ORGANIC LETTERS

2004
Vol. 6, No. 22
3977−3980

Efficient Synthesis of Acylsilanes Using Morpholine Amides

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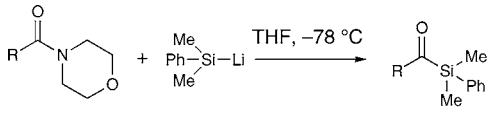
Received August 13, 2004

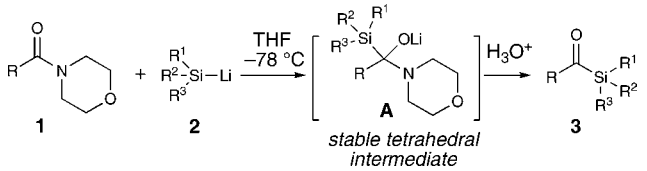
ABSTRACT



A general synthesis of acylsilanes from the corresponding morpholine amides and silyllithium species is described. The use of morpholine amides is economical and prevents over-addition by the silyl nucleophile. The procedure cleanly affords acylsilanes in good yields and circumvents the use of stoichiometric copper(I) cyanide typically employed to synthesize these compounds from acid chlorides.

Acylsilanes are valuable compounds in organic synthesis primarily due to their ability to access the Brook rearrangement manifold upon the addition of a strong nucleophile. This important 1,2-silyl migration from carbon to oxygen was initially described by Brook, and subsequent investigations of this process have firmly established its utility.[1] For example, acylsilanes have been employed in the synthesis of enolsilanes[2] and alcohols[3] and provide direct access to homoenolates upon addition of vinyl or alkynyl organometallic reagents.[4] More recently, acylsilanes undergoing the Brook rearrangement have been the cornerstone for the development of tandem annulation reactions,[5] and the unique properties of the resulting anions have been exploited in the development of new catalytic acyl anion addition reactions.[6] However, although acylsilanes are useful entities, standard procedures for accessing these compounds have numerous limitations such as low overall efficiency and a reliance on stoichiometric quantities of a transition metal. Herein, we report an efficient synthesis of acylsilanes (**3**, Scheme 1) from the corresponding morpholine amides (**1**) via tetrahedral intermediate **A**. This approach allows for the efficient access

Scheme 1. General Synthesis of Acylsilanes from Morpholine Amides



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10.1021/ol0483854 CCC: $27.50
Published on Web 10/06/2004

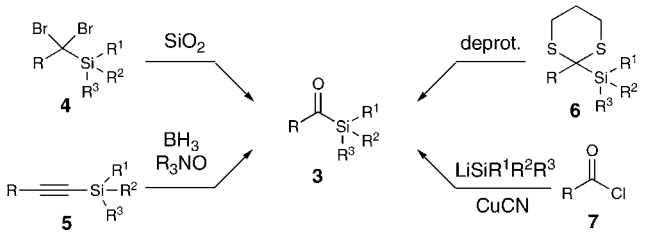


Figure 1. Survey of various acylsilane syntheses.

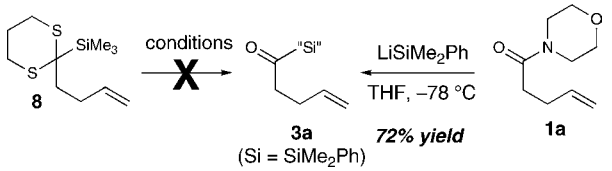
of acylsilanes in one step from the corresponding amide and an easily prepared silyl anion.

There are numerous synthetic approaches to construct the carbonyl carbon−silicon bond (Figure 1).[7] Unconventional approaches include the conversion of α,α-dibromobenzylsilanes (**4**) to acylsilanes on silica gel[8] and the hydroboration of silylalkynes (**5**).[9] The trapping of deprotonated dithianes with chlorosilanes has been employed for decades, but this strategy always requires the unmasking of the α-silyl dithiane (**6**), which is not always compatible with the substrate (vide infra).[10] Additionally, benzotriazol-1-yl phenoxyalkanes are useful precursors to a variety of acylsilane structures.[11] Not surprisingly, many of these processes are potentially difficult due to the unavailability of starting materials or their lack of atom economy.[12] α,*β*-Unsaturated acylsilanes can be prepared either by a Horner−Wadsworth−Emmons reaction of α-(phosphonoacyl)-silanes[13] or the silyl-Wittig rearrangement of allylic alcohols followed by oxidation.[14] Interestingly, the palladium-catalyzed conversion of aryl acid chlorides to aryl acylsilanes has been reported, but this reaction is limited to the trimethylsilyl group and undergoes decarbonylation with electron-deficient aromatic systems.[15]

The addition of anionic silyl nucleophiles to acid chlorides is typically the most direct method for the synthesis of acylsilanes, but this method requires at least 2 equiv of the silyllithium reagent and suffers largely from *stoichiometric* copper(I) cyanide required for the reaction to proceed in high yield.[16] Unfortunately, on a preparative scale, this process becomes prohibitive. As an alternate approach, Fleming and co-workers first noted that the addition of silyl anions to amides afforded acylsilanes, but this process was not adequately explored as an efficient and less toxic strategy to construct acylsilanes.[17]

We were prompted to reexamine various acylsilane syntheses when trying to prepare acylsilane **3a** (Scheme 2).

Scheme 2. Dithiane Deprotection Complications and Conversion of Amide **1a** to Acylsilane **3a**[a]



[a] Conditions: 1) $(NH_4)_2Ce(NO_3)_6$, aq. $NaHCO_3$, $MeCN/CH_2Cl_2$, −30 °C, 5 min; 2) $PhI(OTFA)_2$, aq. $NaHCO_3$, THF/MeCN, 0 °C, 15 min.

The conventional dithiane approach allowed for the preparation of gram quantities of dithiane **8**, but we were unable to convert this material to **3a** without destroying the terminal alkene. We wanted to avoid using mercury(II) chloride, due to the toxicity of mercury and the possible interactions of the metal with the olefin. A search of the literature yielded only two reagents for the deprotection of dithianes in the presence of terminal olefins: ceric ammonium nitrate[18] and [bis(trifluoroacetoxy)-iodo]benzene.[19] Unfortunately, the use of either of these reagents under various conditions did not afford the desired acylsilane.

We envisioned that a morpholine amide **1a** would be a better acylsilane precursor for **3a** and that this approach would be applicable toward many other acylsilanes. The direct addition of organometallic reagents to morpholine amides without over-addition has been reported,[20] and this process is more economical than the corresponding Weinreb amides.[21] Gratifyingly, the addition of 1.5 equiv of dimethylphenylsilyllithium to a −78 °C solution of morpholine amide **1a** in THF for 90 min followed by the addition of aqueous ammonium chloride affords the desired acylsilane **3a** in 72% yield.[22] To probe the scope of this reaction, the

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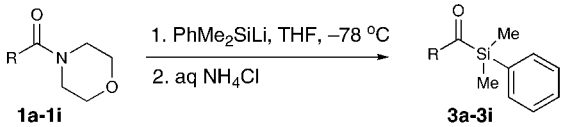
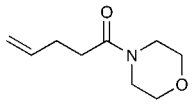
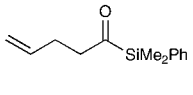
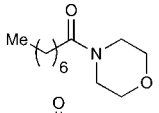
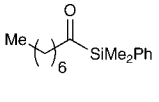
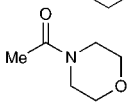
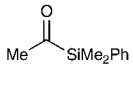
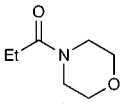
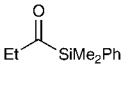
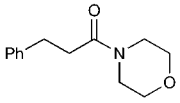
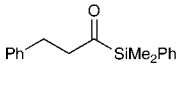
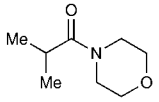
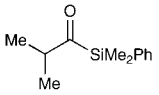
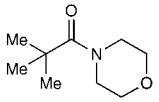
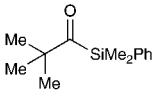
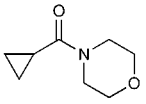
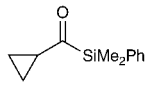
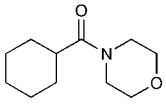
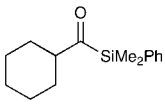
(21) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (b) Sigma-Aldrich pricing: *N*,*O*-dimethylhydroxylamine·HCl costs $195/mol, while morpholine is only $13/mol (calculation based on 100 g bottles).

Table 1. Synthesis of Acylsilanes from Alkyl Morpholine Amides[a]



1a-1i **3a-3i**

entry	amide	acylsilane		yield
1			**3a**	72%
2			**3b**	81%
3			**3c**	76%
4			**3d**	75%
5			**3e**	80%
6			**3f**	60%
7			**3g**	65%
8			**3h**	82%
9			**3i**	65%

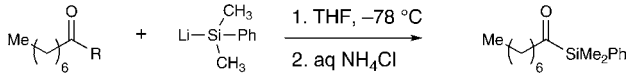
[a] All reactions were carried out 0.3 M in substrate in THF with 1.5 equivalents of phenyldimethylsilyllithium for 1.5 h at −78 °C. Reactions were quenched at −78 °C by the addition of saturated aqueous ammonium chloride and were stirred for 30 min. Following workup, the residue was purified by silica gel chromatography.

addition of dimethylphenylsilyllithium to a number of morpholine amides has been examined (Table 1).

The addition of dimethylphenylsilyllithium to morpholine amides occurs in good yields and is a general process for the synthesis of alkyl acylsilanes (entries 1−9). Gratifyingly, no double addition was observed for any of the substrates. Both linear and branched alkyl morpholine amides are suitable substrates for the reaction and are efficiently transformed into alkyl acylsilanes.[23]

With a suitable procedure in hand for the synthesis of acylsilanes from morpholine amides, we questioned whether other tertiary amides were equally effective in this transformation. To explore these possibilities, a small range of octanoyl amides were treated with dimethylphenylsilyllithium under our established reaction conditions (Table 2). Surprisingly, only the morpholine, *N*,*N*-dimethyl, and piperidyl

Table 2. Synthesis of Acylsilanes from Octanoyl Amides[a]



9 **3b**

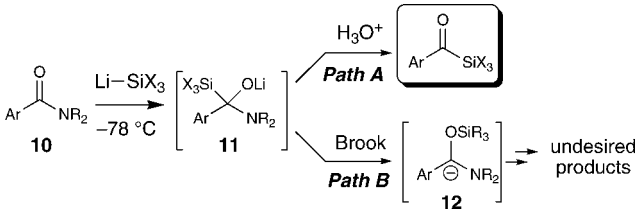
entry	R	yield (%)
1	morpholine (**1b**)	81
2	NMe_2	46
3	NEt_2	0[b]
4	NBn_2	0[b]
5	piperidine	10
6	NMe(OMe)	0[b]

[a] All reactions were carried out 0.3 M in substrate in THF with 1.5 equiv of phenyldimethylsilyllithium for 1.5 h at −78 °C. Reactions were quenched at −78 °C by the addition of saturated ammonium chloride and stirred for 30 min. Following workup, the residue was purified by silica gel chromatography. [b] Complex mixture.

amides gave any acylsilane product under these conditions. Although the morpholine amide is clearly beneficial for the overall reaction, its special nature is currently not well understood.

The extension of this methodology to the use of aromatic morpholine amides is currently problematic. Straightforward additions of silyl anions to aromatic amides (**10**) usually undergo a Brook rearrangement after formation of the tetrahedral intermediate (**11**), presumably due to stabilization of the resulting carbanion **12** by the aromatic moiety (Scheme 3, path B). Surprisingly, this anion subsequently undergoes

Scheme 3. Rearrangement of Aryl Morpholine Amides



an α-elimination of the silyloxy substituent and the ensuing carbene either encounters an additional equivalent of the silyllithium species or dimerizes.[24] Not unexpectedly, the use

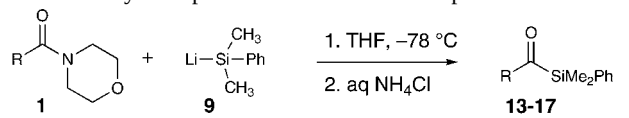
(22) Dimethylphenylsilyllithium is easily prepared from the incubation of commercially available dimethylphenylsilyl chloride and finely cut lithium metal in THF at 0 °C for 40 h. The resulting dark red suspension is used after titration according to: Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527−2532.

(23) Table 2, entry 3, has been performed on a 55 mmol scale to yield acylsilane **3c**. See Supporting Information for details.

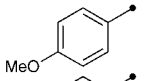
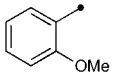
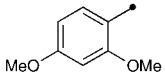
(24) For the first reported observation of this behavior, see: Fleming, I.; Ghosh, U. *J. Chem. Soc., Perkin Trans. 1* **1994**, 257−262. (b) Buswell, M.; Fleming, I. *Chem. Commun.* **2003**, 202−203 and references therein.

of *N*-benzoylmorpholine as a substrate did not fare better, yielding no acylsilane. We hypothesized that use of more electron-donating aryl groups could inhibit the deleterious Brook rearrangement (path B) and allow for the reaction to proceed via the desired path A. To investigate this possibility, we attempted to synthesize acylsilanes from a variety of electron-rich aryl morpholine amides (Table 3). The placement of a single electron-donating substituent on the phenyl ring of the amide did not inhibit reaction path B (entries 2 and 3). The use of a 2,4-dimethoxyphenyl amide did allow for isolation of the desired acylsilane (**15**), albeit in low yield. Unexpectedly, the 2-furyl morpholine amide afforded the corresponding acylsilane in moderate yield (60%, entry 5).[25]

Table 3. Aryl Morpholine Amides as Electrophiles[a]



1 9 13-17

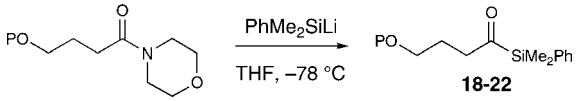
entry	R	acylsilane	yield (%)
1		**13**	0[b]
2		**14**	0[b]
3		**15**	0[b]
4		**16**	35%
5		**17**	61%

[a] All reactions were carried out 0.3 M in substrate in THF with 1.5 equivalents of phenyldimethylsilyllithium for 5 min at −78 °C. Reactions were quenched at −78 °C (aq NH_4Cl), then purified (SiO_2). [b] Complex mixture.

To further probe the scope of the reaction, we examined the addition of other silyllithium species to **1b**. The addition of diphenylmethylsilyllithium afforded no acylsilane, possibly due to complications from a faster Brook rearrangement facilitated by the additional phenyl group on the silicon. Surprisingly, the reaction of trimethylsilyllithium[26] with **1b** did not yield an acylsilane. In addition, use of 2-methoxyphenyldimethylsilyllithium and 2-(5-methylfuryl)dimethylsilyllithium[27] resulted in no desired products. Interestingly, the syntheses of these additional silyl anions require hexamethylphosphoramide (HMPA), and we questioned whether this additive was incompatible with our optimized reaction conditions. Accordingly, amide **1b** was reacted under the optimized conditions with silyl anion **9**, except that THF was replaced with a 2:1 (v/v) mixture of THF/HMPA. In this event, no acylsilane was recovered, thus determining that the use of HMPA as a solvent is unsuited for this methodology.

In addition, we sought to determine the tolerance of this reaction to various hydroxyl-protecting groups. To this end, various O-protected 4-hydroxybutyryl morpholine amides were synthesized and treated with dimethylphenylsilyllithium under the optimized reaction conditions. Gratifyingly, alkyl- or silyl-protected hydroxy amines underwent smooth addition to yield acylsilanes (**18**−**22**) in moderate to high yields (Table 4).

Table 4. Synthesis of Protected Acylsilanes[a]



18-22

entry	R	acylsilane	yield (%)
1	$PhCH_2$	**18**	85%
2	$MeOCH_2OCH_2$[b]	**19**	67%
3	Ph_3C	**20**	75%
4	*i*-$BuPh_2Si$	**21**	60%
5	*i*-Pr_3Si	**22**	79%

[a] All reactions were carried out 0.3 M in substrate in THF with 1.5 equiv of phenyldimethylsilyllithium for 1.5 h at −78 °C. Reactions were quenched at −78 °C by the addition of saturated ammonium chloride and stirred for 30 min. Following workup, the residue was purified by silica gel chromatography.

In conclusion, a direct and efficient synthesis of acylsilanes from amides has been described. The use of the morpholine amide is a key feature since it minimizes over-addition of the silyl nucleophile and also provides the highest yields of the amides surveyed. The additions of silyllithium species to aromatic amides are hampered by a nonproductive Brook rearrangement. The overall process has been developed to be highly preparative in nature, avoids the use of transition metals, and tolerates varied alkyl amide structures, including various protecting groups. The application of this methodology to facilitate investigations into the reactivity and utility of acylsilanes is in progress in our laboratory.

Acknowledgment. We thank Northwestern University for support of this work. We are grateful to Wacker Chemical Co. (Specialties Division, Adrian, MI) for kindly supplying various organosilicon reagents.

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

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(25) Employing additional 2-substituted aromatic heterocycles (e.g., *N*-methyl pyrroyl, thiophen-2-yl) was not successful using the current reaction conditions.

(26) Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063−3064.
(27) Lee, T. W.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3337−3339.