2002**, *42*, 5813–5815; Aronica, L. A.; Raffa, P.; Caporusso, A. M.; Salvadori, P. *J. Org. Chem.* **2003**, *68*, 9292–9298.

6. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, 7503–7509; Sato, T.; Arai, M.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, 5827–5828; Traas, P. C.; Takken, H. J.; Boelens, H. *Tetrahedron Lett.* **1977**, *23*, 2027–2030; Baumann, F.; Wurthwein, E. U. *Tetrahedron Lett.* **1991**, *32*, 4683–4686; Chandrasekhar, S.; Takhi, M.; Reddy, Y. R.; Mohapatra, S.; Rao, C. R.; Reddy, K. V. *Tetrahedron* **1997**, *53*, 14997–15004; Hagiwara, H.; Ono, H.; Komatsubara, N.; Hoshi, T.; Suzuki, T.; Ando, M. *Tetrahedron Lett.* **1999**, *40*, 6627–6630; Kiyooka, S.; Fujimoto, H.; Mishima, M.; Kobayashi, S.; Uddin, K. M.; Fujio, M. *Tetrahedron Lett.* **2003**, *44*, 927–930; Shi, M.; Xu, Y. M.; Shi, Y. L. *Chem. Eur. J.* **2005**, *11*, 1794–1802; Hagiwara, H.; Hamaya, J.; Hoshi, T.; Yokoyama, C. *Tetrahedron Lett.* **2005**, *46*, 393–395.

7. Aronica, L. A.; Terreni, S.; Caporusso, A. M.; Salvadori, P. *Eur. J. Org. Chem.* **2001**, *22*, 4321–4329.

8. Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957–5978.

9. Luois, C.; Mill, S.; Mancuso, V.; Hootele, C. *Can. J. Chem.* **1994**, *72*, 1347; Davis, F. A.; Szewczyk, J. M. *Tetrahedron Lett.* **1998**, *39*, 5951–5954; Davies, S. B.; McKervey, A. *Tetrahedron Lett.* **1999**, *40*, 1229–1232.

10. Limal, D.; Quesnel, A.; Briand, J. P. *Tetrahedron Lett.* **1998**, *39*, 4239–4242; Davis, F. A.; Prasad, K. R.; Brad Nolt, M.; Wu, Y. *Org. Lett.* **2003**, *5*, 925–927; Davis, F. A.; Yang, B. *Org. Lett.* **2003**, *5*, 5011–5014.

11. Toujas, J. L.; Toupet, L.; Vaultier, M. *Tetrahedron* **2000**, *56*, 2665–2672.