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SHORT COMMUNICATION

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Synthesis of 3-Substituted Tetrahydrofuran and 4-Substituted Tetrahydropyran Derivatives by Cyclization of Dicarboxylic Acids with $InBr_3$/TMDS

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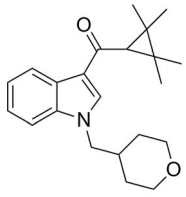
An efficient reduction followed by cyclization of diacid compounds with the $InBr_3$/TMDS system is reported. This system allows the formation of five- and six-membered ring ethers substituted in the 3- or 4-position.

Introduction

Cyclic ethers, such as substituted tetrahydrofurans, tetrahydropyrans, oxepans, and so on are present in the structures of natural products and drugs. For example, the molecule A-834,735 developed by Abbot Laboratories is a potent cannabinoid receptor (Scheme 1).[1]



A-834,735

Scheme 1. Structure of A-834,735.

Numerous methods have been described for the synthesis of tetrahydrofurans (THFs) and tetrahydropyrans (THPs) in racemic or asymmetric versions substituted in the 2- and 5-positions or the 6-position.[2] However the synthesis of THF and THP derivatives substituted in the 3-position (for THF) and the 3- or 4-position (for THP) is less described. The formation of these five- and six-membered rings can be performed from diols, activated by iodine,[3] or proceed through a unique oxidation–reduction step of orthodiols with activated MnO_2 and Et_3SiH/CF_3COOH.[4] The heating of dihalogenated compounds in the presence of alumina allows the formation of five-, six-, or seven-membered rings in moderate to good yields.[5] The synthesis of 3- or 4-substituted cyclic ethers was also described under radical conditions. Thus, the cyclization of 1,6-dienes by using CCl_4 in the presence of diethylphosphite or diphenylphosphane oxide permits access to 3,4-substituted THF;[6] radical cyclizations of β-allyloxyalkylphenyl selenides[7] and those of bis-(allenes)[8] or iodoalkenes[9] are also described. A highly enantioselective "ene"-type cyclization of 1,6-enyne catalyzed by the BINAP-Pd complex leads to a 3,4-substituted THF.[10] A palladium complex was also described by Yamamoto for a two-component alkoxyallylation reaction between an activated olefin and hydroxylated allylic carbonate, which leads to five-membered rings in 29 to 76% yield according to the initial olefin.[11] At last, a three-component reaction catalyzed by a Pd complex was developed for the synthesis of 3-arylidene (or 3-alkylidene) THF, but the methodology also requires substitution at the 2-position.[12] THF can also be prepared by hydrogenation from maleic acid or succinic acid by using a Pd/Re/C[13] or Ru/Re catalyst.[14] However, in addition to a high temperature and pressure, these methodologies lead to a mixture of THF and alcohols. Recently, a ruthenium–Triphos complex was found to reduce levulinic acid at 100 bar and 160 °C into the corresponding diol and a small amount of 2-MeTHF was observed. If the same conditions were applied to a lactone, the corresponding THF was obtained as the major product.[15]

To the best of our knowledge, an indium catalyst has never been employed with a source of hydride for the synthesis of cyclic ethers such as THF and THP substituted in the 3- or 4-position. However, during our investigation Sakai and co-workers described the reduction of carboxylic acids into alcohols by using an indium catalyst and TMDS. This methodology requires the use of $InBr_3$ (5 mol-%) and occurs in chloroform.[16] In our laboratory, TMDS (tet-

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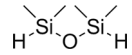
ramethyldisiloxane, Scheme 2) has been used a source of hydride and employed for several reductive systems associated with a metal catalyst.[17] This use is interesting, as unlike other reducing agents ($NaBH_4$, $LiAlH_4$, etc.), a large excess amount of hydride is not necessary and treatment does not require hydrolysis or specific attention. Moreover, no toxicity has been reported and its cost is easily affordable. Herein is described the association of $InBr_3$ and TMDS for the synthesis of THF and THP derivatives.

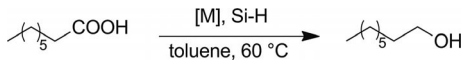


Scheme 2. Structure of TMDS.

Results and Discussion

At the beginning of this study, the goal was to reduce carboxylic acids by using a hydrosiloxane as the hydride source. Different catalysts were tested with octanoic acid (Table 1), although publication of similar conditions were reported by Sakai during our study.

Table 1. Reduction of octanoic acid with different metals.

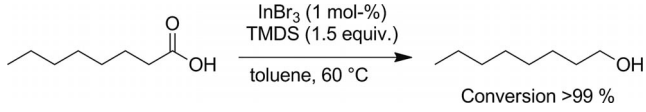


Entry	[M] (mol-%)	Si-H (equiv.)	Conversion[a] [%] (alcohol/ether)
1	$Pd(OAc)_2$ (5)	TMDS (1)	0
2	$V(O)(OiPr)_3$ (5)	TMDS (1.5)	0
3	$Cu(OTf)_2$ (5)	TMDS (1.5)	26 (26:0)
4	$Ce(OTf)_x$ (5)	TMDS (1.5)	36 (36:0)
5	$Bi(OTf)_3$ (5)	TMDS (1.5)	0
6	$In(OTf)_3$ (1)	TMDS (1.5)	0
7	$In(OAc)_3$ (1)	TMDS (1.5)	0
8	$InBr_3$ (5)	TMDS (3)	100 (97:3)
9	$InBr_3$ (1)	TMDS (1.5)	100 (100:0)
10	$InBr_3$ (1)	PMHS (3)	58
11	$In(acac)_3$ (1)	TMDS (1.5)	0
12	$GaBr_3$ (1)	TMDS (1.5)	75(60:15)

[a] Determined by ^1H NMR spectroscopy.

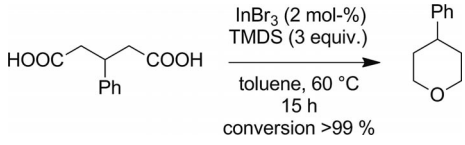
Octanoic acid (1 M in toluene) at 60 °C in the presence of $Pd(OAc)_2$ or $V(O)(OiPr)_3$ associated with TMDS was not reduced in 24 h (Table 1, entries 1 and 2). Some interesting results were noticed when $Cu(OTf)_2$ and $Ce(OTf)_x$ were used. However, conversions into alcohol were not complete (Table 1, entries 3 and 4). Because the triflate ligand seemed favorable with copper and cerium, $Bi(OTf)_3$ and $In(OTf)_3$ were also tested, but only the starting material was recovered (Table 1, entries 5 and 6). Other indium catalysts were tested including $In(OAc)_3$, $InBr_3$, and $In(acac)_3$. With the acetate derivative (Table 1, entry 7), no interesting result was observed; however, with $InBr_3$ (5 mol-%) a complete conversion was noticed (Table 1, entry 8). Under these conditions, 97% yield of the expected alcohol was obtained along with 3% yield of the ether. When decreasing the amount of indium and TMDS to 1 mol-% and 1.5 equiv. respectively, the conversion was still complete and no ether was observed (Table 1, entry 9). When the hydride source was switched to PMHS (polymethylhydrosiloxane), a gel was formed and the reaction proceeded slowly; conversion into 1-octanol reached only 58% for the same reaction time frame. Unlike $InBr_3$, no transformation was noticed with $In(acac)_3$ (Table 1, entry 11). Finally, reaction with $GaBr_3$ gave 75% conversion, but the selectivity was less interesting, as an alcohol/ether ratio of 60:15 was obtained (Table 1, entry 12).

The $InBr_3$/TMDS reductive system applied to octanoic acid in toluene at 60 °C gave the best result (Scheme 3), and under these conditions, different aliphatic acids were efficiently reduced with good selectivity and conversions.



Scheme 3.

As a consequence, we decided to test the reactivity of diacids to prepare cyclic ethers. 3-Phenylglutaric acid was first tested under our reductive conditions. Because two carboxylic acid functions needed to be reduced, 2 mol-% of $InBr_3$ and 3 equiv. of TMDS were added in toluene at 60 °C. After 15 h, the cyclization occurred with complete conversion (Scheme 4).



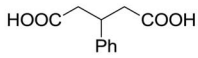
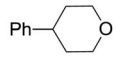
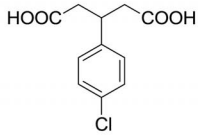
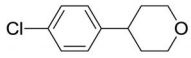
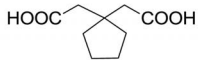
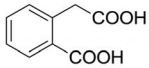
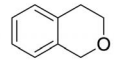
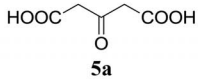
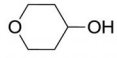
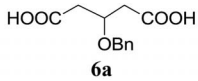
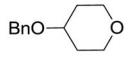
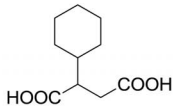
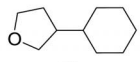
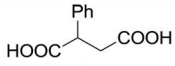
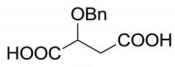
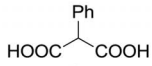
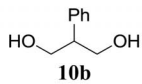
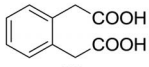
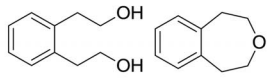
Scheme 4.

Under these conditions, 4-phenyltetrahydropyran was isolated in high yield (Table 2, entry 1). Consequently, different diacids were then considered to synthesize four-, five-, six-, or seven-membered rings (Table 2).

With chlorine in the *para*-position of the aromatic ring, the conversion was still complete. The isolated yield of THP **2b** reached 53% (Table 2, entry 2). With the cyclopentane derivative, the cyclization occurred with complete conversion, and spirotetramethyleneTHP **3b** was isolated in 73% yield (Table 2, entry 3). The transformation of homophthalic acid (**4a**) allowed the formation of isochroman (**4b**) in 80% yield (Table 2, entry 4). The formation of 4-hydroxytetrahydropyran was then envisaged. From 1,3-acetonedicarboxylic acid (**5a**), the main product appeared to be the volatile 4-hydroxyTHP (**5b**), which was isolated after silica gel chromatography in only 17% yield (Table 2, entry 5). Therefore, the protection of the hydroxy group was envisaged to improve the yield of the final molecule. Several approaches were studied (oxime, tosyl, etc.) and finally the preparation of the benzyl derivative was obtained (Scheme 5).

Following a literature procedure, the protection of diethyl 3-hydroxyglutarate (**6a1**) allowed the formation of benzyl derivative **6a2** in 78% isolated yield. The next step consisted

Table 2. Cyclization of different dicarboxylic diacids.[a]

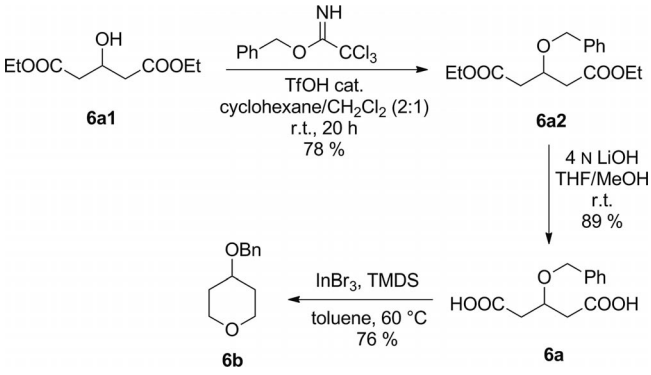
Entry	Dicarboxylic acid	Product	Conversion[b] [%] Total (Product + Other)	Yield [%][c]
1	 **1a**	 **1b**	>99	>98
2	 **2a**	 **2b**	>99	53[e]
3	 **3a**	 **3b**	>99	73
4	 **4a**	 **4b**	>95	80
5	 **5a**	 **5b**	>95 (t = 1 h)	17[f]
6	 **6a**	 **6b**	80 (t = 4 h)	76[d]
7	 **7a**	 **7b**	>95	40[e]
8	 **8a**	 **8b**	>95	34
9	 **9a**	 **9b**	71	26[d]
10	 **10a**	 **10b**	>95	54
11	 **11a**	 **11b** **11b'**	>95	65

[a] Conditions: Diacid (5 mmol), $InBr_3$ (2 mol-%, 0.1 mmol.), TMDS (3 equiv.), anhydrous toluene (c = 1 M), 60 °C, 15 h. [b] Determined by ^1H NMR spectroscopy. [c] Isolated yield after purification by flash chromatography. [d] Reaction was carried out with 5 mol-% $InBr_3$. [e] Low UV sensibility and lack of reactivity with different dips. [f] Very soluble in water and can form an azeotrope with solvents used for purification.

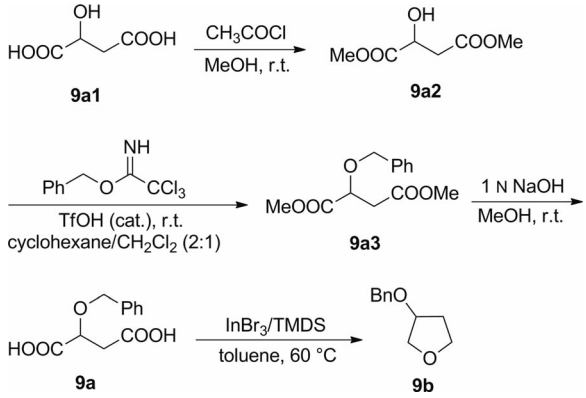
in the preparation of diacid **6a**, which was obtained in 89% yield. Conditions for the cyclization were then applied on **6a** and 4-benzyloxyTHP (**6b**) was isolated in 76% yield (Table 2, entry 6).

The synthesis of five-membered rings was then studied. The reaction of 2-cyclohexylsuccinic acid (**7a**) was almost complete after 15 h, and 3-cyclohexylTHF (**7b**) was isolated in 40% yield (Table 2, entry 7). The cyclohexyl group was then replaced by a phenyl group, and corresponding THF **8b** was collected in 34% yield. As detailed above for the preparation of the benzyl derivative, the same procedure was followed for the synthesis of 3-benzylTHF (**9b**, Scheme 6).

The synthesis started from the preparation of diester **9a2** from malic acid (**9a1**). The hydroxy function was then protected with a benzyl group to give compound **9a2**. After saponification, diacid **9a** underwent cyclization to give THF derivative **9b** in 26% yield (Table 2, entry 9). In this case, the conversion reached only 46%. Compound **9a** was obtained as a very viscous oil, in which some ethyl acetate (solvent of purification) was trapped. This could explain the low reactivity in the cyclization step.

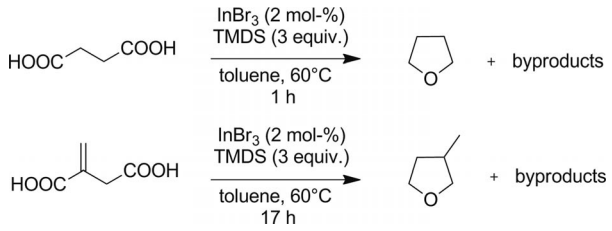


Scheme 5.



Scheme 6.

Access to THF and 3-MeTHF from succinic acid and itaconic acid was also controlled under these conditions, but because of their volatility they were not isolated. ^{1}H NMR revealed complete conversion for the preparation of THF after a reaction time of 1 h, but the presence of a minor unidentified product was also detected. The conversion rate of itaconic acid reached 50%. The reduction of the activated double bond finally led to 3-methylTHF (Scheme 7).



Scheme 7.

Preparation of the THF derivatives was less efficient than the preparation of THP derivatives. Although conversions were good, the probable formation of the diol limits the yield of the cyclic ethers. Moreover, certain cyclic compounds are not visible under UV light or with staining solutions, which make purification more difficult.

At last, the preparation of oxetan and oxepan was considered. Some tests on phenylmalonic acid (**10a**) were made, which led to diol **10b** after complete conversion (Table 2, entry 10). The formation of the cycle was not detected, which could be due to the strained conformation of oxetans. Applying the conditions to 1,2-phenylenediacetic acid (**11a**) led to the formation of both seven-membered ring **11b** and diol **11b′**. Diol **11b′** was isolated in 65%.

From a mechanistic point of view and by analogy with the Sakai proposition, the formed silyl ether reacts intramolecularly with a second molecule of the carboxylic acid.[17] The resulting ester is then reduce. The Lewis acid properties of indium should assist the cyclization step.

Conclusions

A new method for the preparation of five- and six-membered cyclic ethers was described. The reductive $InBr_3$/TMDS system allowed formation of THP derivatives in good yields and the formation of THF derivatives in moderate yields. Oxepan can also be formed but the corresponding diol is also observed.

Experimental Section

Procedure for the Cyclization of Diacid Compounds: To a solution of diacid compound **a** (5 mmol) in anhydrous toluene (c = 0.5–1 M) was added $InBr_3$ (2 mol-%, 0.05 equiv., 35.5 mg). TMDS was then added very carefully and slowly (formation of bubbles) over several minutes. The solution turned bright orange in color. The reaction mixture was heated to 60 °C. After 15 h, ^{1}H NMR spectroscopic analysis of an aliquot was made to check for complete conversion of the starting material. Toluene was then evaporated, and the crude material was purified by column chromatography on silica gel. Cyclic ethers were in general apolar so the purification was done with pure cyclohexane. UV light and Pancaldi were used for analysis of the TLC plates. After evaporation, cyclic ether **b** was obtained as an oil or a solid.

Supporting Information (see footnote on the first page of this article): Characterization data, NMR spectra, and GC–MS analyses.

Acknowledgments

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