Synthesis of Homopropargyl Cycloalkanols by Pd-Catalyzed Samarium Diiodide-Promoted Intramolecular Coupling of Alkynyl Esters with Aldehydes and Ketones

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Summary: Treatment of 1-(4-oxoalkyl)-2-alkynyl esters with SmI_2/Pd^0 results in intramolecular cyclization to afford homopropargyl cycloalkanols. The same products are also obtained starting from isomeric γ-alkynyl-substituted lactol esters.

Homopropargyl alcohols have attracted the attention of the synthetic chemist both as structural components of a number of biologically important molecules[1-10] and as valuable synthetic intermediates.[11-17] The existing methodology for the synthesis of homopropargyl alcohols employs for the most part either the ring opening of suitable epoxides with alkynyl organometallics[18] or the use of organometallic propargyl anion equivalents.[19] Both methods often encounter regioselectivity problems, due in the former case to the inherent difficulty in controlling the site of ring-opening and in the latter to the well known allenic–propargylic equilibrium of the corresponding organometallic derivatives that often causes the formation of allene products. A propargyl anion cyclization route to homopropargyl cycloalkanols would certainly surmount both problems since the regiochemistry of cyclization is forced by the electrophilic site and formation of undesired allene products would be precluded for geometrical reasons. While allenic–propargylic organometallics have participated in cyclization reactions,[17,20] the synthesis of simple homopropargyl cycloalkanols has not been reported using this methodology. We would like to disclose here preliminary results on the realization of these ideas using substrates **1** in a new intramolecular Pd(0)/samarium diiodide (SmI_2)[21]-mediated coupling between tethered propargyl ester and carbonyl functionalities[22] (Scheme 1), as well as an unprecedented ring contraction from structurally related lactol esters **2**, leading to the same products, that complements this methodology. The reaction is thought[22] to proceed through the allenylpalladium complex **3** which is reduced by 2 equiv of SmI_2 to the organosamarium[23] intermediate **4** that undergoes intramolecular cyclization to afford the cyclic homopropargyl alcohols **5**, after protonation, during aqueous workup, of an initially formed samarium alkoxide.

Scheme 1

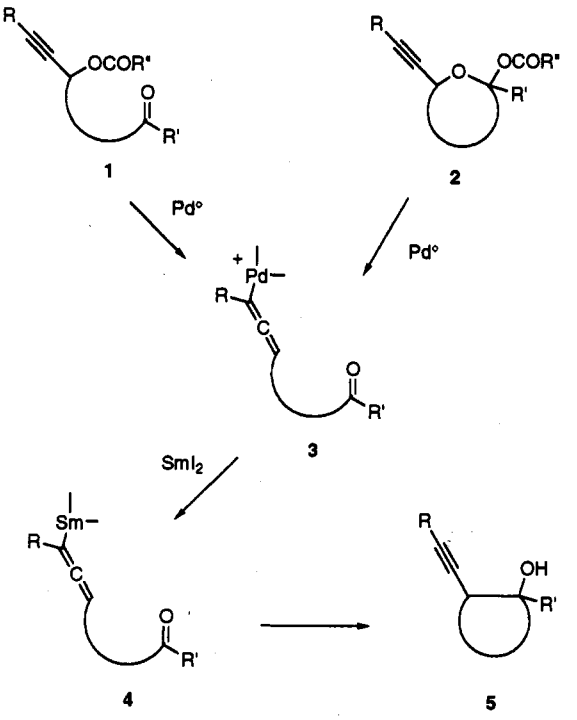

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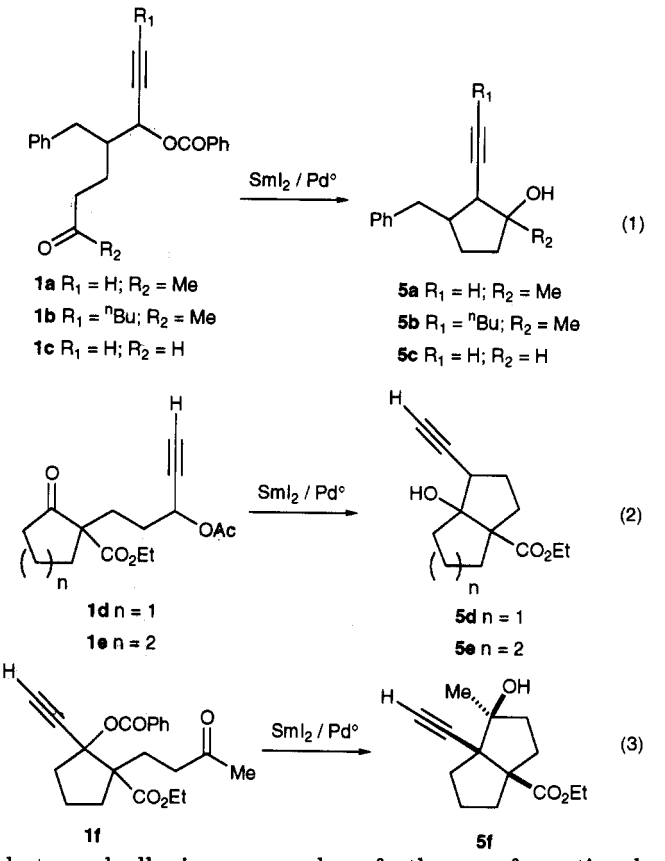
Table 1. SmI_2–Pd^0-Mediated Formation of Cyclopentanols from Alkynyl Esters 1 and 2

entry	substrate	method[a]	products (yield, %)
1	**1a**	A	**5a** (91)[b]
2	**1b**	A	**5b** (87)[c]
3	**1c**	A[d]	**5c** (18)[c]
4	**1d**	A	**5d** (24)[e]
5	**1d**	B	**5d** (87)[e]
6	**1e**	B[d]	**5e** (88)[f]
7	**1f**	A[d]	**5f** (51)[g]
8	**2a**	A	**5d** (73)[e]
9	**2b**	A	**5g** (84)[e]

[a] Method A: A solution of the substrate (0.65–1.05 mmol) and $Pd(PPh_3)_4$ [8.9–20.3/1.0 mole ratio of substrate/$Pd(PPh_3)_4$] added to a THF solution of SmI_2 (2.2 equiv) at 25 °C. Method B: The SmI_2 solution added to the solution of the substrate and $Pd(PPh_3)_4$.] [b] Mixture of four diastereomers in a ratio of 1.5 (two isomers):1.5:1. [c] Diastereomeric ratio was not determined. [d] A 8.9–10.0 mole ratio of substrate/[$Pd(PPh_3)_4$ was used. [e] A single diastereomer. [f] Diastereomeric ratio 24:1. [g] 3:1 diastereomeric ratio. Major isomer shown.

Representative results are shown in eqs 1–3 and Table 1.[24] The addition of a mixture of a propargyl ester substrate **1**[26] (0.65–1.0 mmol) and $Pd(PPh_3)_4$ [8.9–20.3/1.0 mole ratio of **1**/$Pd(PPh_3)_4$] to SmI_2 (2.2 equiv) at 25 °C (method A) generally resulted in the formation of the corresponding homopropargyl cyclopentanols **5** in good yields, without the concomitant formation of allenic products derived from the alternative intermolecular coupling. While simple ketones reacted cleanly in this way, the method was not suitable for δ-keto esters (entry 4). In these substrates the ester functionality activates the ketone carbonyl toward reduction[28] by SmI_2, thus significantly lowering the cyclization yield. The slow dropwise addition of SmI_2 to the mixture of substrate and catalyst (method B, entry 5) overcame this problem, and high yields of cyclized products could be realized with those functionalized substrates. As shown in Table 1 both internal and terminal alkynes are effective in the cyclization process. Particularly remarkable is the successful coupling of two tertiary centers in a very reasonable yield[29] and moderate stereoselectivity (entry 7). Not unexpectedly,[22] the aldehyde functionality was too reactive toward SmI_2, and competing side reactions prevailed over cyclization regardless of the method used (entry 3).[30] The stereoselectivity of the process is low for acyclic substrates



but markedly improves when further conformational constraints are imposed by an existing ring in the substrate and is indeed very high when, additionally, one of the coupling termini is a secondary carbon (entries 5 and 6; *vide infra*), in which case a single diastereomer overwhelmingly predominates.

As already mentioned, aldehydes are not suitable substrates for the reductive intramolecular coupling described here. In the search for a solution to this problem we reasoned that a substrate **2** (Scheme 1) would in effect act as a masked aldehyde or ketone delivering at a given time only a small amount (equal to the molar percentage of catalyst used) of the presumed key reactive intermediate **4**, therefore minimizing side reactions. As anticipated, the treatment of bicyclic esters **2a**[31] and **2b**[32] with SmI_2/Pd^0 (eqs 4 and 5) cleanly afforded high yields of the homopropargyl alcohols **5d** and **5g**, respectively, as single diastereomers, in a process that overall achieves the formation of a carbocycle by ring contraction[33] of a carbohydrate-like substrate. Furthermore, the product obtained from the reaction of **2a** was identical in all physical properties[24] to the one synthesized from the ketone **1d** (eq 2), probably indicating that both reactions share a common reactive intermediate, as suggested by the mechanism depicted in Scheme 1.

(23) The involvement of related alkylsamarium species in Barbier-type reactions has been demonstrated. See: Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943.

(24) All products were characterized by ^1H and ^{13}C NMR, IR and combustion analysis, or HR-MS. The stereochemistry of diastereomeric **5f** was determined from ^1H and ^{13}C NMR C_4-Me chemical shift differences in the individual isomers, as well as by comparison with relevant examples from ref 25. The stereochemistry of product **5g** was deduced from the chemical shift differences found in the carbinolic protons of the diastereomeric mixture obtained from the $NaBH_4$ reduction of the ketone resulting from the PDC oxidation of **5g**. The unambiguous determination of the stereochemistry of products **5d** and **5e** by spectroscopic means has not been possible. Full details are given in the supplementary material.

(25) Whitesell, J. K.; Minton, M. A. *Stereochemical Analysis of Alycyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: London, 1987.

(26) Substrates **1a–c,f** were prepared by alkylation of an appropriate aldehyde or ketone with a 3-halo acetal derivative, followed by alkynyllithium carbonyl addition, benzoylation, and acetal hydrolysis. Substrates **1d,e** were prepared by selective[27] lithium acetylide addition to the aldehyde carbonyl of ethyl 1-(2-formylethyl)-2-oxocyclopentanecarboxylate or ethyl 1-(2-formylethyl)-2-oxocyclohexanecarboxylate, respectively, followed by acetylation of the resulting alcohol.

(27) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421.

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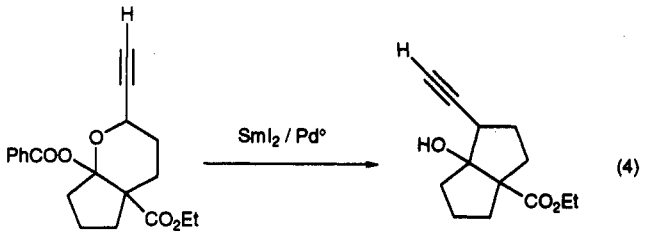
(29) The lowered yield is due to the formation of side products, presumably of dimeric nature, likely the result of a double intermolecular coupling.

(30) Formation of pinacols from aldehydes and SmI_2 is particularly fast. See: Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227. For competing pinacol formation in SmI_2-promoted cyclization reactions see: Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *31*, 1063.

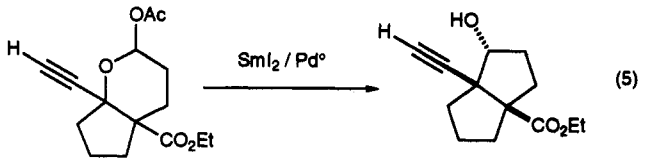
(31) Prepared by selective lithium acetylide addition to ethyl 1-(2-formylethyl)-2-oxocyclopentanecarboxylate, followed by in situ quenching of the resulting alkoxide with benzoyl chloride.

(32) Prepared by selective protection of the aldehyde group in 1-(2-formylethyl)-2-oxocyclopentanecarboxylate as the *N*-((*N'*,*N'*-dibenzylamino)alkyl)benzotriazole derivative, followed by lithium acetylide addition to the ketone carbonyl, hydrolysis, and acetylation of the resulting alcohol.

(33) For a related process see: Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835 and references cited therein.



2a 5d (4)



2b 5g (5)

In summary, the work presented here features the use of the stable and convenient propargyl ester functionality as a propargyl anion synthetic equivalent in carbocycle ring-forming reactions. The use of lactol esters extends the scope of the method by formally utilizing the otherwise impractical aldehydic carbonyl group and offers an effective entry into useful carbohydrate to carbocycle conversions. Since the methodology for chemoselectively acting over 1,5-dicarbonyl substrates is available,[27,34] substrate preparation[26,31,32] becomes a simple and expedient task and the overall cyclization strategy benefits from the use of simple and readily available starting-materials. Further work on the scope and applications of these two processes is in progress and will be reported in due course.

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Supplementary Material Available: Experimental procedures and spectral data for all products (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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