Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 25 Jul 2007.

To cite this article: Zhiyi Yao , Deju Ye , Hong Liu , Kaixian Chen & Hualiang Jiang (2007): Transformation of Aryl Acyloin O-Alkyl and O-Phenyl Derivatives to Ketones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:1, 149-156

To link to this article: http://dx.doi.org/10.1080/00397910600978564

Synthetic Communications®, 37: 149–156, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910600978564

Transformation of Aryl Acyloin *O*-Alkyl and *O*-Phenyl Derivatives to Ketones

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Abstract: The treatment of aryl acyloin (α-hydroxyketone) *O*-alkyl and *O*-phenyl derivatives with 2–3 equiv of Zn and 1–2 equiv of NH_4Cl in ethanol, refluxing for 20–120 min, gave the corresponding ketones with excellent yields. Further, α,β-epoxy ketones can be efficiently transformed to β-hydroxy ketones, and 2,2-dialkoxy-1-phenyl ketone also can be dealkoxylated to 1-phenyl ketone.

Keywords: aryl acyloin *O*-derivatives, deoxygenation, 2,2-dialkoxy-1-phenyl ethanone, α,β-epoxy ketones

INTRODUCTION

The reductive transformation of acyloins and acyloin *O*-acyl derivatives to ketones is one of the important processes in the synthesis of natural products.[1] Reactions utilizing various reagents for this kind of transformation

Received in Japan March 24, 2006
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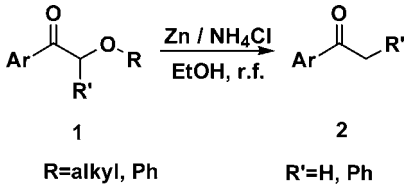


Scheme 1. Transformation of aryl acyloin *O*-derivatives to ketones with Zn/NH_4Cl.

have been reported.[2–5] However, not only are the reported reagents complex and difficult to prepare, but also the yields of reaction are not ideal. Therefore, several methods have been devised to try to improve the reaction.[6] First, Yanagita et al.[7] reported that acyloin *O*-acyl derivatives can be transformed to ketones with Zn in glacial acetic acid after refluxing for 24 h with a yield of 50%, and then Ibuka et al.[8] reported and optimized the transformation of acyloin *O*-acyl and *O*-mesyl derivatives to ketones with a yield of 99%. However, the reagents reported for the transformation of acyloin *O*-alkyl and *O*-phenyl derivatives to the corresponding ketones are limited.[9]

In the present communication, we used Zn/NH_4Cl as the reagent for this transformation and good to excellent yields were reached (Scheme 1). The application of this reagent is summarized in Table 1. The aryl acyloin *O*-phenyl was synthesized by the reaction of the corresponding 2-bromo-1-aryl-ethanones with phenol in the presence of potassium carbonate at reflux in good yields.[10] All the aryl acyloin *O*-alkyl derivatives were purchased from Aldrich.

RESULTS AND DISCUSSION

Using phenyl acyloin *O*-phenyl (**1a**) as a model compound, we optimized the reaction conditions by testing several parameters, such as reaction solvent, different amounts of Zn and NH_4Cl, and reaction time. The results are summarized in Table 2. We compared the reaction yields using ethanol and CH_2Cl_2 as reaction solvents during the synthesis of compound **2a**. The result indicated that the reaction is more efficient when taking ethanol as solvent (99%, 30 min) than when taking CH_2Cl_2 as solvent (27%, 18 h). Compound **1a** was separately dephenoxylated with 0.1, 1.5, and 2.5 equiv of Zn and 1.5 equiv of NH_4Cl in ethanol at reflux and different reaction times. After 30 min, the conversion rate of **1a** achieved 100% (yield 99%) using 2.5 equiv of Zn (Entry 6). When using 2.5 equiv of Zn without NH_4Cl, nearly no depheoxylation was produced (Entry 7), and with 0.5, 1.0, and 1.5 equiv of NH_4Cl, the yields increased with the amounts of NH_4Cl. With 1.5 equiv of NH_4Cl, the reaction completed (yield 99%). After 2 h, the reactions with the lower amount of 1.5 equiv of Zn were incomplete with a corresponding conversion rate of 80% (yield 75%). This

Table 1. Examples of transformation from aryl acyloin *O*-alkyl and *O*-phenyl derivatives to ketones with Zn/NH_4Cl

Compound	Substrate	Compound	Product	Time (min)	Yield (%)[a]
1a	$PhCOCH_2OPh$	**2a**	PhCOMe	30	99
1b	$PhCOCH_2OMe$	**2a**	PhCOMe	30	93
1c	$PhCOCH_2OAc$	**2a**	PhCOMe	20	99
1d	$PhCOCH_2OCH_2(Me)_2$	**2a**	PhCOMe	30	99
1e	2,3-(OCH_2CH_2O)-$PhCOCH_2OMe$	**2e**	2,3-(OCH_2CH_2O)-PhCOMe	30	90
1f	2,3-(OCH_2CH_2O)-$PhCOCH_2OPh$	**2e**	2,3-(OCH_2CH_2O)-PhCOMe	30	96
1g	2,3-(OCH_2CH_2O)-Ph $COCH_2OCH(Me)_2$	**2e**	2,3-(OCH_2CH_2O)-PhCOMe	30	93
1h	4-MeOPh$COCH_2OPh$	**2h**	4-MeOPhCOMe	30	99
1i	2,5-$(MeO)_2$Ph $COCH_2OPh$	**2i**	2,5-$(MeO)_2$ PhCOMe	30	99
1j	4-ClPh$COCH_2OPh$	**2j**	4-ClPhCOMe	30	97
1k	4-CF_3Ph$COCH_2OPh$	**2k**	4-CF_3PhCOMe	30	74
1l	4-FPh$COCH_2OPh$	**2l**	4-FPhCOMe	30	90
1m	PhCOCH(Ph)OMe	**2m**	$PhCOCH_2Ph$	120	93
1n	PhCOCH(Ph)OPh	**2m**	$PhCOCH_2Ph$	120	99
1o	PhCOCH(Ph) $OCH(CH_3)_2$	**2m**	$PhCOCH_2Ph$	120	96
1p	$PhCH_2CH_2OPh$		No reaction	30	0
1q	3-PhOPhCOOH		No reaction	30	0

[a]Isolated yields.

Table 2. Comparison of dephenoxylation methods for compound **1a**

Entry	Zn (equiv)	NH_4Cl (equiv)	Time (min)	Product (yield, %)
1[a]	2.5	1.5	30	0
2[a]	2.5	1.5	18 h	27
3	0.1	1.5	30	10
4	1.5	1.5	30	57
5	1.5	1.5	2 h	75
6	2.5	1.5	30	99
7[b]	2.5	0.0	30	0
8	2.5	0.5	30	55
9	2.5	1.0	30	70
10	2.5	1.5	60	99

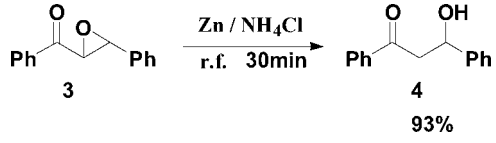
[a]The solvent is dry CH_2Cl_2.
[b]The reaction was refluxing in absolute EtOH under N_2.

indicates that the optimization of the dephenoxylation conditions by increasing the amount of Zn may be more useful than extending the reaction time. The optimum results were usually obtained when 5 mM of the starting material was allowed to react with 2–3 equiv of Zn and 1–2 equiv of NH_4Cl turning in 5–10 mL of ethanol at reflux for 20–120 min. The products were obtained by column chromatography with silica gel.

The reactions of dealkoxylation and dephenoxylation of aryl acyloin *O*-derivatives under the optimized conditions are summarized in Table 1. The results indicate that *O*-phenyl derivatives (compounds **1a** and **1f**, in Table 1) are easy to reductively cleave by Zn/NH_4Cl, but the *O*-methyl group is relatively stable under the same condition (compounds **1b** and **1e**). No obvious change has been seen for the yields of dealkoxylate and dephenoxylate when the phenyl of phenyl acyloin (compounds **1a**–**1d**) was changed to 1,4-benzodioxane (compounds **1e**–**1g**). Moreover, compounds with electron-donating groups such as *p*-MeO- and 2,5-MeO- (compounds **1h, 1i**) are much easily dephenoxylated, whereas compounds with strong electron-withdrawing groups such as *p*-CF_3- or *p*-F- (compounds **1k, 1l**) gave lower product yields. At last, introduction of a phenyl to the C_α atoms for the compounds **1m**–**1o** prolonged the reaction time. All of the C_α-phenyl substituted aryl acyloin *O*-derivatives need ~2 h to finish the reaction, and yields are excellent (Table 1).

To determine whether the reagent had an effect on the dephenoxylation of aryl ether without carbonyl, we mixed benzyl phenyl ether (compound **1p**) and 3-phenoxybenzoic acid (compound **1q**) with Zn/NH_4Cl. No product was determined after 30 min for these two reactions, indicating that the adjacent carbonyl is necessary in the substrates to be dephenoxylated by Zn/NH_4Cl.

Yamakawa and Nishitani[11] has reported using zinc in acetic acid to open the α,β-epoxy ketones to get the β-hydroxy ketones in only 53% yield, together with enone as a side product, and then Hasegawa et al. used an effective photoinduced reagent of 1,3-dimethyl-2-phenylbenzimidazoline (DMPBI) acetic acid[12] to optimize the transformation. All of the conversions are 100% (yield >80%) after 1 h. However, the side products of this reaction could not be isolated completely. Here, we applied our reagent to this transformation by taking *trans*-1,3-diphenyl-2,3-epxoypropane-1-one (**3**, in Scheme 2) as the substrate; the yield of the β-hydroxy ketone (**4**) is 93% after 30 min in CH_2Cl_2 at reflux. In the whole process, no α-hydroxy



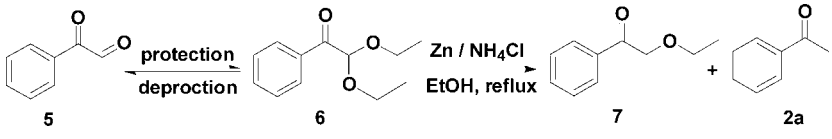
Scheme 2. Transformation of α,β-epoxy ketones to β-hydroxy ketones.

ketone and enone were generated, and the β-hydroxy ketone is the exclusive product. Our method may be an efficient and clean approach for the transformation of α,β-epoxy ketones to β-hydroxy ketones.

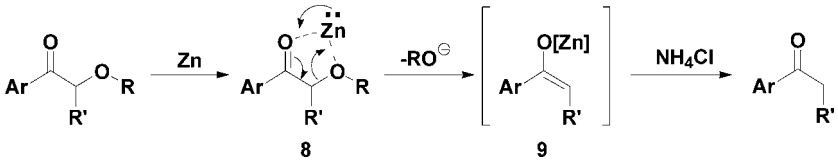
To date, most of the reports on the 2,2-dialkoxy-1-phenyl ethanone, which can be easily transformed from the oxo-phenylacetaldehyde[13] (**5**), are about their deprotections to give the corresponding 1,2-dione[14] (Scheme 3). We tried to apply our reagent to the 2,2-diethoxy-1-phenyl ethanone (**6**) by using 2–3 equiv of Zn and 1–2 equiv of NH_4Cl in ethanol at reflux; after 30 min, the yields of 2-ethoxyl-1-phenyl-ethanone (**7**) and 1-phenyl ethanone (**2a**) are 36% and 56%, respectively, whereas with additional 2–3 equiv of Zn and 1–2 equiv of NH_4Cl and expanding the time to 4 h, 1-phenyl ethanone was the exclusive product (yield 99%), as shown in Scheme 3. The results indicate that Zn/NH_4Cl may provide a novel method for transforming 1,2-dione to ketone. Remarkably, the dealkoxylation and dephenoxylation of aryl acyloin *O*-alkyl and *O*-phenyl derivatives with Zn/NH_4Cl can be carried out in an aqueous medium with very mild conditions.

We propose a reaction mechanism (Scheme 4) for the transformation. Initially, a zinc atom coordinates with the ketone and C_α-oxygen atoms, forming a five-membered cyclic transition state (**8**). This complexation forces a flat conformation, facilitating the donation of a pair of electrons from the zinc to the ketone oxygen and then promoting the release of the anion of the *O*-alkyl or *O*-phenyl to form a zinc enolate (**9**), which is the same as the intermediate depicted by Fürstner in which the metal was Ti.[9] Afterward, the final ketone will be produced through neutralization and tautomerization. The experiment of deuteration of the intermediacy of zinc enolate **9** using D_2O instead of NH_4Cl was done. After one night, the conversion rate of 2-methoxy-1-phenyl-ethanone (**1b**) to 2-deuterio-1-phenyl-ethanone is nearly 100%.

In summary, a convenient and efficient method for dealkoxylation and dephenoxylation of aryl acyloin *O*-alkyl and *O*-phenyl derivatives with Zn/NH_4Cl in EtOH is described, and its mechanism is proposed. This method can also be efficient for the transformation of α,β-epoxy ketones to β-hydroxy ketones. We also reported, for the first time, a direct way of transforming 2,2-dialkoxy-1-phenyl ethanone to 1-phenyl ethanone.



Scheme 3. Transformation of 2,2-diethoxy-1-phenyl ethanone with Zn/NH_4Cl: (a) 2–3 equiv of Zn and 1–2 equiv of NH_4Cl, 30 min, **7**: 36%, **2a**: 56%; (b) 4–6 equiv of Zn and 2–4 equiv of NH_4Cl, 4 h, **7**: 0%, **2a**: 99%.



Scheme 4. Proposed mechanism for the dealkoxylation and dephenoxylation of aryl acyloin *O*-alkyl and *O*-phenyl derivatives by Zn/NH_4Cl.

EXPERIMENTAL

IR spectra were measured with a Perkin-Elmer 598B spectrometer using KBr pellets. NMR spectra were determined on a Bruker AMX-400 instrument in $CDCl_3$. MS spectra were recorded on a MAT-95 spectrometer. Products are characterized by comparison of their spectral data (^{1}H NMR, IR) to those reported in the literature.

A typical procedure is as follow: 5 mmol each of aryl *O*-derivatives were dissolved in 5 mL of EtOH, and a certain amount of Zn and NH_4Cl were added. Then the mixture was stirred for a period of time at reflux. Zn was filtered off, and EtOH was removed under vacuum. Then 5 mL of H_2O was added to the remains and the system was extracted with CH_2Cl_2 three times. On evaporation of the solvent, pure ketones were obtained by column chromatography with silica gel.

1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-ethanone.[15] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H), 4.24 (m, 2H), 4.26 (m, 2H), 6.90 (d, 1H, $J = 8.8$ Hz), 7.48 (d, 1H, $J = 8.8$ Hz), 7.50 (s, 1H).

3-Hydroxy-1,3-diphenyl-1-propanone.[16] ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38 (d, 2H, $J = 6.4$ Hz), 3.60 (s, 1H, OH), 5.35 (t, 1H, $J = 6.4$ Hz), 7.32 (t, 1H, $J = 7.2$), 7.38 (t, 2H, $J = 7.2$), 7.46 (m, 4H), 7.59 (t, 1H, $J = 7.2$), 7.96 (d, 2H, $J = 7.2$).

2-Ethoxy-1-phenyl-ethanone.[17] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (t, 3H, $J = 7.0$), 4.25 (q, 2H, $J = 7.0$), 5.22 (s, 2H), 7.30 (t, 1H, $J = 7.2$), 7.38 (t, 2H, $J = 7.2$), 7.90 (d, 2H, $J = 7.2$).

ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the State Key Program of Basic Research of China (Grant 2002CB512802), the National Natural Science Foundation of China (Grants 20372069, 29725203, and 20472094), the Basic Research Project for Talent Research Group from the Shanghai Science and Technology Commission, the Key Project from the Shanghai

Science and Technology Commission (Grant 02DJ14006), the Key Project for New Drug Research from Chinese Academy of Sciences (CAS), and the 863 Hi-Tech Program (Grants 2002AA233061, 2002AA104270, 2002AA233011, and 2003AA235030).

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