# The Thiazolium-Catalyzed Sila-Stetter Reaction: Conjugate Addition of Acylsilanes to Unsaturated Esters and Ketones

Anita E. Mattson, Ashwin R. Bharadwaj, and Karl A. Scheidt*

Department of Chemistry, Northwestern University, Evanston, Illinois 60208

Received December 19, 2003; E-mail: scheidt@northwestern.edu

The inversions of normal reactivity patterns (umpolung) are powerful strategies in organic synthesis that provide unconventional access to important materials.[1] A prominent class of umpolung reactions employs organic catalysts (thiazolium salts) to induce aldehydes to undergo nucleophilic addition reactions.[2] Typically, this aldehyde nucleophile is added either to another aldehyde (benzoin condensation)[3] or to a conjugate acceptor. This second process, or Stetter reaction, is an efficient method to generate useful 1,4-dicarbonyl compounds.[4] However, the Stetter reaction is significantly limited by the high reactivity of the aldehyde, which results in large amounts of self-condensation, or benzoin, products.[5] We envisioned acylsilanes as unconventional acyl anion precursors accessible via the addition of a neutral Lewis base catalyst. This strategy generates an acyl anion nucleophile that adds selectively to the conjugate acceptor over remaining acylsilane, thus completely avoiding benzoin product formation. Herein, we report the realization of this new general approach employing acylsilanes (**1**), conjugate acceptors (**2**), and thiazolium salts (**4**) as the nucleophilic catalyst precursors (eq 1).
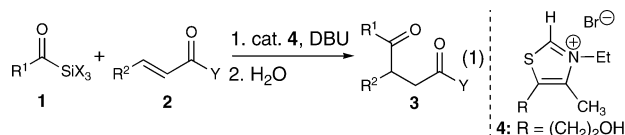
The use of acylsilanes[6] as acyl anion precursors typically involves the addition of highly charged, potentially toxic catalysts such as cyanide and fluoride anions.[7] These approaches ensure significant charge density on the oxygen of the resulting tetrahedral intermediate to promote a 1,2-silyl group shift (Brook rearrangement) and render the acylsilane carbon nucleophilic.[8] However, to our knowledge, Brook rearrangements have not been previously induced with neutral Lewis basic species, such as carbenes. Specifically, the use of thiazolium salts in the presence of an appropriate base to generate the desired carbene (or zwitterionic) catalyst in situ is an appealing, yet uncharted, platform for the development of acylsilanes as tunable acyl anion equivalents with appropriate conjugate acceptors.

After considerable experimentation with the acyl addition reaction of acylsilane **1a** and chalcone (**2a**), we identified THF and DBU as the optimal solvent and base, respectively, in the presence of stoichiometric amounts of commercially available **4** (Table 1, eq 2).[9] Initially, the use of thiazolium salts without an alcohol or catalyst loading below 100 mol % afforded significantly reduced yields of **5** (entry 6),[10] and we postulated that the hydroxyl moiety plays an important role in the reaction. Gratifyingly, straightforward addition of 4 equiv of 2-propanol allows for the reduction of catalyst to 30 mol % without impacting the yield (entry 8).

With the optimal solvent/base combination and alcohol additive, the scope of the reaction was examined (Table 2, eq 3). The reaction is tolerant of electron-donating aryl substituents on either side of

Table 1. Effect of Reaction Conditions on the Thiazolium-Catalyzed Addition of Acylsilane **1a** to Chalcone (**2a**)[a]

entry	base	solvent	mol% 4	equiv of i-PrOH[b]	yield (%)[c]
1	DBU	THF	100	0	71
2	NEt₃	THF	100	0	40
3	KOt-Bu	THF	100	0	0
4	DBU	CH₂Cl₂	100	0	39
5	DBU	PhCH₃	100	0	0
6	DBU	THF	30	0	43
7	DBU	THF	50	4.0	78
8	DBU	THF	30	4.0	77
9	DBU	THF	10	4.0	44

[a] All reactions were performed at reflux temperature in the solvent indicated. [b] Equivalents relative to chalcone (**2a**). [c] Isolated yield after chromatographic purification.

Table 2. Catalytic Sila-Stetter Reactions with Acylsilane **1a** and β-Aryl Unsaturated Phenyl Ketones (**2**)[a]

entry	R¹	R²	yield (%)[b]	product
1	Ph	4-ClPh	82	**6**
2	Ph	4-OMePh	80	**7**
3	1-Napth	Ph	72	**8**
4	4-BrPh	Ph	66	**9**
5	4-ClPh	Ph	74	**10**
6	2-ClPh	Ph	68	**11**
7	4-MePh	Ph	84	**12**
8	3-OMePh	Ph	75	**13**
9	4-OMePh	Ph	77	**14**
10	4-HOPh	Ph	50[c]	**15**

[a] All reactions were performed at 0.8 M at 70 °C for 12−24 h. See Supporting Information for details. [b] Isolated yield after chromatographic purification. [c] Based on 70% conversion.

the α,β-unsaturated system. Additionally, moderate to high yields are observed for the 1,4-dicarbonyl products when aryl substituents with electron-withdrawing groups are employed (entries 1, 4−6). Notably, the reaction proceeds moderately with an unprotected phenol (entry 10).

The influence of acylsilane structure on the reaction has also been investigated (Table 3, eq 4). The placement of a substituent on the phenyl ring of benzoyltrimethylsilane (entries 2 and 3) or the use of a dimethylphenylsilyl group (entry 4) affords high yields of 1,4-dicarbonyl products. Remarkably, enolizable alkyl acylsilanes such as **1e** and **1f** are functional acyl anion precursors without a deleterious effect on conversion or yield (entries 5 and 6).

Table 3. Influence of Acylsilane Structure on Acyl Anion Reaction[a]

entry	acylsilane	R^1	R^2	yield (%)[b]	product
1	**1a**	Ph	CH_3	77	**5**
2	**1b**	4-ClPh	CH_3	82	**16**
3	**1c**	$4\text{-}CH_3Ph$	CH_3	70	**17**
4	**1d**	Ph	Ph	61	**5**
5	**1e**	CH_3	Ph	70	**18**
6	**1f**	cyclohexyl	Ph	63	**19**

[a] All reactions were performed at 0.8 M for 12 h at 70 °C. See Supporting Information for details. [b] Isolated yield after chromatographic purification.

The scope of this new sila-Stetter reaction has been further examined by employing various classes of α,β-unsaturated carbonyl electrophiles (Table 4, eq 5). Utilizing either reactive diethyl fumarate (entry 1) or dimethyl maleate (entry 2) affords the desired tricarbonyl products. Remarkably, using highly reactive methyl vinyl ketone and ethyl acrylate as substrates produces dicarbonyls **22** and **23** cleanly (entries 3 and 4). Use of the more reactive 4-chlorobenzoyltrimethylsilane (**1b**) allows for the incorporation of nonbisaryl α,β-unsaturated ketones as substrates (entries 5 and 6), although why these reactions stall is under investigation.[11]

Table 4. Catalytic Sila-Stetter Reactions with α,β-Unsaturated Carbonyl Electrophiles[a]

entry	R^1	R^2	R^3	Ar	yield (%)[b]	product
1	EtO_2C	H	OEt	Ph	65	**20**
2	H	CH_3O_2C	OCH_3	Ph	72	**21**
3	H	H	OEt	Ph	72	**22**
4	H	H	CH_3	Ph	75	**23**
5	Ph	H	CH_3	4-ClPh	63[c]	**24**
6	Ph	H	t-Bu	4-ClPh	48[d]	**25**

[a] All reactions were performed at 0.8 M at 70 °C for 2–12 h. [b] Isolated yield after purification. [c] 64% conversion. [d] 59% conversion.

A plausible catalytic cycle for this reaction is depicted in Scheme 1.[12] The carbene (or zwitterion) catalyst (**I**) addition to the acylsilane promotes a Brook rearrangement that affords silylated intermediate **II**. The alcohol additive present in the reaction desilylates **II**, which produces intermediate **III**.[13] Under normal thiazolium-catalyzed benzoin or Stetter reactions, this nucleophilic intermediate can intercept another aldehyde. However, due to the attenuated electrophilicity of the acylsilane (relative to an aldehyde), the reaction proceeds via the preferred 1,4-addition manifold to produce **IV**.[14] Formation of the aryl ketone expels the carbene catalyst and affords the desired dicarbonyl compounds **5**–**25**.

In conclusion, we have disclosed a new silyl variant of the Stetter reaction between acylsilanes and α,β-unsaturated conjugate acceptors promoted by an organic catalyst. This catalytic process rapidly accesses useful 1,4-dicarbonyl products and significantly increases

Scheme 1. Proposed Catalytic Cycle for Thiazolium-Catalyzed Acylsilane Additions to α,β-Unsaturated Ketones
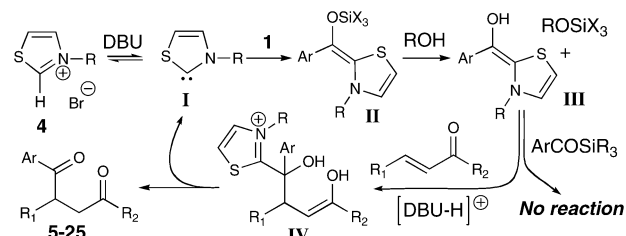
the scope of the Stetter reaction by utilizing acylsilanes as tunable acyl anion progenitors. In addition, remarkably mild carbenes have been employed as new and effective nucleophilic catalysts for 1,2-silyl (Brook) rearrangements. Further development of this reaction and studies regarding the reaction mechanism are being pursued and will be reported in due course.

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

References

(1) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239−258. (b) Fernandez, R.; Lassaletta, J. M. *Synlett* **2000**, 1228−1240. (c) Eisch, J. J. *J. Organomet. Chem.* **1995**, *500*, 101−115.
(2) (a) Ukai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296−300. (b) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719−3726.
(3) Stetter, H.; Kuhlmann, H. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley and Sons: New York, 1991; Vol. 40.
(4) (a) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639−712. (b) Stetter, H.; Kuhlmann, H. *Chem. Ber.* **1976**, *109*, 2890−2896.
(5) Tethering the aldehyde to the conjugate acceptor (intramolecular reaction) or significant excess of aldehyde can alleviate the problem of benzoin formation in the Stetter reaction, see: (a) Trost, B. M.; Shuey, C. D.; Dininno, F.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1284−1285. (b) Ciganek, E. *Synthesis* **1995**, 1311−1314. (c) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899−1902. (d) Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299. (e) Raghavan, S.; Anuradha, K. *Tetrahedron Lett.* **2002**, *43*, 5181−5183.
(6) For reviews on acylsilanes and their chemistry, see: (a) Ricci, A.; Degl'Innocenti, A. *Synthesis* **1989**, 647−660. (b) Page, P. C. B.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147−195. (c) Cirillo, P. F.; Panek, J. S. *Org. Prep. Proced. Int.* **1992**, *24*, 553−582.
(7) (a) Schinzer, D.; Heathcock, C. H. *Tetrahedron Lett* **1981**, *22*, 1881−1884. (b) Degl'Innocenti, A.; Ricci, A.; Mordini, A.; Reginato, G.; Colotta, V. *Gazz. Chim. Ital.* **1987**, *117*, 645−648. (c) Degl'Innocenti, A.; Pike, S.; Walton, D. R. M.; Seconi, G.; Ricci, A.; Fiorenza, M. *J. Chem. Soc., Chem. Commun.* **1980**, 1201−1202. (d) Xin, L. H.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534−2536.
(8) (a) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77−84 and references therein. (b) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065−2084.
(9) Control experiments omitting either DBU (1,8-diazabicyclo-[5.4.0]-undecane) or **4** resulted in no product formation.
(10) Thiazolium salts such as 3-benzyl-4,5-dimethylthiazolium bromide afford no product when exogenous alcohols were omitted from the reaction.
(11) The use of benzoyltrimethylsilane (**1a**) for these reactions results in significantly reduced conversion. This observation is under investigation.
(12) For mechanistic investigations of thiazolium salts as catalysts, see: (a) Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241−8242. (b) Chen, Y. T.; Barletta, G. L.; Haghjoo, K.; Cheng, J. T.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 7714−7722 and references therein.
(13) The use of 3-octanol in the reaction affords 3-trimethylsilyloxyoctane (observed by gas chromatography), thus implicating the alcohol as the ultimate silyl acceptor. See Supporting Information for details.
(14) Replacing **1a** with PhCHO affords mainly benzoin and only 20−30% of **5**.

JA0318380