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Photoinduced Multicomponent Synthesis of α-Silyloxy Acrylamides, an Unexplored Class of Silyl Enol Ethers

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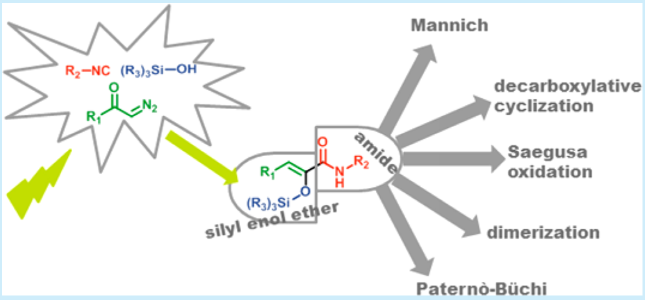
Supporting Information

ABSTRACT: The photoinduced, multicomponent reaction of α-diazoketones, silanols, and isocyanides affords α-silyloxy acrylamides, formally derived from α-keto amides. The presence of a secondary amido group makes classic preparative methods for silyl enol ethers unfeasible in this case, while the mild conditions required by this photochemical approach allow their synthesis in good yields; moreover, the general structure can be easily modified by varying each component of the multicomponent reaction. Fine-tuning of the reaction conditions (i.e., solvents, radiation, additives) can be exploited to obtain complete *Z* selectivity. The reactivity of this overlooked class of silyl enol ethers has been investigated, and features that could pave the way to new applications have been found.



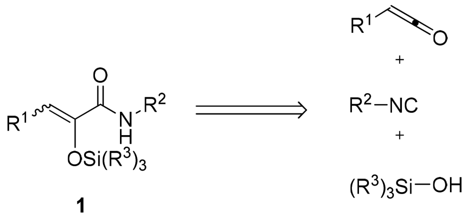
The chemistry of silyl enol ethers is now solid, and their use has grown tremendously over the years as they are valuable intermediates in a wide variety of reactions.[1] Many preparative syntheses have been developed to improve both yield and stereoselectivity; silyl enol ethers can now be prepared from a wide range of starting compounds: not only aldehydes and ketones, but also enones, esters, thioesters, and ketoesters can be conveniently transformed into this class of molecules.[2] Despite great advances in the field, preparation of these compounds from α-ketoamides remains a challenge, especially considering secondary amides bearing an acidic hydrogen. In this case, no general preparative methods are available, and a very limited number of specific preparations includes the synthesis from stable heterocyclic enol derivatives[3] and from α-phosphono-α-silyloxy amides through an olefination reaction.[4] On the contrary, α-silyloxy acrylic esters have been extensively used for the preparation of biomolecules,[5] in radical reactions,[6] or for the synthesis of α,β-unsaturated ketoesters.[7]

A general synthesis of α-silyloxy acrylamides is therefore highly desirable, and the possibility of obtaining them through a multicomponent approach attracted our interest. Based on our recent experience with photoinduced multicomponent reactions,[8] we reasoned that compounds of general formula **1** could be assembled in one pot by a combination of a ketene, an isocyanide, and a silanol (Scheme 1).

Ketenes are generally unstable compounds; nevertheless, we have recently shown that they can be efficiently generated in situ through the Wolff rearrangement of diazoketones.[9]

Silanols, on the other hand, are easily manipulated and stored, and although they are not widely used organosilicon compounds, one of the few examples of real synthetic applicability is the cross-coupling reaction of Hiyama−Denmark.[10] From a structural point of view, they are comparable to carboxylic acids, showing a dual reactivity: nucleophilic, thanks to the hydroxyl group, and electrophilic, through the silicon atom. Some silanols are commercially available, but they can be also conveniently prepared from the corresponding chlorides.[11]

Scheme 1. Retrosynthetic Scheme to α-Silyloxy Acrylamides 1



Our initial investigation began by reacting benzyldiazoketone **2a** with cyclohexyl isocyanide **3a** and triphenylsilanol **4a** under UV irradiation. Product **1a** was isolated as a mixture of geometric isomers. The choice for silanol **4a** was dictated by the mechanism postulated for the reaction: according to what is depicted in Scheme 2, substituents able to enhance the electrophilicity of the silicon atom should favor its migration (through a pentacoordinate intermediate), allowing conversion of **5** into **6** and subsequent stabilization of the product via tautomerization.

Optimization of the reaction conditions involved lamps with three different emission maxima, two different reactors, acetone or toluene as solvent, and *trans*-stilbene as additive. The results

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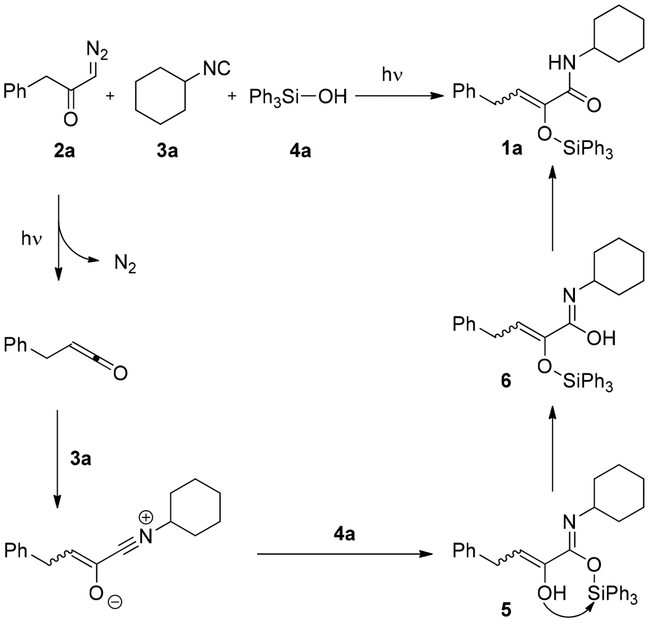
Scheme 2. Postulated Mechanism for the Three-Component Reaction of Benzyldiazoketone, Cyclohexylisocyanide, and Triphenylsilanol



are summarized in Table 1. In accordance with our previous experience,[9b] the addition of *trans*-stilbene was beneficial for the stereoselective outcome of the reaction, as this triplet quencher molecule could inhibit *Z*/*E* isomerization occurring during irradiation. This was evident by comparing entries 2 and 3, where the presence/absence of the additive strongly influenced the stereochemical ratio. The effect of *trans*-stilbene, on the other hand, was less evident when the reaction was performed at 300 or 352 nm. At 300 nm, however, its presence dramatically increased the reaction time (by comparison of entries 7 and 8), an observation that can be explained by the fact that *trans*-stilbene displays an absorption maximum at ca. 300 nm.

Table 1. Investigation of the Reaction Conditions[a]

entry	λ_{max} (nm)	solvent	reactor[b]	additive (equiv)	time (h)	yield[c] (%) (*Z*/*E*)[d]
1	254	toluene	A	1.0	6	67 (83:17)
2	254	acetone	A	1.0	6	73 (80:20)
3	254	acetone	A	0.0	6	75 (53:47)
4	352	acetone	A	0.0	24	22 (88:12)
5	352	toluene	A	0.0	16	47 (96:4)
6	352	toluene	A	1.0	24	60 (97:3)
7	300	toluene	A	0.0	5	38 (96:4)
8	300	toluene	A	1.0	22	55 (96:4)
9	300	toluene	A	0.1	6	72 (96:4)
10	300	acetone	A	1.0	28	40 (90:10)
11	300	toluene	B	0.1	9	56 (100:0)
12	300	toluene	B	0.1	14	66[e] (100:0)

[a]Reactions were performed in a Rayonet apparatus; a degassed 1:1:1 mixture of **2a**, **3a**, and **4a** (0.3 mmol each) in the solvent (3 mL) was irradiated until consumption of **2a**. [b]A = quartz; B = borosilicate glass. [c]Isolated yield after column chromatography. [d]Diastereomeric ratio determined by NMR on the crude material. [e]Reaction was scaled up to 2 mmol of diazoketone.

Toluene generally performed better than acetone (by comparison of entry 4 with 5 or entry 8 with 10), although, with more energetic radiation, results were comparable both in terms of yield and selectivity (comparison of entry 1 with 2). When the quartz test tube (A) was replaced with a reactor made of borosilicate glass (B), *Z* selectivity was complete (entry 11). Under the latter conditions, the reaction could be also scaled up without loss of selectivity and with improvement of the overall yield (entry 12). Although use of an excess of one of the three components could slightly improve the overall yield, all reactions were always performed with equimolar amounts of the reagents for a better process economy.

During further optimization studies, we also observed that when aromatic diazoketones were employed better results were obtained working at 352 nm with 0.2 equiv of *trans*-stilbene.

With these results in hand, we proceeded to investigate the scope of the reaction, employing the building blocks illustrated in Figure 1; the results are reported in Table 2.

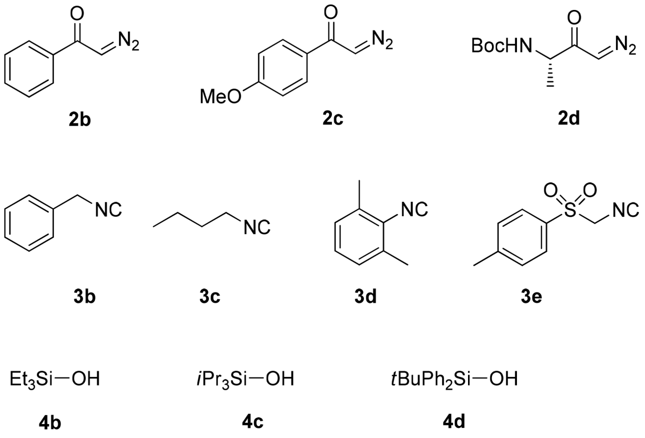


Figure 1. Building blocks employed to investigate the scope of the multicomponent reaction.

Compounds **1b**–**k** were obtained with yields ranging from moderate to good, usually with good or complete *Z*/*E* selectivities (except for entry 4). Yields were affected by partial decomposition of the products during silica-gel purification,

Table 2. Investigation of the Reaction Scope[a]

entry	diazoketone	isocyanide	silanol	product	yield[b] (%) (*Z*/*E*)[c]
1	**2b**[e]	**3a**	**4b**	**1b**	27 (98:2)
2	**2a**	**3a**	**4b**	**1c**	49 (100:0)
3	**2b**[e]	**3a**	**4a**	**1d**	80 (98:2)
4	**2c**[e]	**3a**	**4a**	**1e**	75 (67:33)
5	**2d**	**3b**	**4a**	**1f**	35 (100:0)
6	**2a**	**3d**	**4a**	**1g**	69 (93:7)
7	**2a**	**3c**	**4a**	**1h**	68 (100:0)
8	**2a**	**3e**	**4a**	**1i**	80[d] (100:0)
9	**2a**	**3a**	**4c**	**1j**	30 (100:0)
10	**2a**	**3a**	**4d**	**1k**	50 (91:9)

[a]Reactions were performed in a Rayonet apparatus; a degassed 1:1:1 mixture of **2**, **3**, and **4** (0.3 mmol each) in toluene (3 mL) was irradiated with 300 nm lamps until consumption of **2**. [b]Isolated yield after column chromatography. [c]*Z*/*E* ratio determined by NMR on the crude material. [d]Yield determined by NMR with an internal standard. [e]Reaction performed with 352 nm lamps with 0.2 equiv of *trans*-stilbene.

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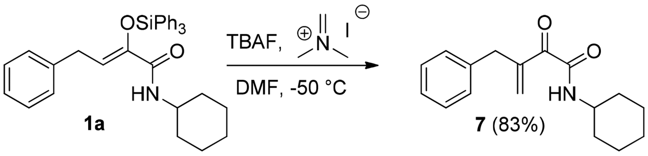
although NMRs of crude materials were usually very clean (entry 8). Triphenylsilanol **4a** usually performed better than others.

The applicability of our method was tested by subjecting compounds **1** to various reaction conditions typical of silyl enol ethers. Not surprisingly, these compounds were found to be less stable in acidic and basic conditions, compared to the corresponding *α*-silyloxy acrylesters. In fact, the higher nucleophilic character of the amidic carbonyl, compared to esters, could destabilize the neighboring silicon atom and facilitate its premature cleavage, through a transient migration to the carbonyl itself.

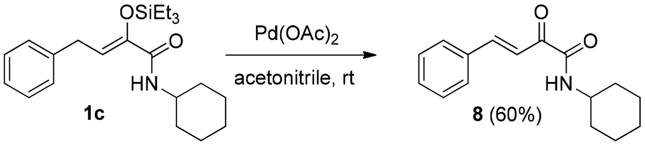
For this reason, reactions with aldehydes under Mukayama conditions failed to afford the desired products, and employment of organocatalysis afforded the aldol products in unsatisfactory yields. Nevertheless, generation of the enolate in situ with addition of TBAF was successful: Mannich reaction of **1a** with Eschenmoser's salt gave the desired elimination product **7** in 83% yield (Scheme 3); *α*,*β*-unsaturated ketoesters have been efficiently employed in asymmetrical conjugate additions[12] and cycloadditions;[13] therefore, our method offers new substrates to assemble isoxazolines,[14] carbazoles,[13] dihydropyrans,[15] or cyclic nitrones[16] with an additional amide functional group.

Scheme 3. Mannich Reaction with Eschenmoser's Salt



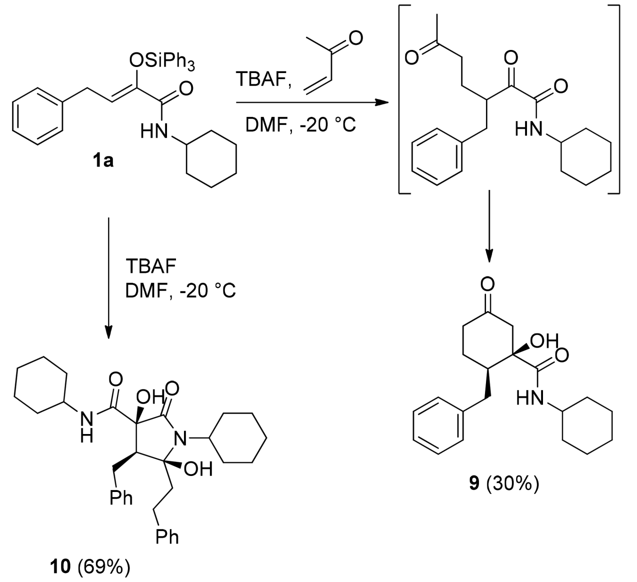
Moreover, Saegusa oxidation of **1c** with Pd(OAc)$_2$ resulted in the formation of *α*,*β*-unsaturated ketoamide **8** in 60% yield (Scheme 4). Therefore, unsaturated ketoamides **7** and **8** could be alternatively obtained by simply varying the reaction conditions.

Scheme 4. Saegusa Oxidation of Silyl Enol Ether 1c



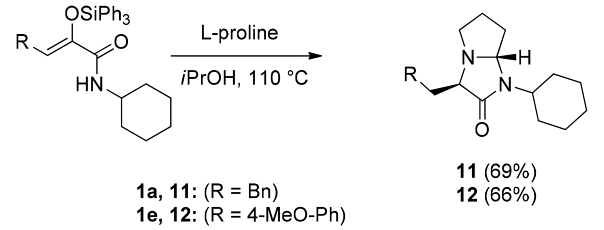
In addition, conjugate addition of **1a** with butenone gave interesting results, affording the Michael–aldol product **9** in moderate yield as the *trans* diastereoisomer (Scheme 5). Under the mild conditions developed, a competitive formation of **10** was observed, presumably derived from an aldol dimerization followed by cyclization. When butenone was not added to the reaction mixture, compound **10** was isolated as the sole product in 69% yield. Compound **10** is a simplified analogue of anchinopeptolides[17] (peptide alkaloids isolated from Mediterranean sponges), and the stereochemistry was assigned in accordance with NMR similarities with known compounds.[18] This is the first example of aldol dimerization and hemiaminal formation performed on silyl enol ethers; moreover, the complete stereoselectivity observed opens up the route to the total synthesis of these natural products and analogues.

Scheme 5. One-Pot Michael/Aldol Condensation with Butenone and Concomitant Formation of Dimerization Product 10



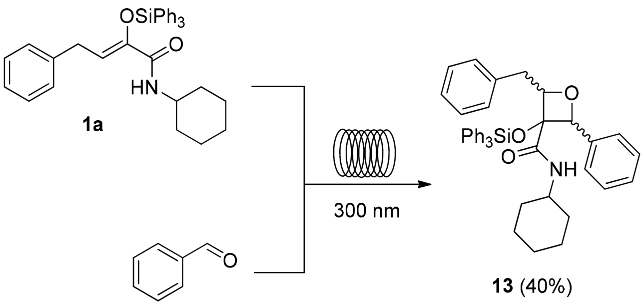
Very recently, Wu reported the decarboxylative cyclization of *α*-amino acids and *α*-ketoamides.[19] Intrigued by the possibility that compounds **1** could also undergo a similar transformation, we reacted compounds **1a** and **1e** with proline in 2-propanol at 110 °C. Tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazole-2-ones **11** and **12** were isolated with 69% and 66% yield, respectively (Scheme 6). The nature of the R group had no influence on the outcome of the reaction, and moreover, the final compounds were obtained in a completely stereoselective fashion. Noteworthy, Wu reported only one example with an aliphatic substituent in position 3 of the imidazolone ring, and in that case a dr of 10:1 was obtained. When the reactions with proline were performed directly with the *α*-ketoamide derived from **1a**, compound **11** was isolated, but in lower yield (53%). Apparently, the in situ cleavage of the silyl group was beneficial for the outcome of the reaction, possibly through a slow release of the reacting ketoamide.

Scheme 6. Decarboxylative Cyclization of Proline with Compounds 1a and 1e



Finally, we investigated the reactivity of compounds **1** in cycloaddition reactions. Silyl enol ethers have been used as substrates in [2 + 2] cycloaddition with carbonyl derivatives as a modification of the classic Paternò–Büchi reaction.[20] When compound **1a** was irradiated at 300 nm in the presence of benzaldehyde, oxetane **13** was isolated in a modest 15% yield. Notably, the resulting cycloadduct bears three stereogenic centers, an amide functional group, and a silyl protected tertiary alcohol. Moreover, by performing the reaction under continuous flow conditions, the yield was improved to 40% (Scheme 7). Regioselectivity of the reaction was complete and assigned through 2D NMR experiments; moreover, only one diastereoisomer was detected in the crude mixture. Unfortunately, NOE experiments were not conclusive to assign the correct stereochemistry, and analysis of the coupling constants in the ^{1}H NMR spectrum was fruitless. Further improvements are under investigation.

Scheme 7. Paternò−Büchi Reaction of Compounds 1a with Benzaldehyde under Continuous Flow Conditions



In conclusion, we have demonstrated that a photochemical approach and a multicomponent reaction can be fruitfully combined to afford a class of compounds that could hardly be obtained by other means. This strategy has displayed generality and versatility and has allowed the preparation of variably substituted *α*-silyloxy acrylamides. Moreover, the choice of opportune reaction conditions has led, in most of the cases, to a complete stereoselectivity in favor of the *Z* isomer. A preliminary investigation of the chemical properties of this unexplored class of compounds has shown that they possess a unique reactivity and that they can afford a variety of distinct structural motifs, including those of natural product analogues. Yields can be likely improved with further optimization of the reaction conditions, but such an issue was outside the scope of the present work. Studies are still ongoing to find more applications. In particular, by reducing the nucleophilicity of the amidic carbonyl (i.e., employing opportunely designed isocyanides), we expect to render these compounds suitable also for classic aldol reactions. The results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00009.

Experimental procedures, full characterization of new compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Rasmussen, J. K. *Synthesis* **1977**, *1977*, 91−110.

(2) (a) Chan, T. H.; Zheng, G. Z. *Tetrahedron Lett.* **1993**, *34*, 3095−3098. (b) Okabayashi, T.; Iida, A.; Takai, K.; Nawate, Y.; Misaki, T.; Tanabe, Y. *J. Org. Chem.* **2007**, *72*, 8142−8145. (c) Choi, J.; Imai, E.; Mihara, M.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *J. Org. Chem.* **2003**, *68*, 6164−6171.

(3) Crisp, G. T.; Flynn, B. L. *Tetrahedron* **1993**, *49*, 5873−5890.

(4) (a) Krafft, G. A.; Garcia, E. A.; Guram, A.; O'Shaughnessy, B.; Xu, X. *Tetrahedron Lett.* **1986**, *27*, 2691−2694. (b) Gergely, J.; Morgan, J. B.; Overman, L. E. *J. Org. Chem.* **2006**, *71*, 9144−9152.

(5) (a) Ruland, Y.; Noereuil, P.; Baltas, M. *Tetrahedron* **2005**, *61*, 8895−8903. (b) Selig, P.; Bach, T. *Synthesis* **2008**, *2008*, 2177−2182.

(6) Barton, D. H. R.; Chern, C.-Y.; Jaszberenyi, J. C. *Tetrahedron* **1995**, *51*, 1867−1886.

(7) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160−163.

(8) Garbarino, S.; Ravelli, D.; Protti, S.; Basso, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 15476−15485.

(9) (a) Basso, A.; Garbarino, S.; Banfi, L.; Riva, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 2096−2099. (b) Garbarino, S.; Banfi, L.; Riva, R.; Basso, A. *J. Org. Chem.* **2014**, *79*, 3615−3622. (c) Garbarino, S.; Protti, S.; Basso, A. *Synthesis* **2015**, *47*, 2385−2390.

(10) Denmark, S. E.; Baird, J. D. *Chem. - Eur. J.* **2006**, *12*, 4954−4963.

(11) Soderquist, J. A.; Vaquer, J.; Diaz, M. J.; Rane, A. M.; Bordwell, F. G.; Zhang, S. *Tetrahedron Lett.* **1996**, *37*, 2561−2564.

(12) Gremaud, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 794−797.

(13) Ouyang, B.; Yu, T.; Luo, R.; Lu, G. *Org. Biomol. Chem.* **2014**, *12*, 4172−4176.

(14) Noël, R.; Gembus, V.; Levacher, V.; Brière, J.-F. *Org. Biomol. Chem.* **2014**, *12*, 1245−1249.

(15) Vu, C. S.; Guisot, N.; Guillarme, S.; Martel, A.; Dujardin, G.; Pipelier, M.; Dubreuil, D.; Saluzzo, C. *Eur. J. Org. Chem.* **2012**, *2012*, 3727−3731.

(16) Zhang, S.; Xu, K.; Guo, F.; Hu, Y.; Zha, Z.; Wang, Z. *Chem. - Eur. J.* **2014**, *20*, 979−982.

(17) Casapullo, A.; Minale, L.; Zollo, F.; Lavayre, J. *J. Nat. Prod.* **1994**, *57*, 1227−1233.

(18) Snider, B. B.; Song, F.; Foxman, B. M. *J. Org. Chem.* **2000**, *65*, 793−800.

(19) Wu, J.-S.; Jiang, H.-J.; Yang, J.-G.; Jin, Z.-N.; Chen, D.-B. *Tetrahedron Lett.* **2017**, *58*, 546−551.

(20) Vogt, F.; Jödicke, K.; Schröder, J.; Bach, T. *Synthesis* **2009**, 4268−4273.