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Facile cyclization of amidyl radicals generated from *N*-acyltriazenes

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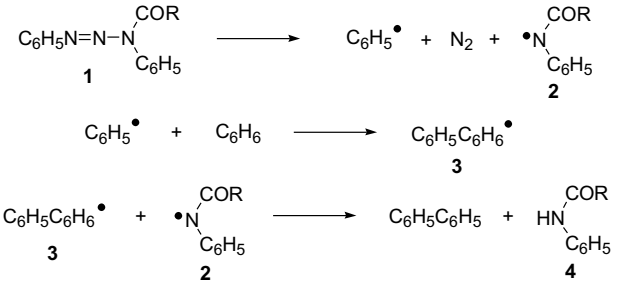
Abstract—*N*-Acyltriazenes serve as a tin-free and initiator-free source for amidyl radicals. Thermal decomposition of *N*,*N*′-diaryl-*N*-(4-pentenoyl)triazenes in refluxing toluene led to the formation of monocyclic and tricyclic lactams in satisfactory yields via 5-*exo* amidyl radical cyclization.

Amidyl radicals are highly reactive and electrophilic radicals.[1] This Umpolung reactivity offers a great potential in organic synthesis via intramolecular cyclization to afford lactams or cyclic amines. However, amidyl radical-based synthetic methodologies have drawn much less attention than they deserve.[2] This is, in part, because most of the amidyl radical precursors are either very unstable or difficult to prepare. For example, precursors such as *N*-halo amides[3] and *N*-hydroxypyridine-2-thione imidate esters[4,5] are very unstable. Other precursors such as *N*-(phenylthio)amides[6] or *N*-(*O*-ethyl thiocarbonylsulfanyl)amides[2b] suffer from the low yields of preparation in many cases. Recently, Nicolaou et al. reported the *o*-iodoxybenzoic acid (IBX)-initiated amidyl radical cyclization with the direct use of amides as the substrates.[2a] However, only the 5-*exo* cyclization reactions of *N*-aryl-substituted amides could proceed under the IBX-mediated conditions. It is therefore desirable to develop novel methods to conduct amidyl radical reactions. We report here, that *N*-acyltriazenes serve as a convenient precursor for unsaturated amidyl radicals under tin-free and initiator-free conditions.

N-Acyltriazenes have been known for a long time.[7] They can be easily prepared from the reaction of an amide with an arenediazonium ion with NaH as the base,[8] or from the reaction of an amine with an arenediazonium salt followed by the treatment with an acyl chloride and triethylamine in a one-pot, two-stage manner.[9] Thermal decomposition of *N*-acytriazenes (**1**) in aromatic solvents leads to a free radical arylation reaction, as shown in Scheme 1.[8] We envisioned that, if the R group in **1** bears a C=C double bond, the amidyl radical **2a** might undergo cyclization (to give the cyclized carbon-centered radical **5**) rather than H-abstraction (to give the amide **4**). The cyclized radical **5** then might abstract a hydrogen presumably from radical **3** to afford the corresponding lactam **6a** as the final product (Scheme 2). This would provide a facile entry to the generation and cyclization of amidyl radicals under tin-free and initiator-free conditions. However, to our surprise, such a process was never examined in the literature. Based on the above discussion, we carried out the following investigation.

Thus, *N*,*N*′-diphenyl-*N*-(4-pentenoyl)triazene **1a** was prepared from aniline, benzenediazonium fluoroborate and 4-pentenoyl chloride in 85% yield according to the literature method.[9] Compound **1a** turned out to be very stable and no decomposition was observed in benzene at



Scheme 1.

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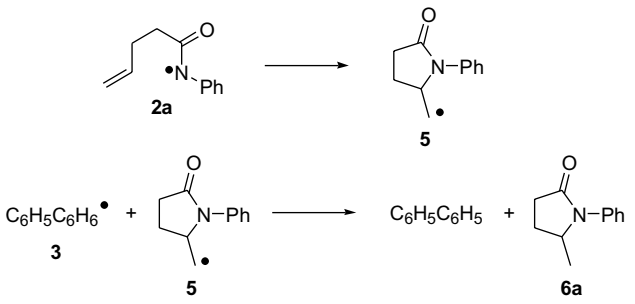
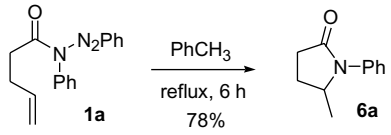


Scheme 2.

refluxing temperature. Direct photolysis of **1a** in benzene at room temperature with the aid of a 125 W high-pressure mercury lamp gave a complicated mixture in which *N*-phenyl-4-pentenamide (**4a**) was isolated in 24% yield and the desired cyclized product γ-lactam **6a** was obtained in 14% yield. However, to our delight, when **1a** was heated up in toluene at reflux (110 °C) for 6 h, the expected cyclization product **6a** was achieved in 78% isolated yield (Eq. 1).

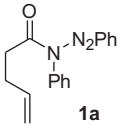
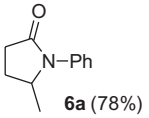
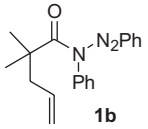
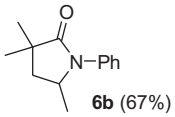
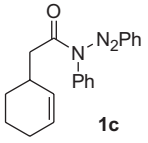
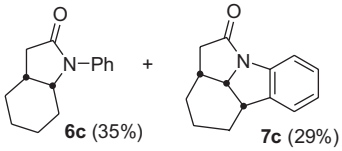
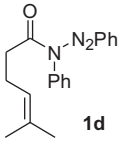
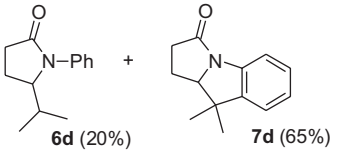
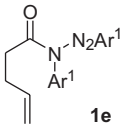
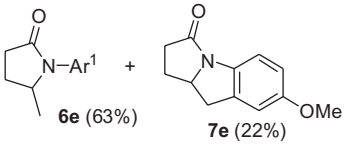
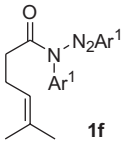
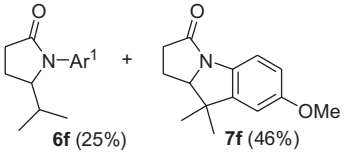
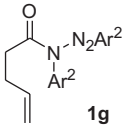
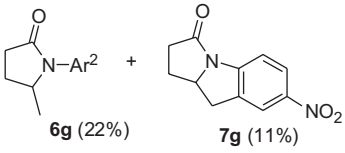
We then synthesized a number of *N*-acyltriazenes **1a**–**g** to explore the scope and limitation of the above method. The results are summarized in Table 1.



(1)

As can be seen in Table 1, the 5-*exo* cyclization products **6a** and **b** were obtained in high yields in the thermal decomposition of triazenes **1a** and **b** with a mono-substituted terminal double bond (Table 1, entries 1 and 2). With substrate **1c** having an internal double bond, the corresponding 5-*exo* cyclization product **6c** was isolated in 35% yield along with the formation of tetracyclic compound **7c** as a single stereoisomer in 29% yield (Table 1, entry 3). Apparently, product **7c** resulted from the further addition of the cyclized radical similar to **5** to the phenyl ring. For triazene **1d** with a dimethyl-substitution at the C=C double bond, the 5-*exo* cyclization product **6d** was obtained in 20% yield while the tricyclic product **7d** was achieved in 65% yield (Table 1, entry 4). These results indicate that the formation of tricyclic products such as **7d** is encouraged by the terminal substitution at the C=C double bond. This trend might be rationalized by the enhanced stability of the corresponding cyclized radical **5** from a primary carbon radical (such as in the case of **1a**) to a tertiary carbon radical (in the case of **1d**), which allows the addition of **5** to the phenyl ring to become a competitive process to the direct H-abstraction of **5**. It is worth mentioning that the formation of tricyclic products **7** was not observed in the IBX-mediated reactions of unsaturated *N*-arylamides.

Table 1. Thermal decomposition of triazenes **1** at 110 °C

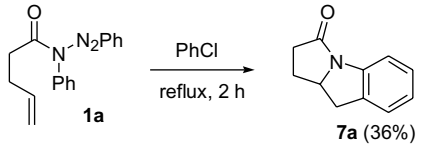
Entry	Substrate[a]	Product (yield)[b]
1	 **1a**	 **6a** (78%)
2	 **1b**	 **6b** (67%)
3	 **1c**	 **6c** (35%) **7c** (29%)
4	 **1d**	 **6d** (20%) **7d** (65%)
5	 **1e**	 **6e** (63%) **7e** (22%)
6	 **1f**	 **6f** (25%) **7f** (46%)
7	 **1g**	 **6g** (22%) **7g** (11%)

[a] Ar^1: *p*-methoxyphenyl, Ar^2: *p*-nitrophenyl.
[b] Isolated yield based on **1**.

We next, tested the effect of *N*-aryl groups on the cyclization. With *N*,*N*′-di(*p*-methoxyphenyl)-substituted substrate **1e** and **f**, both the expected monocyclization products **6** and the tricyclic products **7** were achieved in satisfactory overall yields (Table 1, entries 5 and 6). On the other hand, the *N*,*N*′-di(*p*-nitrophenyl)-substituted triazene **1g** gave the mixture of **6g** and **7g** in low yield. The comparison between **1a** and **e** showed that the *p*-methoxy-substitution at the phenyl group encourages the formation of the tricyclic products **7**. However, the reason remains unclear.

The formation of tricyclic products **7** is certainly of great interest in organic synthesis as this tricyclic skeleton is widely embedded in a number of biologically active natural products such as mitomycins.[10] In order to increase the yield of **7**, we carried out the thermal decomposition of **1** at higher temperature. Indeed, when **1a** was added into chlorobenzene at reflux (~132 °C), the corresponding tricyclic product **7a** was obtained in 36% yield while

no **6a** could be isolated (Eq. 2). However, the thermolysis of **1e** in refluxing chlorobenzene gave **7e** in only 19% yield along with a significant amount of unidentified byproducts. Nevertheless, the results in Eqs. 1 and 2 clearly indicate that, under certain experimental conditions, the reaction of **1** could be pushed towards the formation of tricyclic products **7**, thus of more synthetic value. This is now actively pursued in our laboratory.



(2)

In summary, the above preliminary results clearly demonstrate that the thermal decomposition of unsaturated *N*-acyltriazenes provides a convenient entry to the generation and cyclization of amidyl radicals.[11] Tandem radical cyclization leading to the formation of tricyclic lactams could also be achieved via this method, which should be of important application in organic synthesis.

Acknowledgements

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References and notes

1. For reviews, see: (a) Esker, J.; Newcomb, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1993; Vol. 58, p 1; (b) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543; (c) Stella, L. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, p 407.
2. For recent examples, see: (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233; (b) Gagosz, F.; Moutrille, C.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 2707; (c) Tang, Y.; Li, C. *Org. Lett.* **2004**, *6*, 3229; (d) Chen, Q.; Shen, M.; Tang, Y.; Li, C. *Org. Lett.* **2005**, *7*, 1625.
3. (a) Barton, D. H. R.; Beckwith, A. L. J.; Goosen, A. *J. Chem. Soc.* **1965**, 181; (b) Neale, R. S. *Synthesis* **1971**, 1.
4. Newcomb, M.; Esker, J. L. *Tetrahedron Lett.* **1991**, *32*, 1035.
5. (a) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1992**, *33*, 5913; (b) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517.
6. Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1993**, *34*, 6877.
7. Campbell, T. W.; Day, B. F. *Chem. Rev.* **1951**, *48*, 299.
8. Curtin, D. Y.; Druliner, J. D. *J. Org. Chem.* **1967**, *32*, 1552.
9. Klages, F.; Mesch, W. *Chem. Ber.* **1955**, *88*, 388.
10. (a) Webbs, J. S.; Cosulich, D. B.; Mowat, J. H.; Patrick, J. B.; Broschard, R. W.; Meyer, W. E.; Williams, R. P.; Wolf, C. F.; Fulmor, W.; Pidacks, C.; Lancaster, J. E. *J. Am. Chem. Soc.* **1962**, *84*, 3185; (b) Webbs, J. S.; Cosulich, D. B.; Mowat, J. H.; Patrick, J. B.; Broschard, R. W.; Meyer, W. E.; Williams, R. P.; Wolf, C. F.; Fulmor, W.; Pidacks, C.; Lancaster, J. E. *J. Am. Chem. Soc.* **1962**, *84*, 3187.
11. Typical procedure for the thermal decomposition of *N*-acyltriazenes **1**. The solution of triazene **1e** (102 mg, 0.3 mmol) in toluene (10 mL) was refluxed for 6 h. The resulting mixture was then concentrated under reduced pressure and the residue was subjected to column chromatography on silica gel with ethyl acetate–hexane (1:4, v/v) as the eluent. The amide **6e** (38.7 mg, 63% yield) was isolated as a white solid, whose spectra were identical with those reported in the literature (Koebel, R. F.; Needham, L. L.; Blantom, C. D. *J. Med. Chem.* **1975**, *18*, 192). Compound **7e** (13.4 mg, 22% yield) was isolated as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92–2.05 (1H, m), 2.42–2.51 (1H, m), 2.58 (1H, dd, $J = 8.1$, 16.5 Hz), 2.78–2.92 (2H, m), 3.14 (1H, dd, $J = 8.4$, 15.6 Hz), 3.78 (3H, s), 4.59–4.70 (1H, m), 6.73–6.76 (2H, m), 7.52 (1H, d, $J = 8.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 29.2, 29.7, 36.2, 55.7, 63.4, 111.3, 112.1, 115.2, 133.0, 135.8, 156.9, 171.2; EIMS: *m*/*z* (rel intensity) 203 (M^+, 74), 188 (16), 148 (100), 117 (14), 104 (14), 89 (5), 77 (9), 63 (4), 55 (8); HRMS calcd for $C_{12}H_{13}NO_2$: 203.0946. Found: 203.0948.