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A reinvestigation of the reaction of allylsilanes with *N*-phenyltriazolinedione: stereoselective synthesis of substituted urazoles by [3+2] cycloaddition

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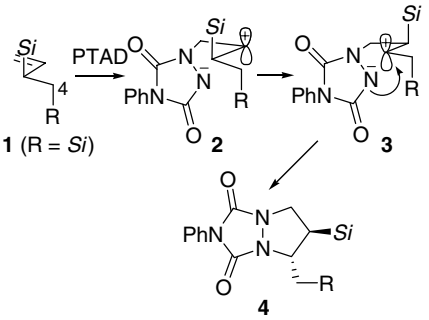
Abstract—A stereoselective synthesis of hydroxy substituted urazoles of potential biological significance has been developed via the [3+2] annulation of α-substituted allylic silanes with *N*-phenyltriazolinedione. The need for complete blocking of the α-CH_2 group of allylsilanes for successful [3+2] annulation, as reported previously, is found to be unnecessary.

The [3+2] annulation reactions of allylsilanes have received significant attention because they provide stereoselective methods for the synthesis of both carbo- and heterocyclic ring systems of biological significance.[1,2] The earliest example of heterocycle synthesis via a [3+2] annulation process was reported by Butler and co-workers who were investigating the reaction of allylsilanes with *N*-phenyltriazolinedione (PTAD).[3] In addition to the expected H-ene and M-ene (Hosomi–Sakurai) products, a minor by-product, a urazole was identified as a [3+2] type cycloadduct. Later observations by Davies and co-worker were consistent with this early report in that allylsilanes do react principally by the H-ene process;[4] however, a switch to [3+2] cycloaddition from the classical H-ene reaction was shown to be possible by replacing silicon with a more electropositive metal, such as germanium. Additionally, this group also reported a single example of exclusive cycloaddition by using an allylsilane whose α-CH_2 group was completely methylated so as to preclude any H-ene type reaction. This synthesis of heterocycles was not pursued further, although substituted urazoles displaying anti-inflammatory or immunosuppressive properties and which are, in principle, obtainable by a [3+2] annulation have been made by multi-step sequences.[5] In continuation of our studies on exploring the synthetic potential of various bimetallic reagents of silicon,[6] we report here that the [3+2] annulation of α-substituted allylsilanes with PTAD is an efficient and stereoselective method for the synthesis of substituted urazoles.

When exposed to powerful electrophilic species, for example, PTAD, 1-silylmethyl allyl silane **1** (R = Si) should form **3** via the rapid 1,2-shift of the silyl group in **2** (Scheme 1). Intermediate **3** is highly stabilized with silicon–carbon bonds overlapping with the empty *p*-orbital on both surfaces of the sp^2 hybridized carbon, thus driving the rearrangement step without any need for nucleophilic participation.[7,8] Cyclization of intermediate **3** anti to the silyl group then gives the cycloadduct **4**. Arguably, if the reaction follows this course, ene and Hosomi–Sakurai type by-products will not form.

Indeed, when 1-silylmethyl allyl silane of type **5a**[6] was exposed to PTAD at room temperature in dichloro-



Scheme 1. Reaction of **1** with PTAD. Si = silyl group.

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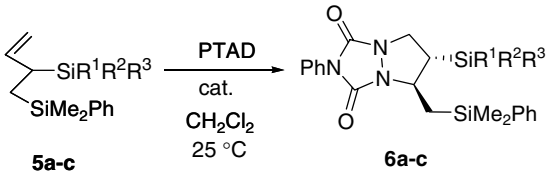
methane, urazole **6a** was formed in 65% yield,[9] the product of a formal [3+2] annulation (Table 1). However, with bulkier silyl appendages, as in the cases of **5b**,**c**[10] no reaction occurred under these conditions and the allylsilanes were recovered unscathed. In these cases, successful [3+2] annulation required Lewis acid activation. Thus, in the presence of $LiClO_4$-doped silica gel as catalyst,[11] the urazoles **6b**,**c** were obtained in moderate yields.[9] No trace of any H-ene or M-ene (Hosomi–Sakurai) products could be detected in the crude products by NMR spectroscopy in all these cases.

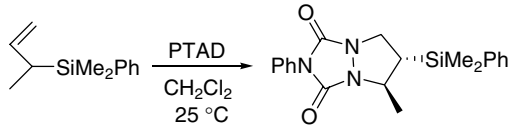
Table 1. Reaction of 1-silylmethylallyl silanes with PTAD



5a-c **6a-c**

Compound	R^{1-3}	Catalyst	Yield[a] (%)
a	$R^1 = R^2 = Me$; $R^3 = Ph$	None	65
b	$R^1 = R^2 = R^3 = Ph$	None	0
b	$R^1 = R^2 = R^3 = Ph$	$LiClO_4$–SiO_2	48
c	$R^1 = R^2 = Ph$; $R^3 = Bu^t$	None	0
c	$R^1 = R^2 = Ph$; $R^3 = Bu^t$	$LiClO_4$–SiO_2	46

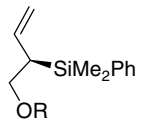
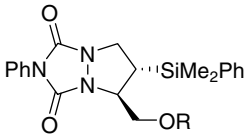
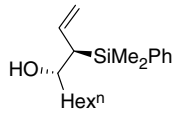
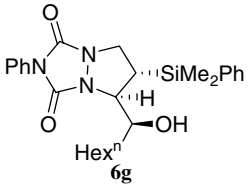
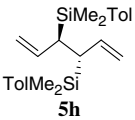
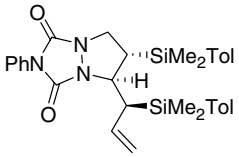
[a] Yields reported for material after column chromatography.



5d **6d**, 80%

Scheme 2. Reaction of allylsilane **5d** with PTAD.

Table 2. [3+2] Annulation of allylsilanes **5** with PTAD to yield urazoles **6**

Allylsilane **5**	Product **6**	Yield[a,b] (%)
		
5e (R = H), 76% ee[c] **5f** (R = TBDPS)	**6e** (R = H), 70% ee[c] **6f** (R = TBDPS)	72 70
 **5g**	 **6g**	62
 **5h**	 **6h**	80

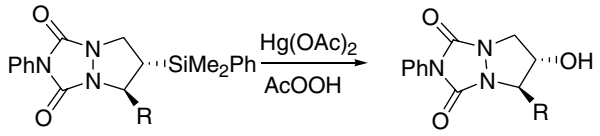
[a] All reactions were carried out in dichloromethane at room temperature; no catalytic activation was required.
[b] Isolated yield of pure material.
[c] Enantiomeric excess determined by Mosher ester analysis.[21]

Hence, our prognosis as outlined in Scheme 1 apparently turned out to be correct. Nevertheless, we felt the need to address an important issue at this point. For the observed selectivity do we really need the silyl substituent at C-4 in **1** or is an alkyl substituent enough to trigger the 1,2-shift[12] to generate a reasonably stable β-silyl carbocation (cf. R = H in **3**), which may collapse to **4**? This led us to subject the readily available allylsilane **5d**[13] to the same reaction conditions, which gave the urazole **6d** as a single diastereomer (Scheme 2) in high yield (80%).[9] This reaction required no catalytic activation and there were no traces of any H-ene or M-ene type products in the crude product.[14]

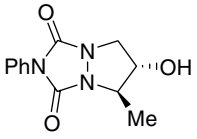
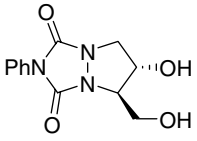
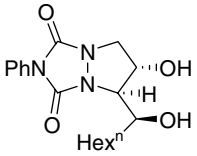
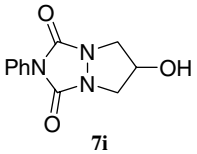
We concluded at this juncture that Davies' and co-worker[4] blocking of the α-CH_2 group of the allylsilane by methylation in order to prevent any H-ene type reaction from occurring, was completely unwarranted.

Encouraged by these findings we set out to investigate the scope of this highly diastereoselective urazole syn-

Table 3. Tamao–Fleming oxidation of urazole **6**



6 **7**

Urazole **6**	Product **7**	Yield[a,b] (%)
6d	 **7d**	52
6e	 **7e**	50
6g	 **7g**	35
6i	 **7i**	55

[a] Isolated yield of pure material.
[b] Racemic **7e** was obtained from **6a** in 48% yield under these conditions.

thesis, the results of which are presented in Table 2. The annulation of enantio-enriched allylsilane **5e**[15] occurred with the retention of enantiomeric purity to give **6e** in 72% yield.[9,16] This example shows the scope of the reaction for the synthesis of optically active urazoles. In an attempt to enhance the yield in the reaction of **5e** with PTAD, the corresponding silyl ether **5f** was also subjected to the same reaction conditions. Urazole **6f** was formed, but no improvement in yield occurred.[9] The more elaborate allylsilane **5g**[17,18] yielded urazole **6g**[18] containing three stereogenic centers as a single diastereomer.[9] These reactions (**5e–g–6e–g**) are remarkable in light of the sluggish reactivity reported for cyclic β-hydroxyallylsilanes in [3+2] annulations with chlorosulfonyl isocyanate.[19] The bis-allylsilane **5h**,[20] similarly, gave urazole **6h** containing a useful allylsilane functionality in 80% yield, also as a single diastereomer.[9] In all the cases presented in Table 2, no traces of any competing H-ene or M-ene type products were formed.

The substituted urazoles **6** synthesized via the [3+2] annulation methodology provide access to the corresponding hydroxylated urazoles **7** by Tamao–Fleming oxidation of the corresponding silicon–carbon bonds (Table 3).[22]

In conclusion, this work indicates that a limitation encountered by others[3,4] in the [3+2] cycloaddition reaction of allylsilanes with PTAD is not as serious as had been thought. More importantly, this work shows that allylsilanes with a single substituent at the allylic carbon undergo exclusive [3+2] annulation to provide rapid access to hydroxy substituted urazoles of potential pharmacological importance.

Acknowledgement

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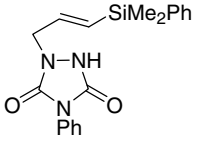
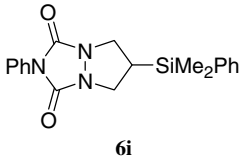
References and notes

1. For recent references on [3+2] annulation reaction of allylsilanes, see: (a) Va, P.; Roush, W. R. *J. Am. Chem. Soc.* **2006**, *128*, 15960–15961; (b) Romero, A.; Woerpel, K. A. *Org. Lett.* **2006**, *8*, 2127–2130; (c) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R.-A. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245–4248.
2. For reviews on cycloaddition reactions of allylsilanes, see: (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293–1316; (b) Knölker, H.-J. *J. Prakt. Chem.* **1997**, *339*, 304–314; (c) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192; (d) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173–3199.
3. Ohashi, S.; Ruch, W. E.; Butler, G. B. *J. Org. Chem.* **1981**, *46*, 614–619.
4. Cai, J.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1743–1746.
5. Launay, M.; Potin, D.; Maillet, M. J. B.; Nicolai, E. A.; Iwanowicz, E. J.; Dhar, T. G. M. PCT Int. Appl. 2002, 44pp. , WO 2002094186.
6. Sarkar, T. K.; Haque, S. A.; Basak, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1417–1419.
7. Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2711–2720.
8. Davis, D. D.; Jackocks, H. M. *J. Organomet. Chem.* **1981**, *206*, 33–47.
9. *General procedure for the [3+2] annulation reaction of PTAD with substituted allylsilanes:*
Procedure A. To a stirred 1 M solution of PTAD (2.5 mmol) in CH_2Cl_2 was added dropwise a solution of the allylsilane (1 mmol) in CH_2Cl_2 at room temperature. The reaction was monitored by TLC. After the completion of the reaction, the solvent was removed under reduced pressure and the crude product was subjected to flash chromatography to give the desired product.*Procedure B*. To a stirred 1 M solution of PTAD (2.5 mmol) in CH_2Cl_2 was added dropwise a solution of the allylsilane (1 mmol) in CH_2Cl_2 at room temperature. To this mixture was added a catalytic amount of $LiClO_4$–SiO_2. The reaction was monitored by TLC. After the completion of the reaction, the solvent was removed under reduced pressure and the crude product was subjected to flash chromatography to give the desired product.
10. Compounds **5b**, **c** were prepared following a similar procedure to that reported for **5a**.[6]
11. Sarkar, T. K.; Nandy, S. K.; Ghorai, B. K.; Mukherjee, B. *Synlett* **1996**, 97–99.
12. Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434–1435, and references cited therein.
13. Fleming, I.; Waterson, D. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1809–1813.
14. That substitution at the allylic carbon necessary for favored [3+2] annulation is shown by independent studies with allyldimethylphenylsilane and PTAD, which gave the major H-ene product **8** (40%) along with the minor urazole **6i** (20%) and the M-ene product (not isolated, but characterized by ^{1}H NMR of the crude reaction product).



8



6i

15. Prepared from [(*E*)-γ-(dimethylphenylsilyl)allyl]diisopinocampheylborane and formaldehyde gas, see: Roush, W. R.; Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41*, 9413–9417.
16. This example shows that both β-silyl carbocation intermediates **2** and **3** must be configurationally stable even at room temperature; see also Ref. 12.
17. Allylsilane **5g** was prepared by Roush's method, see Ref. 15.
18. Optical purity of this compound was not determined.
19. Roberson, C. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 11342–11348.
20. Bis-allylsilane **5h** was prepared by complete reduction of the known diester, dimethyl (3*RS*,4*SR*)-3,4-bis[dimethyl-(4-methylphenyl)silyl]hexane-1,6-dioate[7] with LAH followed by double Grieco dehydration.[13]
21. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
22. Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317–337.