DOI: 10.1002/ejoc.201001294

Sodium Hydride Catalyzed Tishchenko Reaction

Thomas Werner*[a] and Juliane Koch[a]

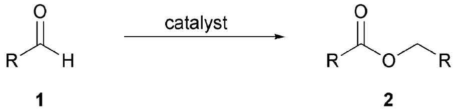
Dedicated to Professor Uwe Rosenthal on the occasion of his 60th birthday

Keywords: Tishchenko Reaction / Dimerization / Sodium hydride / Aldehydes / Synthetic methods

A convenient and practical method for the dimerization of aldehydes is described. The conversion of aromatic and even heteroaromatic aldehydes in the presence of catalytic amounts of sodium hydride leads to the corresponding Tishchenko esters in high yields (up to 95 %). The reaction can be performed under standard laboratory conditions and on a multigram scale (up to 10 g).

Introduction

The development of novel, efficient and environmentally benign reactions and catalysts that make those processes possible are constant challenges for synthetic organic chemists. The atom economic conversion of aldehydes **1** to the analogous carboxylic esters **2** through dimerization, better known as the Tishchenko (or Claisen–Tishchenko) reaction, has been known for more than a century (Scheme 1).[1,2] This well-known reaction is industrially relevant as the homodimers of aldehydes have found numerous applications in e.g. the fragrance and food industries.[2c,3] For example, the homodimer of 3-cyclohexenecarbaldehyde is a precursor for the formation of durable epoxy resins, whereas benzyl benzoate is used as a dye carrier.



Scheme 1. Tishchenko reaction.

Sodium-[1a,4] and, in particular, aluminium[5] alkoxides are traditionally employed as catalysts in the Tishchenko reaction. Many efforts have been made to develop more efficient aluminium-based catalysts.[6] However, many of those catalysts react sluggishly with aromatic aldehydes such as benzaldehyde or provide the corresponding ester product in low yields.[5,6] Other catalytic systems, which show moderate activity for the dimerization of benzaldehyde to benzyl benzoate, have also been reported, including boric acid,[7] transition-metal catalysts based on Fe,[8] Ru,[9] Os,[10] Zr, and Hf.[11] More recently iridium[12] and lanthanide complexes,[13] as well as heavier alkaline earth amides,[14] have been reported as active catalysts for the Tishchenko reaction and mediate the dimerization of aliphatic and aromatic aldehydes to the carboxylic esters. However, these catalysts are either not commercially available, expensive, difficult to prepare, air- and moisture sensitive, slow, only reactive under extreme conditions, or give small yields. Especially, heteroaromatic aldehydes are known to be difficult to dimerize. The heteroatom of the substrate can form hemilabile Lewis acid/Lewis base adducts with the Lewis acid metal center of the catalyst, which thus hampers the Tishchenko reaction. To the best of our knowledge, only a very few examples of metal hydride mediated Tishchenko reactions have been reported. In those cases, yields for the desired esters were only moderate or even low, the scope was very limited, or high-speed ball milling was required.[15]

Results and Discussion

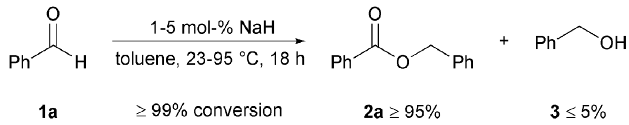
We are interested in the development of novel organocatalysts for redox reactions.[16] While studying the reaction of benzaldehyde (**1a**) in the presence of stoichiometric amounts of various organic and inorganic bases, we observed that sodium hydride acts as an efficient promoter for the dimerization of **1a**. Herein we report that catalytic amounts of inexpensive and commercially available sodium hydride effectively promote the Tishchenko reaction of aromatic and heteroaromatic aldehydes. The reaction is easily performed on a preparative scale of up to several grams of reactant aldehyde under standard laboratory conditions. We initially studied the conversion of benzaldehyde (**1a**) to

---

[a] Leibniz-Institut für Katalyse e. V. an der Universität Rostock,
Albert-Einstein-Str. 29a, 18059 Rostock, Germany
Fax: +49-381-1281-51326
E-mail: Thomas.Werner@catalysis.de

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001294.

benzyl benzoate (**2a**) at 95 °C and room temperature using 1 to 5 mol-% of sodium hydride as the catalyst (Scheme 2). In all cases, the conversion was quantitative after 18 h, even with 1 mol-% catalyst at 23 °C. The only observed by-product was alcohol **3**, which is formed by the reduction of **1a** with sodium hydride.

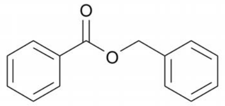
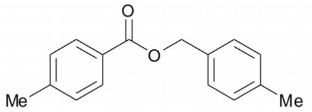
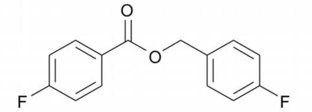
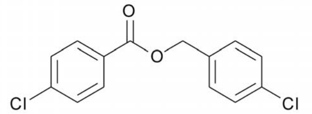
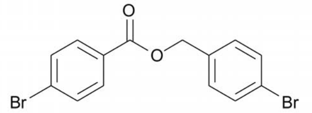
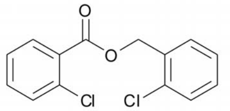
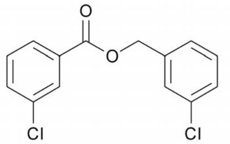
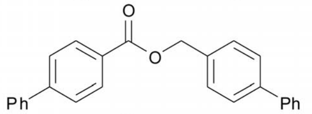
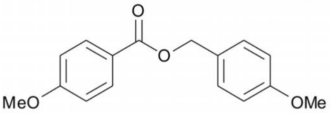
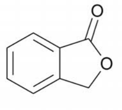


Scheme 2. Sodium hydride catalyzed Tishchenko reaction.

We further investigated the reaction of a range of aromatic aldehydes. In order to achieve full conversion, 5 mol-% sodium hydride was employed. The results are summarized in Table 1. As expected from trial experiments, the conversion of benzaldehyde (**1a**) gave the corresponding product **2a** in an excellent isolated yield of 95% (Entry 1) even on a 10-g scale. Several 4-substituted benzaldehyde derivatives were also converted, and the corresponding dimeric esters **2b**–**e** were obtained in good to excellent yields (Entries 2–5). If 2-chloro- (**1f**) or 3-chloro benzaldehyde (**1g**) is used instead of the 4-isomer **1d** the conversion is <40% at 23 °C. An increase in the reaction temperature to 95 °C leads to quantitative conversion, and **2f** and **2g** were obtained in 95% and 88% yield, respectively (Entries 6 and 7). Under these conditions, very good yields were also obtained for the dimerization products of 4-phenyl- (**1h**) and 4-methoxy benzaldehyde (**1i**) (Entries 8 and 9). Furthermore sodium hydride also effectively mediated the intramolecular Tishchenko reaction of 2-phthalaldehyde (**1j**). The ester product **2j** was isolated in 95% yield after 24 h at 23 °C (Entry 10). When sodium hydride is employed as a 60% dispersion in mineral oil, comparable yields were obtained.

We then turned our attention to the conversion of more challenging heteroaromatic substrates. The results are summarized in Table 2. The conversion of 2-thiophenecarboxaldehyde (**1k**) in the presence of 5 mol-% sodium hydride in toluene at 95 °C gave the corresponding ester **2k** in good yield (Entry 1). Under these conditions, very slow conversion was observed for reactants **1l**–**p**. However, in the presence of 10 mol-% sodium hydride, the dimerization of 2-furaldehyde (**1l**) was quantitative, and **2l** was isolated in 74% yield (Entry 2). Furthermore, the Tishchenko reaction of picoline- (**1m**), nicotine- (**1n**), isonicotine- (**1o**), and chinoline-2-aldehyde (**1p**) gave esters **2m**–**p** in 77, 88, 87, and 86% yield (Entries 3–6), respectively. However, because of the basicity of sodium hydride, this protocol is restricted to aldehydes without an acidic proton in the α-position to the carbonyl group.

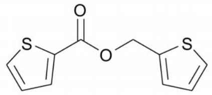
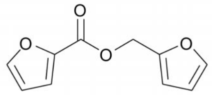
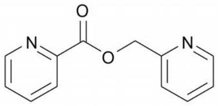
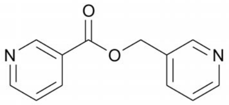
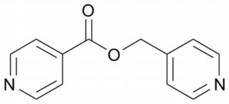
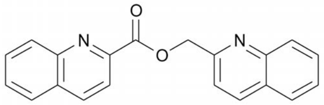
Table 1. Sodium hydride mediated Tishchenko reaction of aromatic aldehydes.[a]

Entry	Ester product		Yield [%][b]
1		**2a**	95[c], (94)[a]
2		**2b**	85
3		**2c**	95
4		**2d**	95
5		**2e**	93
6		**2f**	95[d]
7		**2g**	88[d]
8		**2h**	93[d]
9		**2i**	94[d]
10		**2j**	94[e]

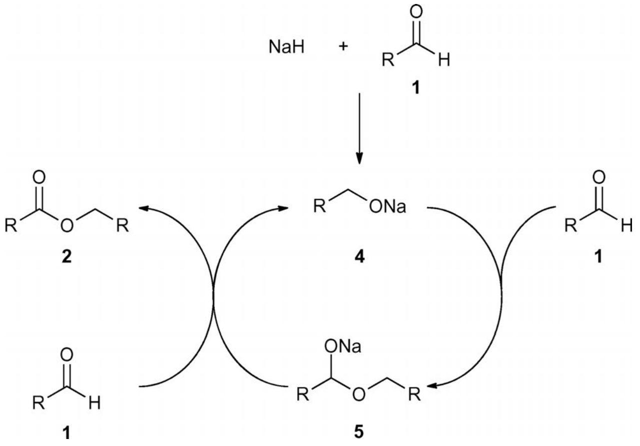
[a] Reaction conditions: 5 mol-% NaH, toluene, 23 °C, 18 h. [b] Isolated yield. [c] 1 mol-% NaH was employed. [d] 95 °C. [e] 24 h.

Even though sodium hydride is generally thought of as a base, it has been demonstrated that it reduces aldehydes to the corresponding alcoholate in the absence of α-hydrogen atoms.[15a,15b] After aqueous work up, the primary alcohols are obtained e.g. benzyl alcohol (**3**). Moreover, sodium alcoholates, such as the sodium salt of benzyl alcohol, undergo Tishchenko reaction in the presence of benzaldehyde.[4] On the basis of those facts, we propose a catalytic cycle for the sodium hydride mediated Tishchenko reaction shown in Scheme 3. The first step is the reduction of aldehyde **1** by sodium hydride, followed by the addition of the formed alcoholate **4** to the carbonyl group of a second aldehyde **1**. A subsequent hydride transfer from intermediate **5** liberates the desired ester **2** and regenerates alcoholate **4**. Thus, sodium hydride might rather be considered as a precatalyst. The proposed mechanism is in agreement with our findings that the corresponding alcohols are formed as a by-product under our reaction conditions.

Table 2. Sodium hydride mediated Tishchenko reaction of heteroaromatic aldehydes.[a]

Entry	Ester product		Yield [%][b]
1		**2k**	78[c]
2		**2l**	74
3		**2m**	77
4		**2n**	88
5		**2o**	87
6		**2p**	86

[a] Reaction conditions: 10 mol-% NaH, toluene, 95 °C, 18 h. [b] Isolated yield. [c] 5 mol-% NaH was employed.



Scheme 3. Proposed catalytic cycle for the sodium hydride catalyzed Tishchenko reaction.

Conclusions

In summary, we introduced an efficient method for the dimerization of aromatic and even heteroaromatic aldehydes to the corresponding esters, promoted by catalytic amounts of inexpensive and commercially available sodium hydride. The reaction can be performed under standard laboratory conditions on a multigram scale. Even ordinary air stable suspensions of sodium hydride in paraffin oil can be employed, which makes this method an attractive alternative to most other procedures. Further mechanistic investigations and the use of other hydride sources are currently under investigation.

Experimental Section

A Typical Procedure: Benzaldehyde (**1a**) (9.62 g, 90.7 mmol) was added to a suspension of NaH (22.9 mg, 0.907 mmol) in absolute toluene (15 mL) at 23 °C. After the reaction mixture was stirred for 18 h at 23 °C, it was diluted with CH_2Cl_2 (60 mL), HCl solution (1 м, 35 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried with $MgSO_4$. After the removal of all volatiles in vacuo, the crude product was purified by Kugelrohr distillation (160 °C, 2.1 mbar) to obtain **2a** as a pale yellow liquid (9.20 g, 43.3 mmol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.41 (s, 2 H), 7.38–7.52 (m, 7 H), 7.56–7.62 (m, 1 H), 8.12–8.15 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 66.56, 128.06, 128.13, 128.27, 128.49, 129.59, 130.01, 132.92, 135.95, 166.29 ppm. $C_{14}H_{12}O_2$ (212.24): calcd. C 79.22, H 5.70; found C 79.35, H 5.68.

Supporting Information (see footnote on the first page of this article): General procedures, experimental details, and compound characterization data are presented.

Acknowledgments

Financial support from the Deutsche Forschungsgemeinschaft (WE 3605/3-1) and the Leibniz-Institut für Katalyse e. V. an der Universität Rostock, as well as support and advice from Prof. M. Beller, are gratefully acknowledged.

---

[1] a) L. Claisen, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 646–650; b) W. Tishchenko, *Chem. Zentralbl.* **1906**, *77*, 1309.
[2] For recent reviews on Tishchenko reactions see: a) O. P. Törmäkangas, A. M. P. Koskinen, *Recent Res. Dev. Org. Chem.* **2001**, *5*, 225–255; b) R. Mahrwald, *Curr. Org. Chem.* **2003**, *7*, 1713–1723; c) T. Seki, T. Nakajo, M. Onaka, *Chem. Lett.* **2006**, *35*, 824–829; d) K. Ekoue-Kovi, C. Wolf, *Chem. Eur. J.* **2008**, *14*, 6302–6315.
[3] *Ullman's Encyclopedia of Industriel Chemistry*, 6th ed., Wiley-VCH, Weinheim, **2002**.
[4] O. Kamm, W. F. Kamm, *Org. Synth.* **1922**, *2*, 5.
[5] a) W. C. Child, H. Adkins, *J. Am. Chem. Soc.* **1925**, *47*, 798–807; b) F. J. Villani, F. F. Nord, *J. Am. Chem. Soc.* **1947**, *69*, 2605–2607; c) I. Lin, A. R. Day, *J. Am. Chem. Soc.* **1952**, *74*, 5133–5135; d) Y. Ogata, A. Kawasaki, I. Kishi, *Tetrahedron* **1967**, *23*, 825–830; e) Y. Ogata, A. Kawasaki, *Tetrahedron* **1969**, *25*, 929–935.
[6] a) T. Ooi, T. Miura, K. Takaya, K. Maruoka, *Tetrahedron Lett.* **1999**, *40*, 7695–7698; b) I. Simpura, V. Nevalainen, *Tetrahedron* **2001**, *57*, 9867–9872; c) T. Ooi, K. Ohmatsu, K. Sasaki, T. Miura, K. Maruoka, *Tetrahedron Lett.* **2003**, *44*, 3191–3193.
[7] P. R. Stapp, *J. Org. Chem.* **1973**, *38*, 1433–1434.
[8] a) M. Yamashita, Y. Watanabe, T. A. Mitsudo, Y. Takegami, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3597–3600; b) M. Yamashita, T. Ohishi, *Appl. Organomet. Chem.* **1993**, *7*, 357–361.
[9] a) H. Horino, T. Ito, A. Yamamoto, *Chem. Lett.* **1978**, 17–20; b) T. Ito, H. Horino, Y. Koshiro, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 504–512; c) S. Omura, T. Fukuyama, Y. Murakami, H. Okamoto, I. Ryu, *Chem. Commun.* **2009**, 6741–6743; d) M.-O. Simon, S. Darses, *Adv. Synth. Catal.* **2010**, *352*, 305–308.
[10] P. Barrio, M. A. Esteruelas, E. Onate, *Organometallics* **2004**, *23*, 1340–1348.
[11] K. Morita, Y. Nishiyama, Y. Ishii, *Organometallics* **1993**, *12*, 3748–3752.
[12] T. Suzuki, T. Yamada, T. Matsuo, K. Watanabe, T. Katoh, *Synlett* **2005**, 1450–1452.
[13] a) S.-y. Onozawa, T. Sakakura, M. Tanaka, M. Shiro, *Tetrahedron* **1996**, *52*, 4291–4302; b) H. Berberich, P. W. Roesky, *An-*

gew. Chem. **1998**, *110*, 1618–1620; *Angew. Chem. Int. Ed.* **1998**, *37*, 1569–1571; c) M. R. Bürgstein, H. Berberich, P. W. Roesky, *Chem. Eur. J.* **2001**, *7*, 3078–3085; d) G. B. Deacon, A. Gitlits, P. W. Roesky, M. R. Bürgstein, K. C. Lim, B. W. Skelton, A. H. White, *Chem. Eur. J.* **2001**, *7*, 127–138; e) A. Zulys, P. W. Roesky, G. B. Deacon, K. Konstas, P. C. Junk, *Eur. J. Org. Chem.* **2008**, 693–697.

[14] M. R. Crimmin, A. G. M. Barrett, M. S. Hil, P. A. Procopiou, *Org. Lett.* **2007**, *9*, 331–333.

[15] a) F. W. Swamer, C. R. Hauser, *J. Am. Chem. Soc.* **1946**, *68*, 2647–2649; b) G. E. Lewis, *J. Org. Chem.* **1965**, *30*, 2433–2436; c) M. Govindan, H. W. Pinnick, *J. Org. Chem.* **1981**, *46*, 5011–5014; d) Y.-S. Hon, C.-P. Chang, Y.-C. Wong, *Tetrahedron Lett.* **2004**, *45*, 3313–3315; e) Y.-S. Hon, Y.-C. Wong, C.-P. Chang, C.-H. Hsieh, *Tetrahedron* **2007**, *63*, 11325–11340; f) D. C. Waddell, J. Mack, *Green Chem.* **2009**, *11*, 79–82.

[16] T. Werner, *Adv. Synth. Catal.* **2009**, *351*, 1469–1481.

Received: September 16, 2010