SHORT COMMUNICATION

EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201500655

Synthesis of *N*-Acyl-N,O-acetals from Aldehydes, Amides and Alcohols

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Keywords: N,O-Acetals / Hemiaminals / *N*-Acylimines / Synthetic methods / Aldehydes

A general synthesis of *N*-acyl-N,O-acetals from aldehydes, amides and alcohols is reported. This new method consists of two single steps: (a) magnesium-mediated addition of an amide or carbamate to an aldehyde and (b) acid-catalyzed conversion of the *N*-acylhemiaminal to the *N*-acyl-N,O-acetal. This two-step protocol allows the multigram synthesis of various *N*-acyl-*O*-alkyl-N,O-acetals.

Introduction

The *N*-acyl-N,O-acetal motif is an important substructure in organic chemistry. Such N,O-acetals are useful building blocks for organic synthesis and synthetic equivalents of unstable *N*-acylimines.[1] On the one hand *N*-acyl-N,O-acetals are stable towards air and water and have an extended shelf-life. On the other hand they can be activated with suitable Lewis or Brønsted acids to generate reactive *N*-acylimines. In addition the *N*-acyl-N,O-acetal and the analogous *N*-acylhemiaminal motifs are found in a number of natural products with interesting biological activities, such as zampanolide (**1**),[2] psymberin (**2**),[3] or pederin (**3**)[4] (Figure 1).

Due to their importance several synthetic routes to *N*-acyl-N,O-acetals have been developed. Two of the most commonly employed syntheses are Katritzky's benzotriazole method[5] and the preparation via amido-sulfones.[6] In both methods, a suitable precursor, either an *N*-[α-(benzotriazol-l-yl)alkyl]amide or an α-amido-sulfone, is treated with sodium alkoxides. However, for alkyl-aldehyde-derived substrates, these reactions lead to the formation of the corresponding enamides.[7] Another approach is based on the hydrozirconization of nitriles followed by acylation and trapping of the acylimine with an alcohol.[8] Recently, the group of Antilla developed an asymmetric synthesis of *N*-acyl-N,O-acetals starting from unstable *N*-acylimines.[9] Other methods are limited to certain substrate types, such as chloral,[10] glyoxalates[11] or resin-supported amides[12] or were developed for the synthesis of specific natural products, e.g. a Curtius rearrangement in the synthesis of zampanolide (**1**), dactylolide or psymberin (**2**)[13] or by oxidative decarboxylations from suitable *N*-acylamino acids.[14] During our research on *N*-acylimine-based multicomponent reactions[15] we became interested in *N*-acyl-N,O-acetals as stable *N*-acylimine precursors. Therefore, we were looking for an operational simple, scalable and efficient synthesis of *N*-acyl-N,O-acetals. From this point of view the titanium ethoxide mediated 3-component synthesis reported by Huang and Wen looked particularly well suited.[16] However, in our hands this method proved to be unreliable, and we obtained irreproducible yields between 15 and 50% of the desired *N*-acyl-N,O-acetal **8a**. Especially for reactions performed on a larger scale (5–50 mmol) the yield dropped dramatically. We assume, these low yields are associated with decomposition of the product during the difficult and slow filtration of TiO_2 formed during the aqueous workup.[17] Herein we describe a new method for the preparation of *N*-acyl-N,O-acetals from aldehydes, amides and alcohols.

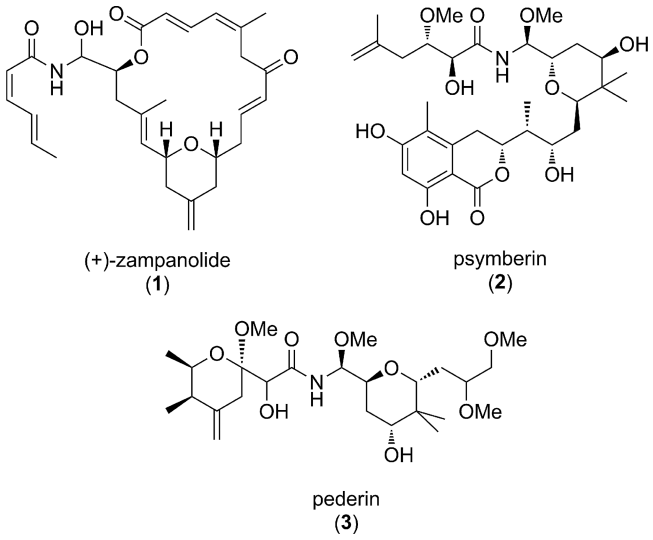

Figure 1. Natural compounds containing the *N*-acyl-N,O-acetal and the analogous *N*-acylhemiaminal motifs.

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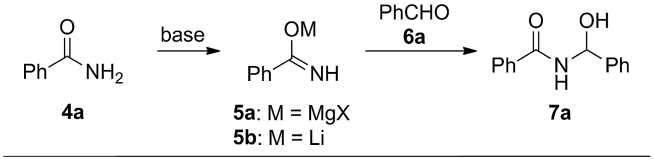
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500655.

Results and Discussion

Our strategy for the *N*-acyl-N,O-acetal synthesis was based on the direct addition of an amide to an aldehyde to give an N,O-hemiaminal followed by acid-catalyzed reaction with an alcohol. Such direct additions of an amide or amide anion have been reported as a suitable method for the preparation of N,O-hemiaminals.[7,18] Indeed, the direct addition of the magnesium carboxoimidoate **5a**, generated from benzamide **4a** and MeMgCl or *i*PrMgCl·LiCl, to benzaldehyde **6a** furnished the desired hemiaminal **7a** in almost quantitative yields (Table 1, Entries 1 and 2). Interestingly, the corresponding lithium carboxoimidoate **5b** did not add to benzaldehyde (Entry 3). Stoichiometric amounts of base were necessary for an efficient addition (Entry 4). In our hands, hemiaminal **7a** proved to be unstable towards column chromatography or upon prolonged storage. Therefore, the crude product mixture was directly used for the second step.[19]

Table 1. Influence of the base on the direct addition.

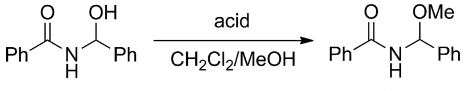


Entry	Base (equiv.)	Yield [%][a]
1	MeMgCl (1.05)	> 95
2	*i*PrMgCl·LiCl (1.05)	> 95
3	*n*BuLi (1.05)	> 5
4	MeMgCl (0.20)	15

[a] Yield determined by NMR spectroscopy.

To our delight, treatment of the crude hemiaminal **7a** with MeOH in the presence of a suitable acidic catalysts furnished the corresponding *N*-acyl-N,O-acetal **8a** in 52–76% yield over two steps (Table 2). Best yields were obtained with $Sc(OTf)_3$ and pyridinium *p*-toluenesulfonate (PPTS) (Entries 2 and 4). *N*-Acyl-N,O-acetal **8a** proved to be stable during column chromatography and upon prolonged storage at room temperature. It is worth mentioning,

Table 2. Influence of the acid on the transacetalization.

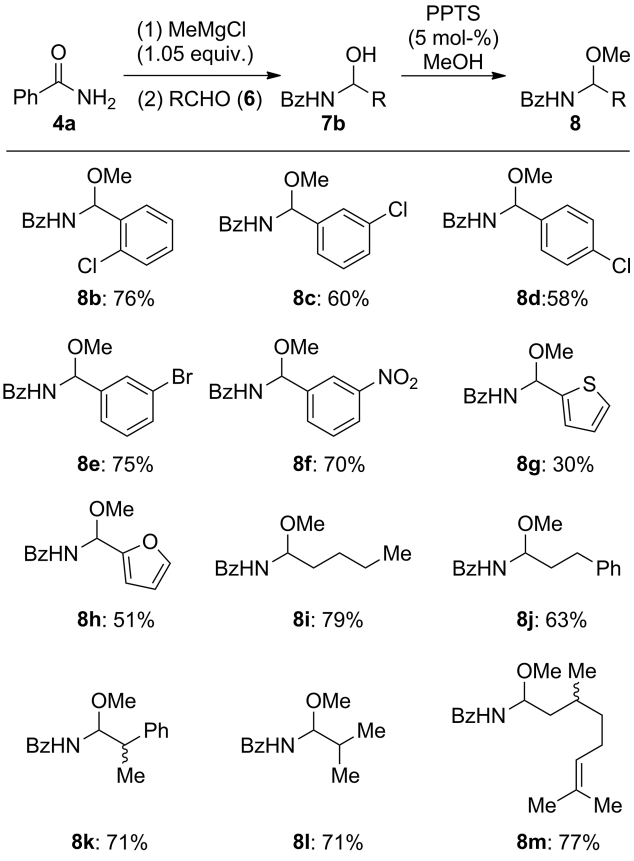


Entry	Acid (equiv.)	Yield [%][a]
1	Amberlyst-15 (0.05)	52
2	$Sc(OTf)_3$ (0.05)	72
3	$TsOH·H_2O$ (0.05)	66
4	PPTS (0.05)	76, 52[b]

[a] Yield of isolated product; yield over two steps based on **4a** as limiting reagent. [b] Reaction performed on a 100 mmol scale.

that this reaction sequence can be easily performed on a multigram scale with a slightly reduced yield.[20] We routinely run this two-step protocol on a 100 mmol scale, thereby obtaining 12.5 g (52% yield) of the *N*-acyl-N,O-acetal **8a** within 1 d.

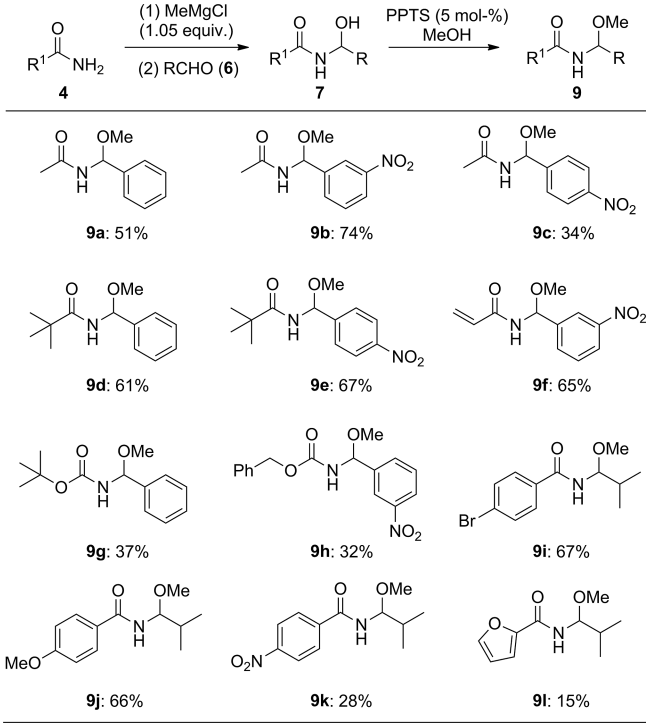
With the reaction conditions in hand we investigated the scope of our method. Various aryl- and heteroarylaldehydes **6b**–**6h** can be transformed into the desired *N*-acyl-N,O-acetals **8b**–**8h** in 30–76% yield over two steps (Scheme 1). Also alkylaldehydes proved to be suitable substrates, and the *N*-acylimine precursors **8i**–**8l** were obtained in 63–79% yield. Interestingly, reaction of citronellal with benzamide followed by transacetalization furnished the *N*-acyl-N,O-acetal **8m** in 77% yield. No intramolecular reactions were observed in this case.



Scheme 1. Reactions with different (hetero)aryl- and alkylaldehydes.

As shown in Scheme 2, various aryl- and alkylamides are suitable substrates for our two-step protocol and furnished the desired *N*-acyl-N,O-acetals **9a**–**f** in 34–67% yield. The reaction of acetamide with different arylaldehydes shows, that the overall yield is dependent on the exact combination of amide and aldehyde. Thus, the *N*-acyl-N,O-acetals **9a**–**c** were obtained in 34%, 51% and 74% yield, respectively.

Carbamates can be used as amide component in our reaction, albeit with lower yields. Thus, reaction of benzyl carbamate or *tert*-butyl carbamate provided the *N*-carbamoyl-N,O-acetals **9g** and **9h** in 37 and 32% yield, respec-



Scheme 2. Selected combinations of aldehydes and amides.

tively. Aromatic amides could be converted into the corresponding *N*-acyl-N,O-acetals **9i** and **9j** in satisfactory yields of 67% and 66%. Only in the case of electron-poor or heteroaromatic amides were the corresponding *N*-acylimine precursors **9k** and **9l** isolated in low yields.

Our two-step protocol is especially suitable for the synthesis of various *N*-acyl-*O*-alkyl-N,O-acetals. Replacement of MeOH by other alcohols in the transacetalization step delivers the expected *O*-alkyl-N,O-acetals in moderate to good yields. In all cases higher yields were obtained with $Sc(OTf)_3$ as catalyst (Scheme 3).

Conclusions

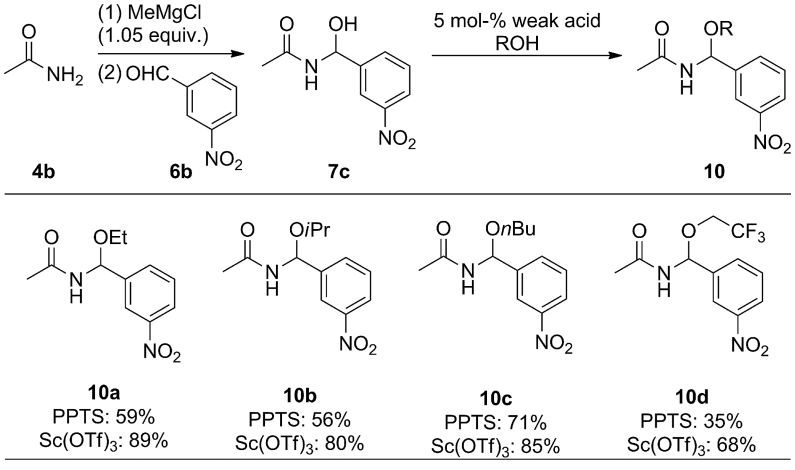
We have developed a new two-step protocol for the synthesis of *N*-acyl-N,O-acetals from aldehydes, amides and alcohols. This method is based on the magnesium-mediated addition of amides to aldehydes followed by an acid-catalyzed transacetalization of the obtained hemiaminal to the desired *N*-acyl-N,O-acetals. This method has a very broad scope, provides an efficient and rapid access to various *N*-acyl-N,O-acetals and is amendable to multigram-scale synthesis.

Experimental Section

General Two-Step Procedure for the Synthesis of N,O-Acetals

Step 1. Synthesis of Hemiaminal: A flame-dried and argon-filled Schlenk flask connected to a Schlenk line was charged with amide **4** (1.0–1.2 equiv., 5.00–6.00 mmol), dry THF (2 mL/mmol amide) and a suitable stirring bar. The resulting solution was cooled to –40 to –50 °C, and MeMgCl (1.05 equiv., 2.55 M in THF) was added slowly through a syringe under vigorous stirring. (***Caution!*** During the addition a rapid evolution of methane takes place; the reactions should not be performed in a closed system!) During the addition a white solid may precipitate, and stirring can become difficult. The resulting mixture was warmed to room temperature and stirred for 15 min. Then the reaction mixture was cooled to 0 °C, and aldehyde **6** (1.0 equiv. to 1.1 equiv., 5.0–5.5 mmol) was added rapidly. The reaction mixture was warmed to room temperature and stirred until TLC analysis showed complete consumption (1 h 25 min to 5 h) of the limiting reagent (amide or aldehyde). After completion, saturated aqueous $NaHCO_3$ (20 mL) was added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted three times with dichloromethane (20 mL). The combined organic layers were dried with Na_2SO_4. (***Note!*** The crude hemiaminals are unstable towards prolonged contact with water; therefore, a rapid workup is recommended!) After evaporation of the solvents, the crude product is dried at room temperature under oil-pump vacuum (10^{-2} mbar) for 2–3 h.

Step 2. Transacetalization: The crude hemiaminal **7** was dissolved in methanol (3 mL/mmol), and 5 mol-% pyridinium *p*-toluenesulf-



Scheme 3. Reactions with different alcohols.

onate or 5 mol-% $Sc(OTf)_3$ was added. In case of insoluble hemiaminals a mixture of methanol and dichloromethane (1:1, v/v) was used. The reaction mixture was warmed to room temperature and stirred until TLC analysis showed complete consumption of the hemiaminal (45 min to 24 h). Then saturated aqueous $NaHCO_3$ (20 mL) and dichloromethane (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted three times with dichloromethane (20 mL). The combined organic layers were dried with Na_2SO_4. After evaporation of the solvents, the crude product was purified by flash chromatography with *n*-hexane/EtOAc (or cyclohexane) + 0.2 vol.-% NEt_3.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, analytical, and spectroscopic data (^1H, ^{13}C NMR) for all new compounds.

Acknowledgments

This work was financially supported by the Fonds der Chemischen Industrie (Liebig fellowship to G. M.), the Evonik Foundation (Ph.D. fellowship to J. H.), and the Polytechnische Gesellschaft Frankfurt am Main (Ph.D. fellowship to T. B.). We would like to thank Rockwood Lithium (Frankfurt), BASF (Ludwigshafen) and Evonik Industries (Darmstadt) for the generous gift of chemicals.

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[19] Analytically pure samples of the hemiaminal can be obtained by recrystallization (*n*-hexane/dichloromethane, 9:1).

[20] The reduced yield is associated with partial decomposition of hemiaminal **7a** during the prolonged aqueous workup for the reaction performed on a >10 mmol scale.

Received: May 20, 2015
Published Online: June 24, 2015

