Pergamon

Tetrahedron Letters 42 (2001) 9175–9178

TETRAHEDRON LETTERS

Homo-Brook route to benzazocenols and congeners via allylsilane-derived aziridines

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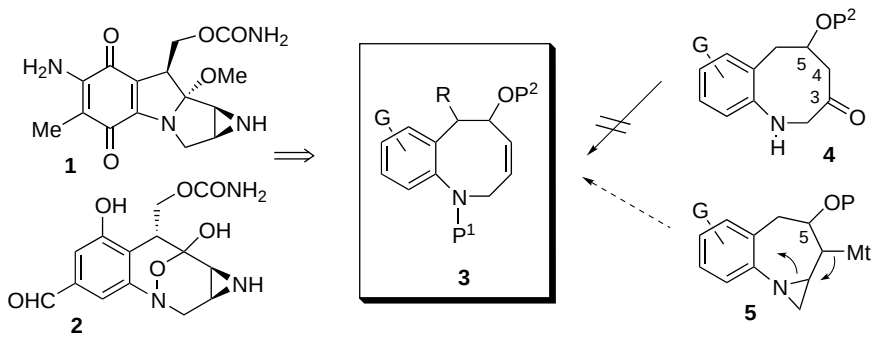
Received 24 October 2001; accepted 25 October 2001

Abstract—We describe a concise entry to benzazocenols intermediates for mitomycinoids via a homo-Brook rearrangement–ring opening sequence of a silylated aziridine. The latter is obtained by intramolecular 1,3-dipolar cycloaddition of an azide with an allylsilane, followed by irradiation of the resulting triazoline. © 2001 Elsevier Science Ltd. All rights reserved.

The antitumor agents, mitomycin C, **1**,[1] FR900482 **2**,[2] and congeners ('mitomycinoids') have been the subject of many synthetic investigations.[3] Even so, much opportunity remains for the development of improved routes to these molecules. A method for the rapid assembly of benzazoc-3-enes **3** (Scheme 1) would be particularly useful in that respect, given the recognized value of **3** as precursors to **1** and **2**.[2a,3a] The known benzazocinones **4**[4] would advance to **3** if their C-3 ketone could be parlayed into a $\Delta^{3,4}\sigma$ bond. Unfortunately, conversion of **4** to **3** proved to be unfeasible.[5] An alternative forerunner of **3** could be **5**, if metallic substituent Mt were to promote selective rupture of the strained aziridine ring, rather than elimination of the C-5 group. We now report that this transformation may be accomplished when $Mt = Si(Me)_3$.

o-Azidophenyl acetaldehyde reacted with complex **6**[6] to give **8** as a single diastereomer. The stereochemical outcome of this process is consistent with a cyclic transition state model (cf. **7**, Scheme 2). Mild thermolysis of **8** induced a fully diastereoselective 1,3-dipolar cycloaddition that yielded triazoline **9**. The structure of this intermediate was confirmed by single-crystal X-ray crystallography,[7a] thus also defining the relative stereochemistry of **8**. Smooth dediazoniation occurred upon irradiation of **9** (550W Hanovia lamp) in benzene. The structure of the resultant aziridine **10** was also confirmed by X-ray crystallography.[7b] Allylsilane-derived aziridines are known only as the corresponding *N*-carbethoxy derivatives.[8] These species are rather unstable and undergo acid-catalyzed rearrangement to a mixture of *N*-(ethoxycarbonyl)allylamines and 2-ethoxyoxazoli-



Scheme 1.

Keywords: allylsilanes; antitumor agents; azides; aziridines; heterocycles; mitomycinoids.

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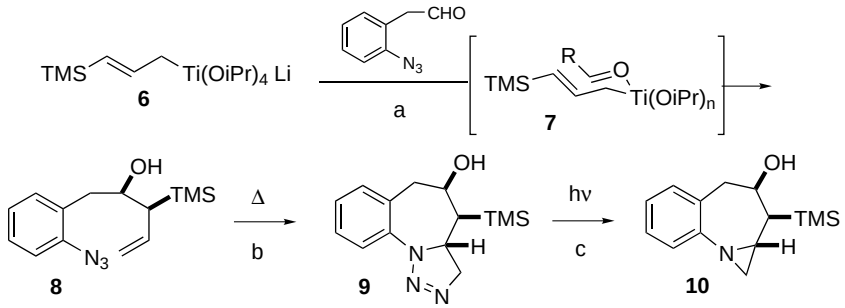
PII: S0040-4039(01)02018-4



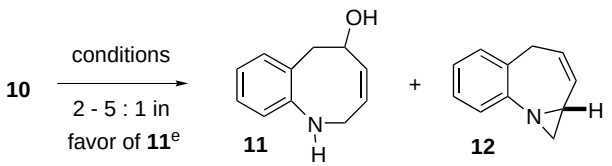
Scheme 2. (a) THF, −78°C, 65%. (b) Toluene, reflux, 3 h, 90%. (c) Benzene, rt, 15 min, 77%.

nes even upon contact with silica gel.[8b–8d] By contrast, no information is available in the literature regarding the chemical behavior of silylated *N*-aryl aziridines such as **10**, which we found to be quite stable. No reaction occurred upon prolonged refluxing of **10** in toluene, or upon contact with aq. HCl, 48% aq. HF, or HF–pyridine complex at 25°C, fortunately, exposure to TBAF or Bu_4NOH in DMF at −20°C (Table 1, entries c and d) promoted conversion to a mixture of desired azocenol **11** (major product) and Peterson olefin **12**.

The mechanistic aspects of this transformation are significant. The reaction proceeded well only when the OH group in **10** was free. Derivative **13** of **10** (Scheme 4) resisted the action of TBAF, whereas acetate **14** gave only the Peterson olefin **12**. Furthermore, acetate elimination required several hours at 25°C, whereas **10** was converted to the mixture of **11** and **12** in 10 min under the same conditions. Aziridine cleavage is not likely to occur by an *anti* elimination, because this would lead to an extremely strained *trans*-benzazocenol **15**. Although subsequent isomerization to **11** could occur, it is doubtful that an intermediate as energetic as **15** is involved here. The above observations are more consistent with a mechanism for aziridine cleavage that involves a preliminary 'homo-Brook' rearrangement leading to an anionic species such as **17**, which ultimately fragments to **11**. Thus, the main function of the fluoride ion contributed by TBAF is probably that of a base for the (reversible) deprotonation of the OH group (cf. **16**, Scheme 3). In support of this surmise, we found that various bases in aprotic media induce conversion **10** to **11** (Table 1), whereas no reaction occurred with TASF (entry a), a less basic source of F^- than TBAF, or with bases in protic solvents (entry g). Reaction of **10** with *t*BuOK in DMF at −20°C produced olefin **18** (Scheme 4), which may result via base-catalyzed rearrangement of **12**. Remarkably, *t*BuONa under identical conditions induced formation of the expected mixture of **11** and **12** (ca. 2:1 ratio), but in lower yield than the weaker bases of Table 1. It is surprising that the significance of the homo-Brook reaction, first described by Hudrlik in 1982,[9] appears to have been largely overlooked in the intervening time.

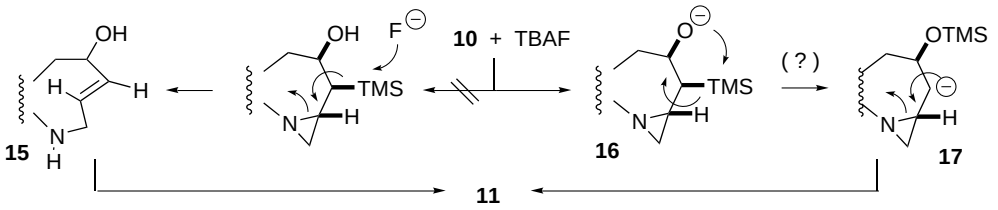
The same reaction sequence produced benzazepenol **22** from 2-azidobenzaldehyde (Scheme 5), but two limitations emerged from studies with aliphatic aldehydes **23** and **26**. Reaction with **6** occurred normally in both cases, but **26** led to **27**, which resisted cyclization even at 180°C. Evidently, a rigidifying element such as an aryl nucleus is required to ensure a favorable juxtaposition of azide and olefin, if the cycloaddition step leads

Table 1. Desilylative cleavage of aziridine **10** to benzazocenol **11**

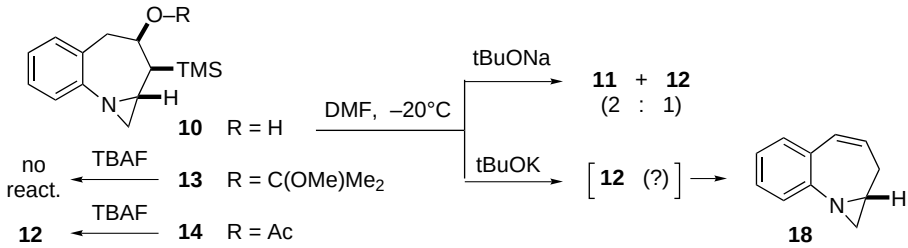


Entry	a	b	c	d	e	f	g	h	i
Conditions	2.5 equiv. TASF[b] DMF rt 12 h	3 equiv. TBAF[c] DMF rt 10 min	3 equiv. TBAF[c] DMF −20°C 1.5 h	1.5 equiv. Bu_4NOH[d] DMF −20°C 30 min	1.5 equiv. Bu_4NOH[d] MeCN −20°C 30 min	1.5 equiv. Bu_4NOH[d] Et_2O −20°C 1 h	1.5 equiv. Bu_4NOH[d] MeOH rt 12 h	3 equiv. CsOH DMF −20°C 30 min	10 equiv. LiOH DMF rt 12 h
Yield of **11**[a]	No reaction	31%	49%	46%	41%	30%	No reaction	30%	No reaction

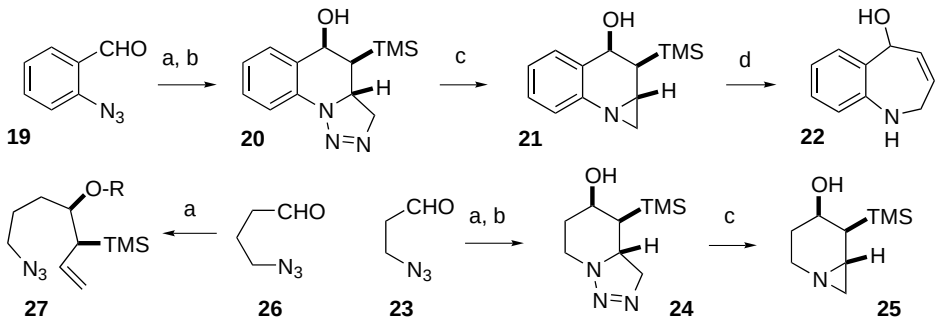
[a] Chromatographed yield.
[b] Tris(dimethylamino)sulfonium difluorotrimethylsilicate.
[c] Trihydrate.
[d] 40% in water.
[e] The observed ratio of **11** to **12** (^{1}H NMR) was somewhat variable because **12** appears to decompose upon prolonged reaction time or contact with silica gel.



Scheme 3.



Scheme 4.



Scheme 5. (a) **6**, THF, −78°C, 90% with **19**; 65% with **23**; 70% with **26**. (b) For **20**: toluene, 90°C, 1 h, 78%; for **24**: toluene, reflux, 3 h, 75%. (c) *hv*, benzene, rt, 15 min, 83% for **21**; 70% for **25**. (d) TBAF, DMF, rt, 32%.

to a medium-sized ring. Aldehyde **23** did afford the expected aziridine **25**, which, however, resisted fragmentation. It thus appears that the N atom must be connected to a group that can disperse developing negative charge during N–C bond cleavage.

In summary, the silicon-directed opening of allylsilane-derived aziridines seems to provide a practical alternative to existing methods for the preparation of medium-ring nitrogen heterocycles.[1–4] Synthetic applications of the new chemistry will be reported in due course.

Acknowledgements

We thank the MENRT (Fellowship to R.D.), the CNRS, and the Région Rhône-Alpes, for support of our research. N.C. is a fellow of the Sokrates-Erasmus Program. M.A.C. is the recipient of a Merck & Co. Academic Development Award (2000, 2001).

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