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Aziridines in one step from hydantoins via Red-Al mediated ring-contraction

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ABSTRACT

We have developed a new method to synthesize aziridines from their corresponding hydantoins in one step using an excess of Red-Al overnight in refluxing toluene. This allows direct access to *N*–H aziridines without the need for protecting group strategies.

Aziridines are of importance in organic chemistry as intermediates[1] within heterocyclic chemistry, medicinal chemistry and total synthesis. Indeed, there are registered drugs bearing the azirdine motif.[1c,2] Synthetic routes leading directly to unprotected aziridines (**3**, $R^3 = H$) are considered especially attractive,[3] but occur significantly less often in the literature than routes containing protection group strategies. As a recent example of development in this area, Xu and co-workers described an improved Wenker reaction, starting from vicinal amino alcohols to give *N*–H aziridines.[4]

During recent work, we were investigating the reduction of hydantoins **1**, which are easily obtained according to well-established methods from either ketones[5] or 1,2-diketones,[6] in order to obtain 2-imidazolidinones **2** to be used in further functionalizations. The transformation of **1** into **2** is well-known, and is typically carried out using a strong reducing agent, such as lithium aluminum hydride (LAH), sometimes in combination with aluminum chloride.[7] Owing to its preferable safety margins and ease of handling, we turned our attention to the commercial 3.5 M solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (Red-Al), which has comparable, but not identical reducing properties to LAH,[8] and which has been used to furnish a 2-imidazolidinone **2** from a hydantoin **1** under conditions strikingly similar to ours.[9]

However in our hands, attempted reductions with Red-Al often resulted in the appearance of a curious by-product in varying proportions. Typically, longer reaction times, elevated temperatures and the use of an excess of Red-Al seemed to favor the formation of this by-product, which we came to identify as aziridine **3**.

Intrigued by these findings, we proceeded to investigate the possibilities of steering the reaction so that it would consistently give aziridine as the major product. It should be noted that until now transformation of hydantoin **1** into the corresponding aziridine **3** is a three- or four-step endeavor, thereby making our new protocol an attractive shortcut. We herein present our preliminary results on a one-step Red-Al mediated reduction/ring-contraction of hydantoins **1** to directly give aziridines **3**, a reaction which to the best of our knowledge has not been reported before. Undemanding access to compounds of this type (2,2-bis-functional N–H aziridines), which occur sparsely in the literature,[10] would potentially be of benefit to chemists in the field.

We chose 5,5-diphenylhydantoin (phenytoin) as the first substrate due to its ready availability and the fact that treatment with Red-Al would directly provide *N*-H aziridine. Encouragingly, we quickly discovered expedient conditions under which the desired aziridine **3** could be isolated and subsequently characterized as the major product (Table 1, entries 1–3).[11]

When one phenyl group was exchanged for a methyl group (entries 4–7), however, the reaction was considerably slower. We tentatively propose that this is due to a less stabilized carbo-cation intermediate (vide infra). When the second phenyl group was exchanged for a methyl group ($R^1 = CH_3$, $R^2 = CH_3$, $R^3 = H$; not depicted), the reaction did not produce any aziridine at all, even after several days at reflux. When the imide-nitrogen of **1** was substituted with a methyl or benzyl group ($R^3 = CH_3$ or $R^3 = Bn$), the reaction was much more rapid and could be performed in a shorter time and at a lower temperature (entries 8–10). Under the conditions described, aryl bromides and aryl chlorides were, somewhat disappointingly, fully dehalogenated (not depicted), despite literature claims of the inertness of Red-Al toward these.[8]

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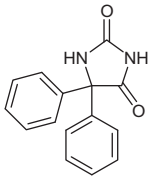
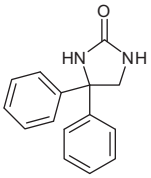
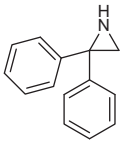
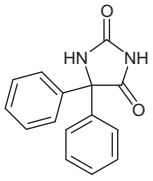
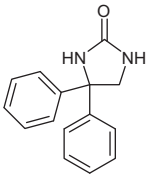
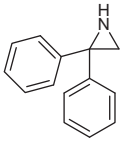
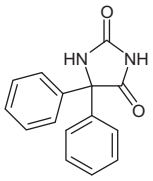
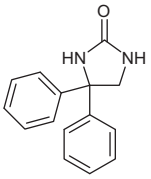
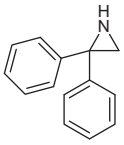
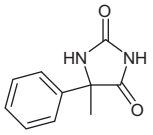
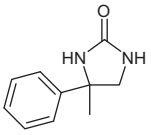
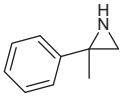
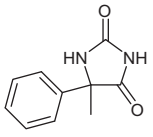
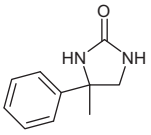
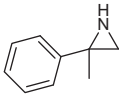
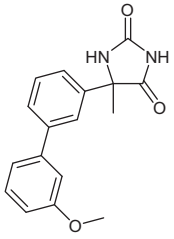
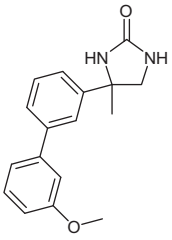
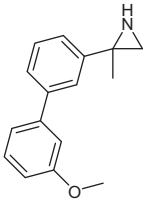
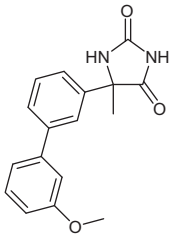
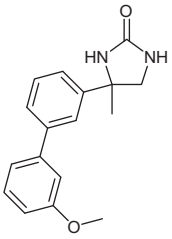
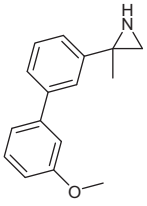
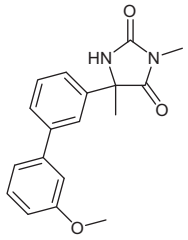
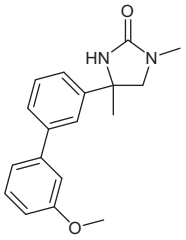
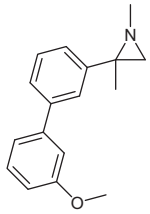
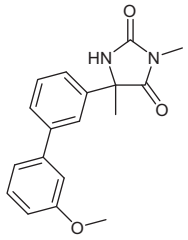
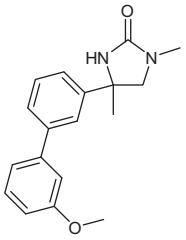
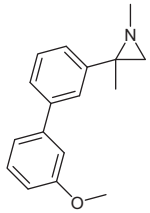
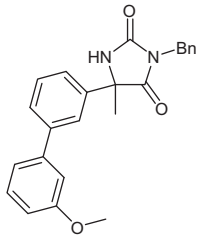
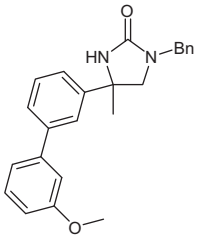
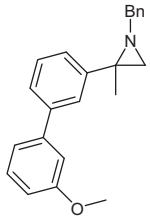
Table 1
Conditions and product distribution via Scheme 1

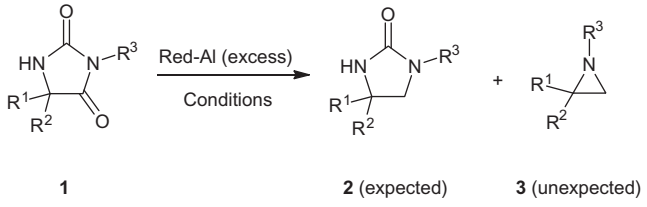
Entry	Starting material **1**	Red-Al (equiv)	Time (h)	Temp[a] (°C)	Yield of **2**[b]	Yield of **3**[b]
1		3.5	1	100	 (70%)	 (30%)
2		4.0	20	Reflux	 (30%)	 (70%)
3		5.0	24	Reflux	 (<20%)	 68% isolated
4		5.0	5	Reflux	 57% isolated	 (0%)
5		5.0	24	Reflux	 (0%)	 (100%)
6		5.0	1	reflux	 71% isolated	 (0%)
7		5.0	24	Reflux	 (60%) 32% isolated	 (40%) 15% isolated

(*continued on next page*)

Table 1 (*continued*)

Entry	Starting material **1**	Red-Al (equiv)	Time (h)	Temp[a] (°C)	Yield of **2**[b]	Yield of **3**[b]
8		5.0	6	55	 33% isolated	 (>50%)
9		5.0	0.5	Reflux	 (0%)	 (100%)
10		5.0	6	55	 48% isolated	 (40%)

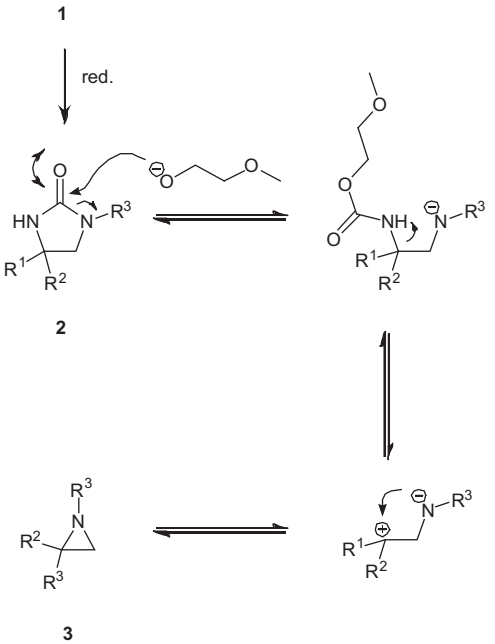
[a] External oil bath temperature. 'Reflux' was oil bath set to 120 °C.
[b] Yields within parentheses were determined by LCMS or GCMS (at full conversion of the starting material).



Scheme 1. Synthesis of aziridines **3** directly from hydantoins **1.**

In conclusion, several hydantoins **1** on treatment with an excess of Red-Al (typically 5 equiv) under reflux for 0.5–24 h, gave aziridines **3** as the major products. Isolated yields were considerably higher when an ion-exchange column was employed in the work-up, as opposed to traditional silica column chromatography.

The exact mechanism for this reaction is at this stage not fully understood. In all cases, 2-imidazolidinones **2** were detected as intermediates, but at no point were imidazolidines observed, which would be the case if the second carbonyl had been reduced. When phenytoin (**1**, R^1 = Ph, R^2 = Ph, R^3 = H) in a separate experiment was treated with 10 equiv of DIBAL-H in toluene, under otherwise identical conditions (reflux overnight), 2-imidazolidinone **2** was obtained as a single product, according to LCMS.



Scheme 2. A proposed mechanism.

Subsequent addition of sodium ethoxide (excess) to the crude reaction mixture together with additional heating did lead to some aziridine formation (approx. 20%). This leads us to believe that Red-Al serves firstly as a reducing agent and secondly as an alkoxide base. Aluminum complexation at some stage of the reaction is also conceivable. Thus we tentatively propose the following mechanism (Scheme 2). The driving force for aziridine formation might be consumption of the leaving group by Red-Al, pushing the equilibrium toward product formation.

The scope, limitations, applicability, possible stereochemical control and functional group tolerance of the herein reported reaction are currently under investigation and the outcomes will be communicated separately.

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References and notes

1. (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619; (b) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743; (c) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194–206.
2. For example see: The mitomycin family as chemotherapeutic agents, see: (a) Danshiitsoodol, N.; de Pinho, C. A.; Matoba, Y.; Kumagai, T.; Sugiyama, M. *J. Mol. Biol* **2006**, *360*, 398–408; Thiothepa, also a chemotherapeutic agent, see: (b) van Maanen, M. J.; Smeets, C. J. M.; Beijnen, J. H. *Cancer Treat. Rev.* **2000**, *26*, 257–268.
3. Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7185–7194.
4. Li, X.; Chen, N.; Xu, J. *Synthesis* **2010**, 3423–3428.
5. For recent examples, see: (a) Stilz, H. U.; Guba, W.; Jablonka, B.; Just, M.; Klingler, O.; Koenig, W.; Wehner, V.; Zoller, G. *J. Med. Chem.* **2001**, *44*, 1158–1176; (b) Chruma, J. J.; Liu, L.; Zhou, W.; Breslow, R. *Bioorg. Med. Chem.* **2005**, *13*, 5873–5883; (c) Czopek, A.; Byrtus, H.; Kolaczkowski, M.; Pawlowski, M.; Dybala, M.; Nowak, G.; Tatarczynska, E.; Wesolowska, A.; Chojnacka-Wojcik, E. *Eur. J. Med. Chem.* **2010**, *45*, 1295–1303.
6. For recent examples, see: (a) Muccioli, G. G.; Poupaert, J. H.; Wouters, J.; Norberg, B.; Poppitz, W.; Scriba, G. K. E.; Lambert, D. M. *Tetrahedron* **2003**, *59*, 1301–1307; (b) Riedner, J.; Vogel, P. *Tetrahedron: Asymmetry* **2004**, *15*, 2657–2660; (c) Safari, J.; Naeimi, H.; Ghanbari, M. M.; Sabzi Fini, O. *Russ. J. Org. Chem.* **2009**, *45*, 477–479; (d) Hashmi, I. M.; Aslam, A.; Ali, S. K.; Ahmed, V.-U.; Ali, F. I. *Synth. Commun.* **2010**, *40*, 2869–2874.
7. (a) Marshall, F. J. *J. Am. Chem. Soc.* **1956**, *78*, 3696–3697; (b) De la Cuesta, E.; Ballesteros, P.; Trigo, G. G. *Heterocycles* **1981**, *16*, 1647–1650; (c) Reinhard, S.; Schnur, R. C.; Belletire, J. L.; Peterson, M. J. *J. Med. Chem.* **1998**, *31*, 230–243; (d) Reichard, G. A.; Stegone, C.; Paliwal, S.; Mergelsberg, I.; Majmundar, S.; Cheng, T.; Tiberi, R.; McPhail, A. T.; Piwinski, J. J.; Shih, N.-Y. *Org. Lett.* **2003**, *5*, 4249–4251.
8. Gugelchuk, M.; Silva, L. F., III; Vasconcelos, R. S.; Quintiliano, S. A. P. Sodium bis(2-methoxyethoxy)aluminum hydride. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 2007. doi:10.1002/047084289X.rs049.pub2. and references cited therein.
9. Marquez, V. E.; Twanmoh, L.-M.; Wood, H. B., Jr.; Driscoll, J. S. *J. Org. Chem.* **1972**, *37*, 2558–2561.
10. A SciFinder search conducted on April 11, 2011 on 2,2-diphenylaziridines with 1- and 3-positions blocked from further substitution resulted in a hit list of only six compounds.
11. *A representative experiment:* 2,2-diphenylaziridine (**3**; R^1 = Ph, R^2 = Ph, R^3 = H): To a stirred slurry of 5,5-diphenylhydantoin (1 mmol, 254 mg) in dry toluene (1 mL) under argon at rt was added Red-Al in toluene (3.5 M, 5 mmol, 1.43 mL) over 20 min. ***CAUTION****: excessive foaming, gas and heat evolution!* When the initial reaction had subsided, the temperature was slowly increased to reflux (oil bath at 120 °C) and the mixture maintained at this temperature for 24 h. The mixture was cooled to 0 °C and the reaction quenched by careful addition of aqueous NaOH (2 M, 5 mL), followed by CH_2Cl_2 (5 mL). The resulting biphasic mixture was stirred at rt for 1 h before the organic phase was separated (Sorbent Phase Separator) and evaporated. The residue was slurried in MeOH (5 mL) and added to a 6 cc PoraPak Rxn CX Retained Base column. The column was flushed with methanol (10 mL), after which the product was eluted with methanolic NH_3 (7 M, 10 mL). The collected fraction was evaporated to give oil, which under high vacuum gave a white solid. Yield: 132 mg (68%).^{1}H NMR (500 MHz, DMSO-d_6) δ 1.96 (s, 2H), 3.26 (s, 1H), 7.10–7.41 (m, 10H)^{13}C NMR (125 MHz, $CDCl_3$) δ 29.1, 46.5, 126.4, 127.6, 128.0, 145.3MS (ES): *m*/*z* $[M+H]^+$ 196.1 (100) HRMS: *m*/*z* calcd for $C_{14}H_{14}N$ $[M+H]^+$: 196.1126; found: 196.1129.