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Triazabicyclodecene: An Effective Isotope Exchange Catalyst in $CDCl_3$

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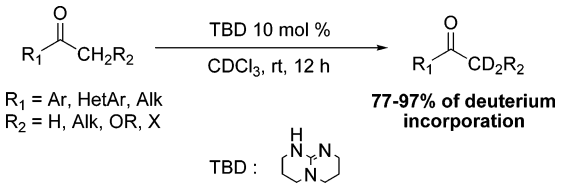

We describe the first effective H/D exchange reaction with acidic substrates in $CDCl_3$ at room temperature. The particularly mild reaction conditions involved (solvent, base, and temperature) allow the chemoselective deuteration of ketones over esters. An NMR study was conducted with the aim of rationalizing the results obtained in the presence of TBD as catalyst.

Deuterium-labeled compounds have become increasingly important, particularly for structure elucidation of large molecules (proteins, oligonucleotides)[1] and for mechanistic studies of chemical[2] and biological[3] transformations in combination with NMR spectroscopy. Deuterium labeling of organic compounds can be achieved by means of syntheses starting from suitable isotope marker precursors or via isotope exchange reactions. The latter approach appears to be more valuable since the deuterium can possibly be introduced post-synthetically. However, most of the H/D exchange reactions reported in the literature for acidic compounds involve fairly strenuous protic conditions[4] that are not compatible with sensitive functional groups. In this note, we report high level of deuterium incorporation of sensitive substrates at room temperature in $CDCl_3$ as deuterium source as well as solvent.

Deuterium incorporation is by far more difficult to achieve in aprotic $CDCl_3$ than in protic polar solvents such as MeOD and D_2O, partly due to limited strength of bases in this medium. In return, the use of $CDCl_3$, a weak nucleophile, as deuterium source would be favorable for the deuteration of sensitive substrates. To the best of our knowledge, the only significant example of deuterium labeling of acidic substrates in $CDCl_3$ has been reported by Messinger.[5] The author described the deuteration of aryl alkyl ketones in refluxing $CDCl_3$ in the presence of basic aluminum oxide. This work prompted us to investigate an alternative procedure at room temperature, more suitable for the deuteration of a wide range of compounds. Initially, we considered the use of a small and diverse collection of usual bases, HONa, MeONa, pyridine, Et_3N, DMAP, and DBU (30 mol % each), for the deuteration of the 4′-methoxyacetophenone **1a** in $CDCl_3$ at room temperature. The total deuterium incorporation was determined by ^1H NMR spectroscopy after 0.5, 12, and 64 h (Table 1). HONa, MeONa, pyridine, Et_3N, and DMAP allowed very poor deuterium incorporation of **1a** in $CDCl_3$ (<22% after 64 h, entries 2−6). Only the stronger base DBU ($pK_a = 23.9$)[6] afforded a moderate deuterium labeling of **1a** after 64 h (62%, entry 7), while this base was known to afford high isotope incorporation in D_2O.[7] On the basis of these initial results, we turned our attention toward guanidine-based compounds, known as highly basic organocatalysts. Surprisingly, treatment of **1a** with the acyclic guanidine 1,1,3,3-tetramethylguanidine (TMG, $pK_a = 23.7$) or with the monocyclic guanidine **2** did not allow any deuterium incorporation. In contrast, a good level of deuterium incorporation was obtained with the bicyclic guanidine MTBD ($pK_a = 25.7$) after 64 h at room temperature (85%, entry 10), and its supported analogue, PSTBD, afforded a similar labeling of **1a** but at 50 °C (86%, entry 16). Finally, the use of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, $pK_a = 26.2$) led to the highest deuterium incorporation, far from the second more active base MTBD, since deuterium incorporation reached 92% within only 0.5 h at room temperature (vs 9% for MTBD, entries 10 and 12). Moreover, the deuteration of **1a** catalyzed by 1 mol % of TBD afforded 76% of deuterium incorporation after 12 h, while only traces of deuteration were observed with MTBD under the same conditions (<2%, entry 11). Finally, an optimization study revealed that 10 mol % of TBD was sufficient to reach 92% of deuterium incorporation within 12 h (entry 14). Finally, reaction carried out with basic aluminum oxide, successfully used by Messinger in refluxing $CDCl_3$, has shown only 9% of isotope incorporation after 64 h at room temperature (entry 17).[5]

To explain the disparity of the catalytic activity observed between TBD and other bases of comparable nature and basicity, the H/D exchange reaction of 4′-methoxyacetophenone **1a** catalyzed by TBD in $CDCl_3$ was investigated by means of ^1H NMR spectroscopy.[8] When TBD was dissolved in $CDCl_3$, no N−H signal was observed, demonstrating a total deuterium exchange. In contrast, TBD underwent no detectable deuterium incorporation in CD_2Cl_2. When 1 equiv of $CDCl_3$ was added to the latter solution, the N−H signal of intensity 1 was half decreased and a singlet signal of intensity 0.5 at 7.27 ppm appeared, corresponding to the chloroform peak. Thus, these

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(1) Hodge, R. P.; Brush, C. K.; Harris, C. M.; Harris, T. M. *J. Org. Chem.* **1991**, *56*, 1553.
(2) Hornback, J. M.; Vadlamani, B. *J. Org. Chem.* **1980**, *45*, 3524.
(3) Schwab, J. M.; Klassen, J. B. *J. Am. Chem. Soc.* **1984**, *106*, 7217.
(4) (a) Arrowsmith, C. H.; Kresge, A. J. *J. Am. Chem. Soc.* **1986**, *108*, 7918. (b) Fodor-Csorba, K.; Galli, G.; Holly, S.; Gács-Baitz, E. *Tetrahedron Lett.* **2002**, *43*, 3789.
(5) Kunick, C.; Messinger, P. *Chem. Ber.* **1986**, *119*, 1429.
(6) (a) The pK_a of conjugate acid in all cases. (b) Kovačević, B.; Maksić, Z. B. *Org. Lett.* **2001**, *3*, 1523.
(7) Berthelette, C.; Scheigetz, J. *J. Labelled Compd. Radiopharm.* **2004**, *47*, 891.
(8) For related NMR spectra, see Supporting Information (S40).

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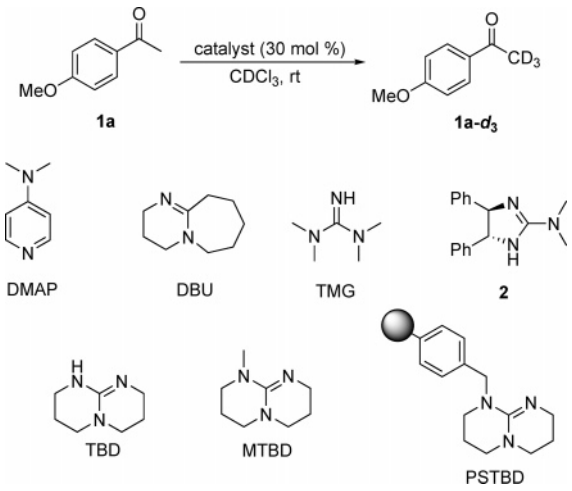
TABLE 1. Bases Screening for Deuteration of 4′-Methoxyacetophenone 1a in $CDCl_3$ at Room Temperature

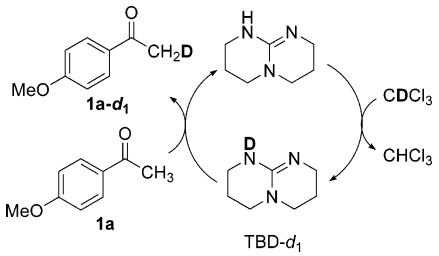


entry	catalyst	Total Incorporation Yield (%)[a] 0.5 h	12 h	64 h
1	–	0	0	0
2	HONa	0	13	22
3	MeONa	2	3	6
4	pyridine	0	0	0
5	Et_3N	0	0	0
6	DMAP	0	0	0
7	DBU	<2	13	62
8	TMG	0	0	0
9	**2**	0	0	nd[b]
10	MTBD	9	43	85
11	MTBD[c]	0	<2	nd
12	TBD	92	92	92
13	TBD[c]	51	76	nd
14	TBD[d]	76	92	92
15	PSTBD	n.d	22	nd
16	PSTBD[e]	n.d	67	86
17	basic aluminum oxide	2	3	9

[a] Calculated on the basis of ^1H NMR spectrum. [b] Not determined. [c] 1 mol %. [d] 10 mol %. [e] Reaction carried out at 50 °C.

results highlight the very efficient isotopic exchange between TBD and $CDCl_3$. To further rationalize the proton−deuterium exchange reaction, 1 equiv of 4′-methoxyacetophenone **1a** was added to a solution of deuterated TBD (TDB-d_1)[9] in CD_2Cl_2. Immediately the singlet signal of intensity 3 at 2.56 ppm corresponding to the methyl ketone group of **1a** was partially replaced by a multiplet of intensity 2, and a peak of intensity 1 at 4.82 ppm corresponding to the NH proton of TBD appeared. This observation suggests a fast and total D/H exchange between TBD-d_1 and the methyl ketone **1a**. On the basis of these NMR studies, we proposed a plausible catalytic cycle (Scheme 1) in which TBD acts as a deuterium transfer catalyst between $CDCl_3$ and the ketone **1a** due to the presence of a labile proton in its structure. Thus, TBD would behave as a neutral base in the course of all the H/D exchange process. None of the other bases tested exhibits both high basicity and a labile proton in their structure. Indeed, replacement of the NH labile proton of TBD with a methyl group (MTBD) did not change significantly its basicity but led to an important loss of the labeling catalyst activity. Moreover, despite the presence of a potential labile N−H proton in TMG and **2**, we did not observe any H/D exchange in $CDCl_3$ by ^1H NMR spectroscopy, which could therefore explain their inefficiency for the deuteration of **1a**.[10] In addition, no example of H/D exchange between a guanidine and $CDCl_3$ is described in the literature. Only a H/D exchange between the N−H proton of an amidine and $CDCl_3$ has been reported.[11]

SCHEME 1. Plausible Deuterium Transfer Involved in Deuteration Reaction Catalyzed by TBD in $CDCl_3$



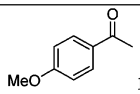
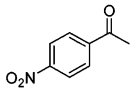
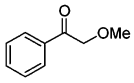
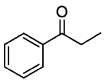
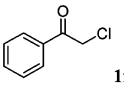
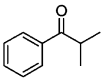
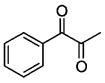
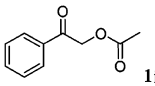
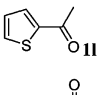
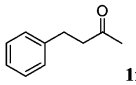
Next, deuterium labeling of a number of ketones **1a**−**n** was explored using the optimized reaction conditions (e.g., 10 mol % of TBD, rt, 12 h). Results obtained are summarized in Table 2.

It is noteworthy that all deuterated products were obtained cleanly in high chemical yield (>95%) after workup, without further purification. Repeating the labeling procedure once with 4′-methoxyacetophenone **1a** afforded complete deuteration of the methyl group of the ketone (>98% yield, entry 1). For other acetophenone derivatives, it appeared that the nature of the substituent on the aromatic ring or methyl group did not have significant effect on the global deuterium incorporation. Indeed, the 4′-nitroacetophenone **1c** gave high level of deuterium labeling (92% yield, entry 3) as well as the 2-methoxy-, 2-methyl-, 2-chloroacetophenones **1d**−**f** with 93, 97, and 85% of deuterium incorporation, respectively (entries 4−6). However, an attempt to deuterate the isobutyrophenone **1g** was less satisfactory (21% yield, entry 7) probably due to steric hindrance. To further demonstrate the scope of this method, highly base-sensitive compounds, such as the 1-phenylpropane-1,2-dione **1h**,[12] were deuterated in good yield (77% yield with 1% TBD, entry 8). In addition, the 2-acetoxyacetophenone **1i** was chemoselectively deuterated at the carbon atom α to the phenyl carbonyl group (95% yield, entry 9) since no deuterium incorporation was detected ($^1H/^2H$ NMR) on the acetyl group. To the best of our knowledge, this is the first example of a selective deuteration of a methylene group of a ketone in the presence of an acetate group. Indeed, an attempt to deuterate **1i** in usual protic media (D_2O, MeOD) with MeONa, HONa, or TBD ended up in partial or complete deprotection of the substrate leading to 2-hydroxyacetophenone. This example underlines the superiority of $CDCl_3$ over protic media for the labeling of compounds bearing sensitive functional groups. In addition, deuterium incorporation at the carbon atom α to the phenyl carbonyl group of **1i** was only 21% with Messinger's methodology (e.g., refluxing $CDCl_3$, 12 h). Moreover, the reaction was successfully extended to heteroaromatic ketones **1k** and **1l** (89 and 90% yield, entries 11 and 12). Finally, deuteration of two aliphatic ketones, benzylacetone **1m** and cyclodecanone **1n**, was successfully achieved with 84 and 94% of deuterium incorporation, respectively (entries 13 and 14).

(9) For TBD-d_1 preparation, see: Kaempfen, U.; Eschenmoser, *A. Helv. Chim. Acta* **1989**, *72*, 185.

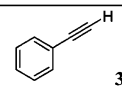
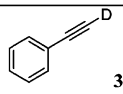
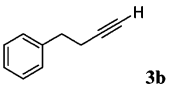
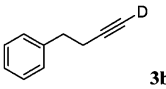
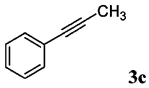
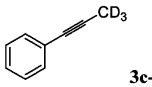
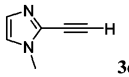
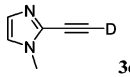
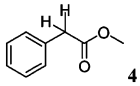
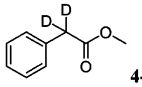
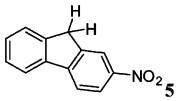
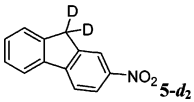
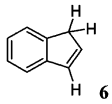
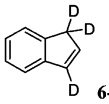
(10) For related NMR spectra, see Supporting Information (S9−S10).
(11) Löfå, S.; Ahlberg, P. *J. Chem. Soc., Chem. Commun.* **1981**, 998.
(12) Turro, N. J.; Lee, T. *J. Am. Chem. Soc.* **1970**, *92*, 7467.

TABLE 2. Deuteration of Ketones 1a−n with 10 mol % of TBD in $CDCl_3$[a]

entry	ketone	total incorporation yield (%)[b]	d0	d1	d2	d3	d4	d5
1	 **1a**	92 >98[c]	<1	2	18	79	n.a[d]	n.a
2	 **1b**	90 86.4[e]	<1 0.6	2 5.3	26 28.5	71 65.6	n.a	n.a
3	 **1c**	92	<1	3	15	80	n.a	n.a
4	 **1d**	93	<1	13	87	n.a	n.a	n.a
5	 **1e**	97	6		94	n.a	n.a	n.a
6	 **1f**	85	3	24	73	n.a	n.a	n.a
7	 **1g**	21	79	21	n.a	n.a	n.a	n.a
8	 **1h**	77[f]	1	12	40	47	n.a	n.a
9	 **1i**	95 21[g]	<1	10	90	n.a	n.a	n.a
10	 **1j**	93	<1	3	15	82	n.a	n.a
11	 **1k**	89	<1	3	25	71	n.a	n.a
12	 **1l**	90	<1	3	25	72	n.a	n.a
13	 **1m**	84 82.3[e]	0.2	0.8	4.3	15.8	39.8	39.1
14	 **1n**	94 88.0[e]	1.2	0.9	5.5	29.7	62.7	n.a

[a] All reactions were carried out with 10 mol % of TBD, 0.72 mmol of the ketone in 3 mL of $CDCl_3$, at room temperature for 12 h. [b] Calculated on the basis of ^{1}H NMR spectrum. [c] After repeating the labeling procedure once with fresh TBD and $CDCl_3$. [d] Not applicable. [e] Calculated on the basis of mass spectroscopy. [f] 1 mol % of TBD. [g] Reaction carried out with Messinger's methodology: basic aluminum oxide in refluxing $CDCl_3$ for 12 h.

TABLE 3. Deuteration of Acidic Compounds Catalyzed by TBD in $CDCl_3$[a]

entry	substrate	product	total incorporation yield (%)[b]
1	 **3a**	 **3a-*d*$_1$**	90
2	 **3b**	 **3b-*d*$_1$**	93
3	 **3c**	 **3c-*d*$_3$**	0[c]
4	 **3d**	 **3d-*d*$_1$**	31 (96)[d] 84[e]
5	 **4**	 **4-*d*$_2$**	93
6	 **5**	 **5-*d*$_2$**	94
7	 **6**	 **6-*d*$_3$**	94[f] 89[g]

[a] All reactions were carried out with 10 mol % of TBD, 0.72 mmol of the substrate in 3 mL of $CDCl_3$, at room temperature for 12 h. [b] Calculated on the basis of ^{1}H NMR spectrum. [c] Unlabeled starting alkyne was recovered. [d] Before workup. [e] 10 mol % of PSTBD at room temperature. [f] Deuteration at the methylene position. [g] Deuteration at the vinyl position.

These results prompted us to investigate the scope of our methodology to other acidic molecules (Table 3). All reactions were carried out using the optimized conditions (e.g., 10 mol % of TBD, rt, 12 h).

First, the deuteration of terminal alkynes was studied and achieved successfully. Labeling of phenylacetylene **3a**, usually carried out by means of strong ionic bases,[13] was obtained in good yield (90%, entry 1). In the case of the 4-phenylbut-1-yne **3b**, deuteration took place exclusively at the terminal position of the alkyne (^{1}H/^{2}H NMR). No deuterium incorporation was observed with the disubstituted alkyne **3c**, and the unlabeled starting alkyne was recovered. The 2-ethynyl-1-methylimidazole **3d** was labeled in 96% yield prior to workup. However, after workup, the deuterium incorporation dropped to 31% yield, presumably due to D/H exchanges with unlabeled water. It is noteworthy that revert D/H exchange was only observed with the compound **3d-*d*$_1$**. Interestingly, the same reaction carried out with PSTBD at room temperature avoided the aqueous treatment and afforded 84% yield of deuterium incorporation of **3d**. Moreover the methyl-1-phenylacetate **4**, a base-sensitive group, was efficiently deuterated with TBD (93%, entry 5).[14] This method should be widely applicable to a variety of alkyl-1-phenylacetate derivatives. It is important to outline that common procedures for the deuteration of alkyl esters in protic solvents led to concomitant transesterification, therefore, they are very substrates limited.[15] Interestingly, indene **6**

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underwent 94% of deuteration at the methylene position and 89% at the vinyl position next to the benzene ring. This result suggests that the proton−deuterium exchange proceeds via an allylic reorganization.[16]

In summary, TBD has shown to be an efficient isotope exchange catalyst in $CDCl_3$ at room temperature toward a wide range of substrates. Our optimized conditions are compatible with sensitive functional groups and allow chemoselective deuteration of ketones over esters. In contrast, bases commonly used in polar protic media did not lead to significant deuterium incorporation in $CDCl_3$. The superior ability of TBD for deuteration could be ascribed to both its high pK_a value and the presence of a labile proton in its structure.

Experimental Section

Representative Procedure for Deuteration Reaction (Compounds in Tables 2 and 3). For compound 1b: To a solution of 10 mol % of TBD (10 mg, 0.072 mmol) in 3 mL of $CDCl_3$ was added **1b** (84 μL, 0.72 mmol). The reaction mixture was stirred at room temperature for 12 h and quenched with 1 N HCl (1 mL). The organic layer was washed with water (2 × 2 mL) and brine (1 mL), dried over anhydrous Na_2SO_4, and filtered. Filtrate was concentrated to afford **1b-*d*$_3$**. The total incorporation yield was determined by ^{1}H NMR spectroscopy relative to the intensity of a nonexchangeable proton in the molecule, or by GC−MS. For example, the global deuterium incorporation of compound **1b-*d*$_3$** determined by GC−MS was calculated as follows: 1/3 × 5.3% + 2/3 × 28.5% + 3/3 × 65.6% = 86.4% of total incorporation. Moreover, the site of deuterium incorporation in the substrate was determined by ^{2}H NMR spectroscopy relative to $CHCl_3$ (7.27 ppm).

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Supporting Information Available: ^{1}H/^{2}H NMR data for all labeled compounds and preparative procedures and characterization data for **2** and **1i**. This material is available free of charge via Internet at http://pubs.acs.org.

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