Radical Reactions

DOI: 10.1002/anie.200905167

Radical Cyclization of α-Bromo Aluminum Acetals: An Easy Approach to γ-Lactols**

Anne Boussonnière, Fabrice Dénès, and Jacques Lebreton**

Aluminum acetals are well-known intermediates whose potential in organic synthesis is a subject of growing interest. The most common access to aluminum acetals involves the reduction of carboxylic acid esters with diisobutylaluminium hydride (DIBAL-H) at −78 °C. Their stability at low temperature allows the selective reduction of carboxylic acid esters into the corresponding aldehydes with limited over-reduction into alcohols.[1,2] Since the 1980s, several applications of aluminum acetals have been reported. The reduction of esters using DIBAL-H at low temperature has been used to form highly unstable or epimerizable aldehydes in situ. The latter are formed either upon warming or by the addition of a protic source or Lewis acid. The resulting aldehydes have been used in carbon–carbon bond-forming reactions with various nucleophiles such as allylstannanes,[3,4] silyl ketene acetals,[5–7] or lithium enolate.[8] Olefination[9,10] and the preparation of alkynes[11] have also been described. The addition of Grignard reagents to aluminum acetals obtained from α-amino esters through reduction with DIBAL-H or DIBAL-H/*i*Bu_3Al have been reported to give 1,2-amino alcohols with a high level of stereoselectivity.[12] A S_N2-like displacement of the aluminum acetal, or alternatively a displacement of a tight ion pair, has been proposed to explain the chiral induction.[12] Aluminum acetals have been successfully trapped by silyl triflates and silyl imidazole or acetic anhydride to give the corresponding monosilyl acetals[13–15] and α-acetoxy acetals,[16,17] respectively. Acid fluorides have also been reported as efficient reagents to trap aluminum acetals.[18] Monosilyl acetals have been employed in condensation reactions with allyl trimethylsilane.[14] In addition, α-acetoxy acetals have proven to be useful precursors of the oxacarbenium ion, which can be trapped by various nucleophiles, including allylstannanes reagents,[16,19] trimethylsilylcyanide,[16] dialkylaluminum (trimethylsilyl)acetylide,[16] triethylsilane,[17] thiophenol,[16] and phenylselenol.[20] Moreover, the oxacarbenium ion has been employed in Prins[21] and oxonia-Cope[22] rearrangements to give polysubstituted tetrahydropyrans. Note that contrary to the Prins rearrangement of α-acetoxy acetals derived from homoallylic alcohols, which gave excellent results both in terms of regio- and stereoselectivity, the related allyl alcohols failed to give the corresponding tetrahydrofuran derivatives.[21c]

In spite of the aforementioned applications of aluminum acetals in ionic processes, their use as intermediates in radical reactions has thus far remained completely unexplored. Herein, we report the formation of α-bromo aluminum acetals derived from *O*-allyl-α-bromo esters and their cyclization in situ under radical conditions to give a variety of polysubstituted γ-lactols.

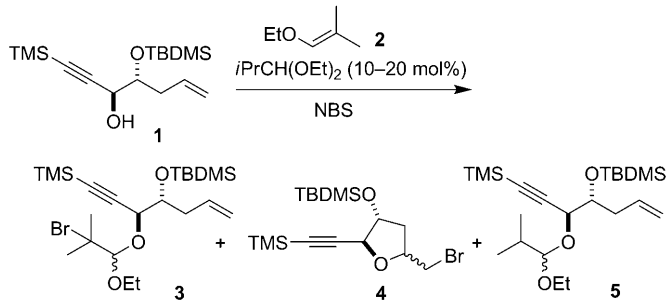
Radical reactions have been intensively investigated during the last two decades.[23] The new synthetic methods that have been developed from this work are characterized by their mildness and their complementarity to ionic processes. The cyclization of α-haloacetals (the Ueno–Stork reaction)[24] was developed independently by Ueno[25] and Stork[26] in the 1980s, and has become a very popular approach for the cyclization of related α-bromo esters under reductive conditions.[27,28] The resulting cyclic acetals have proven to be useful precursors for the preparation of corresponding lactones—even though this transformation often implies the formation of the hemiacetal intermediate under strongly acidic conditions, which limits this approach to substrates without acid-sensitive functional groups. Moreover, the synthesis of the α-haloacetal precursors, as well as the enol ethers employed in their preparation, is not always straightforward and can be somewhat tricky—we have experienced difficulty during the course of our research on the synthesis of biologically relevant heterocyclic compounds. For instance, attempts to prepare α-bromo acetal **3** from propargylic alcohol **1** and enol ether **2** (contaminated with significant amounts of acetal *i*PrCH$(OEt)_2$, which was used for its preparation) under standard reaction conditions gave irreproducible results. A mixture of three compounds was typically obtained and, beside the expected α-bromo acetal **3**, which was usually obtained as the minor compound, bromo ether **4** and acetal **5** were also isolated (Scheme 1).

These observations prompted us to develop a more practical approach to γ-lactols based on a one-pot reaction involving the formation of an α-bromo aluminum acetal and its cyclization under reductive radical conditions at low temperature. We carried out a feasibility study in which various α-bromo aluminum acetals were generated by reduction of the parent α-bromo esters using DIBAL-H, and were subsequently subjected to radical cyclization conditions.

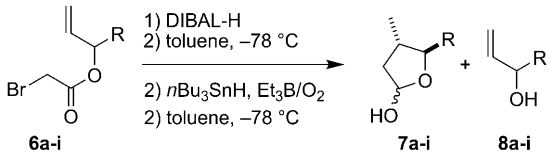
[*] A. Boussonnière, Dr. F. Dénès, Prof. J. Lebreton
Université de Nantes, Laboratoire CEISAM
UMR 6230, UFR des Sciences et des Techniques
2, rue de la Houssinière
BP 92208, 44322 Nantes Cedex 3 (France)
Fax: (+33) 2-5112-5402
E-mail: fabrice.denes@univ-nantes.fr
jacques.lebreton@univ-nantes.fr

[**] This work was supported by the French Ministry of Science. We would like to thank Nathali Henriques, Christian Duchamp, and Dr. Denis Bouchu (Centre Commun de Spectroscopie de Masse—Université Claude Bernard Lyon 1—France) for HRMS measurements.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200905167.



Scheme 1. Some drawbacks of the preparation of α-halo acetals. TBDMS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.



Scheme 2. Preparation of γ-lactols by sequential one-pot reduction/cyclization of α-bromo esters.

α-Bromo esters **6a–i** were easily prepared in high yields from allylic alcohols and α-bromo acids using standard procedures for esterification. They were then tested according to Scheme 2, and the results are shown in Table 1. In most cases, only trace amounts of over-reduction products **8a–i** could be detected. For instance, substrates **6a** and **6b**, which have a substituent at the allylic position, gave the desired γ-lactols **7a** and **7b** in 90% and 95% yield, respectively (entries 1 and 2). Substituents at the carboxylic acid moiety were also tolerated, as illustrated by the cyclization of **6c–f** (entries 3–7). The cyclization of **6d** gave the expected γ-lactol **7d** in somewhat lower yield (59%; entry 4) together with a significant amount (ca. 40%) of recovered alcohol **8d**. The formation of the alcohol could be explained by over-reduction, or alternatively by a hydride transfer (Meerwein–Pondorff–Verley) mechanism.[6,13] Mono- and disusbtitution at the terminal position of the alkene also led to the γ-lactols in high yields (82–99%; entries 4–8).

We then focused our attention on substrates containing acid-sensitive functional groups. Labile protecting groups such as trityl (Tr) or benzyloxymethyl (Bom) were tolerated. The reductive cyclization of esters **6h** and **6i** (entries 9 and 10) gave the γ-lactol **7h** and **7i** in good to excellent yields, thus demonstrating the mildness of the method.

Disregarding the hemiacetal center, the stereoselectivity of the cyclization reaction that led to **7a–d** and **7h–i** (C4–C5 selectivity) was over 95:5 in all cases. For clarity, the selectivity reported in Table 1 does not take into account the hemiacetal center. The selectivity of this reaction is being studied in more detail, and the results will be reported elsewhere.

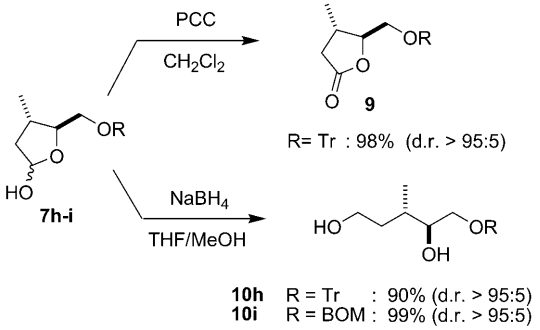
Finally, the versatility of the resulting γ-lactols was illustrated by various transformations. For instance, the reaction with allyltrimethyl silane,[29,30] thiophenol, or Et_3SiH[29] in the presence of $BF_3{\cdot}Et_2O$ gave the corresponding

Table 1: Sequential reduction/cyclization of α-bromo esters.[a]

Entry	Substrate	Product	Yield [%][b]	d.r.[c]	Entry	Substrate[a]	Product	Yield [%][b]	d.r.[c]
1	**6a**	**7a**	90	>95:5	6	(*E*)-**6e**	**7e**	96	54:46[d]
2	**6b**	**7b**	95	>95:5	7	**6f**	**7f**	99	42:58[d]
3	**6c**	**7c**	89	43:57[d]	8	**6g**	**7g**	98	50:50[f]
4	**6d**	**7d**	59[e]	>95:5	9	**6h**[g]	**7h**	97	>95:5
5	(*Z*)-**6e**	**7e**	82	68:32[d]	10	**6i**[g]	**7i**	83	>95:5

[a] All reactions were carried out in toluene at −78 °C on an approximate 5 mmol scale (unless otherwise stated) using DIBAL-H (1 equiv), nBu_3SnH (1 equiv), Et_3B (0.3–1 equiv), air (1 mL). [b] Yield of isolated product. [c] Selectivity is C4–C5, unless otherwise stated. See the Supporting Information for details. [d] Selectivity is C3–C4. [e] Yield determined by ^1H NMR spectroscopy. The product was isolated as a mixture with alcohol **8d** (ca. 40%, based on NMR analysis). [f] Selectivity is C4–C1′. [g] Reactions were carried out on a 2 mmol scale. Bn = benzyl.

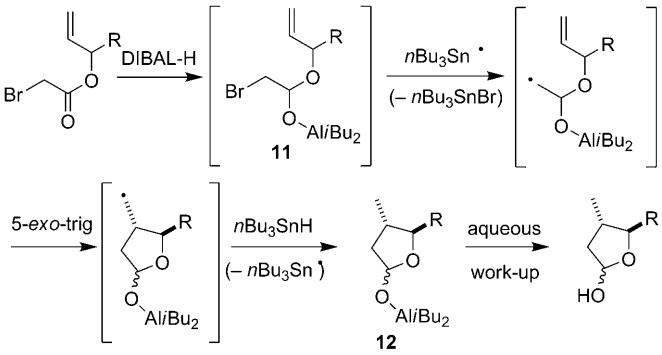
tetrahydrofurans in good yields (> 80% from **7b**, not shown). More interestingly, oxidation of **7i** using PCC gave the lactone **9**. Meanwhile, reduction of γ-lactols **7h** and **7i** into diols **10h** and **10i** could be achieved in high yields under very mild conditions (90% and 99%; Scheme 3). Note that the latter transformations could not be achieved directly from cyclic acetals obtained by the classical Ueno–Stork reaction.



Scheme 3. Illustration of the versatility of γ-lactols for further transformations. PCC = pyridinium chlorochromate.

The mechanism of this cyclization of α-bromo esters merits further investigation, especially to rationalize the stereoselectivity observed. The reaction is very likely to proceed through the formation of the aluminum acetal **11**, which is obtained by reduction of the α-bromo ester with DIBAL-H. Aluminum acetal **11** undergoes a 5-*exo*-trig radical cyclization in the presence of nBu$_3$SnH and Et$_3$B/O$_2$ as a radical initiator. Hydrogen atom abstraction from the tin hydride reagent by the cyclized carbon-centered radical gives the cyclic aluminum acetal **12**, which leads to the γ-lactol upon aqueous work-up (Scheme 4). To the best of our knowledge, this is the first report of a reaction involving a radical aluminum acetal species.

In conclusion, we have shown that aluminum acetals are very useful intermediates that are stable enough at low temperature to achieve radical cyclization. Reduction of α-bromoesters using DIBAL-H, and subsequent addition of nBu$_3$SnH and Et$_3$B/O$_2$ led to γ-lactols in good to excellent yields. Compared to the classical cyclization of α-halo acetals, several advantages of the approach reported here can be highlighted: 1) the precursors are easily prepared in high yields by simple esterification of allylic alcohols with α-bromo acids using standard procedures, 2) the mild reaction conditions are compatible with acid-sensitive functionalities, such as labile hydroxy protecting groups, and 3) the versatility of γ-lactols produced by this reaction makes them particularly attractive for further transformations. Application of this process to the total synthesis of natural products is currently underway in our laboratory.



Scheme 4. Mechanism for the cyclization of α-bromo aluminum acetals.

Experimental Section

DIBAL-H (4.2 mL, 1.2 M in toluene, 5.0 mmol) was added dropwise to a solution of α-bromoester **6b** (1.41 g, 5.0 mmol) in toluene (40 mL) under argon at −78 °C. After complete consumption of starting material (15 min, as evident by TLC), Et$_3$B (2.5 mL, 1 M in hexanes, 2.5 mmol) and nBu$_3$SnH (1.34 mL, 5.0 mmol) were simultaneously added dropwise at −78 °C. Air (1 mL) was introduced via a syringe above the solution and the mixture was kept at −78 °C until complete consumption of alcohol **8b** (as evident by TLC, vanillin dip). The cold bath was removed, and the reaction mixture was quenched with a saturated aqueous solution of NaF. The mixture was stirred vigorously for 15 min, and diluted with CH_2Cl_2 (without agitating) and the organic phase was separated and the procedure repeated twice. The aqueous phase was then extracted several times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/Et$_2$O 80:20) to give γ-lactol **7b** (979 mg, 95%).

Received: September 15, 2009
Published online: November 10, 2009

Keywords: aluminum acetals · cyclization · γ-lactols · radical reactions

[1] E. Winterfeldt, *Synthesis* **1975**, 617.
[2] K. Maruaka, H. Yamamoto, *Tetrahedron* **1988**, *44*, 5001.
[3] T. Ishihara, H. Hayashi, H. Yamanaka, *Tetrahedron Lett.* **1993**, *34*, 5777.
[4] T. Ishihara, A. Takahashi, H. Hayashi, H. Yamanaka, T. Kubota, *Tetrahedron Lett.* **1998**, *39*, 4691.
[5] S.-i. Kiyooka, K. Suzuki, M. Shirouchi, Y. Kaneko, S. Tanimori, *Tetrahedron Lett.* **1993**, *34*, 5729.
[6] S.-i. Kiyooka, M. Shirouchi, *J. Org. Chem.* **1992**, *57*, 1.
[7] D. M. Troast, J. Yuan, J. A. Porco, Jr., *Adv. Synth. Catal.* **2008**, *350*, 1701.
[8] T. Yamazaki, R. Kobayashi, T. Kitazume, T. Kubota, *J. Org. Chem.* **2006**, *71*, 2499.
[9] W. Boland, P. Ney, L. Jaenicke, *Synthesis* **1980**, 1015.
[10] Z.-Y. Wei, E. E. Knaus, *Tetrahedron Lett.* **1994**, *35*, 2305.
[11] H. D. Dickson, S. C. Smith, K. W. Hinkle, *Tetrahedron Lett.* **2004**, *45*, 5597.
[12] R. Polt, M. A. Peterson, L. DeYoung, *J. Org. Chem.* **1992**, *57*, 5469.
[13] S.-i. Kiyooka, M. Shirouchi, Y. Kaneko, *Tetrahedron Lett.* **1993**, *34*, 1491.
[14] D. Sames, Y. Liu, L. DeYoung, R. Polt, *J. Org. Chem.* **1995**, *60*, 2153.
[15] T. Itoh, K. Sakabe, K. Kudo, H. Ohara, Y. Takagi, H. Kihara, P. Zagatti, M. Renou, *J. Org. Chem.* **1999**, *64*, 252.
[16] V. H. Dahanukar, S. D. Rychnovsky, *J. Org. Chem.* **1996**, *61*, 8317.

[17] D. J. Kopecky, S. D. Rychnovsky, *J. Org. Chem.* **2000**, *65*, 191.
[18] Y. Zhang, T. Rovis, *Org. Lett.* **2004**, *6*, 1877.
[19] a) I. Kadota, A. Ohno, K. Matsuda, Y. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 6702; b) I. Kadota, A. Ohno, K. Matsuda, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 3562; c) I. Kadota, H. Takamura, K. Sato, A. Ohno, K. Matsuda, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 46; d) I. Kadota, H. Takamura, K. Sato, A. Ohno, K. Matsuda, M. Satake, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 11893; e) I. Kadota, H. Uyehara, Y. Yamamoto, *Tetrahedron* **2004**, *60*, 7361.
[20] S. D. Rychnovsky, D. J. Skalitzky, *Synlett* **1995**, 555.
[21] a) S. D. Rychnovsky, Y. Hu, B. Ellsworth, *Tetrahedron Lett.* **1998**, *39*, 7271; b) S. D. Rychnovsky, C. R. Thomas, *Org. Lett.* **2000**, *2*, 1217; c) J. J. Jaber, K. Mitsui, S. D. Rychnovsky, *J. Org. Chem.* **2001**, *66*, 4679; d) S. Marumoto, J. J. Jaber, J. P. Vitale, S. D. Rychnovsky, *Org. Lett.* **2002**, *4*, 3919; e) R. Jasti, J. Vitale, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2004**, *126*, 9904.
[22] a) J. E. Dalgard, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2004**, *126*, 15662; b) R. Jasti, C. D. Anderson, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2005**, *127*, 9939.
[23] For general reviews on radical reactions, see: B. Giese, *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Oxford, **1988**; D. P. Curran in *Comprehensive Organic Synthesis*, *Vol. 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1991**, p. 715 and 779; W. B. Motherwell, D. Crich, *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, London, **1992**; J. Fossey, D. Lefort, J. Sorba, *Free Radicals in Organic Synthesis*, Wiley, Chichester, **1995**; *Radicals in Organic Synthesis* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**; S. Zard, *Radical Reaction in Organic Synthesis* Oxford University Press, Oxford, **2003**.
[24] X. J. Salom-Roig, F. Dénès, P. Renaud, *Synthesis* **2004**, 1903.
[25] a) Y. Ueno, K. Chino, M. Watanabe, O. Moriya, M. Okawara, *J. Am. Chem. Soc.* **1982**, *104*, 5564; b) Y. Ueno, K. Chino, M. Watanabe, O. Moriya, M. Okawara, *J. Chem. Soc. Perkin Trans. 1* **1986**, 1351.
[26] a) G. Stork, R. Mook, Jr., S. A. Biller, S. D. Rychnovsky, *J. Am. Chem. Soc.* **1983**, *105*, 3741; b) G. Stork, P. M. Sher, *J. Am. Chem. Soc.* **1983**, *105*, 6765; c) G. Stork, P. M. Sher, H.-L. Chen, *J. Am. Chem. Soc.* **1986**, *108*, 6384; d) G. Stork, P. M. Sher, *J. Am. Chem. Soc.* **1986**, *108*, 303; e) G. Stork, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 149.
[27] Successful cyclizations of α-halo esters have been reported in benzene at reflux using slow addition techniques: S. Hanessian, R. Di Fabio, J.-F. Marcoux, M. Prud'homme, *J. Org. Chem.* **1990**, *55*, 3436.
[28] Another practical solution to achieve efficient cyclization of α-halo esters based on the halogen atom transfer method has been reported: D. P. Curran, C.-T. Chang, *J. Org. Chem.* **1989**, *54*, 3140.
[29] A. Schmitt, H.-U. Reissig, *Eur. J. Org. Chem.* **2000**, 3893.
[30] C. Brueckner, H. Holzinger, H.-U. Reissig, *J. Org. Chem.* **1988**, *53*, 2450.

