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A highly efficient transacetalization of 2-formylpyrrole acetals in alkaline media

Zhao Hua Yan *, Run Hua Kang, Yong Jie Liu, Sen Lin **

Department of Chemistry, Nanchang University, Nanchang 330031, China

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Abstract

The reaction of 2-formylpyrrole acetals with sodium alkoxide in alcohols at reflux temperature smoothly proceeded to generate corresponding transacetalization products in nearly quantitative yields. A plausible mechanism involving the formation of a highly reactive intermediate azafulvene species was proposed to explain the observed transformation.

Keywords: 2-Formylpyrrole acetal; Transacetalization; Sodium alkoxide

Acetal is one of the most widely used and versatile protecting group of carbonyl, hydroxyl, and diol groups in organic synthesis. They are usually prepared through the reaction of carbonyl compound with alcohol, diol, or trialkyl orthoformate in the presence of a protic or lewis acid [1]. Transacetalization has become increasingly useful in organic synthesis. For example, transacetalization is often needed to switch one protecting group to another, and a variety of interesting compounds of 1,3-dioxanes, 1,3-oxazolidines and bioactive products were synthesized by transacetacetalization [2–4]. Traditionally, protic or lewis acid is usually employed to catalyze transacetalization. Recently, 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) [5] and ruthenium, rhodium and iridium complexes [6] have been employed to catalyze transacetalization. However, transacetalization in alkaline media was only sporadically reported in the case of the specific β-keto acetals substrates [7].

2-Formylpyrrole compounds have been widely used in the synthesis of oligopyrrolic compounds, porphyrins and many bioactive natural and non-natural products [8,9]. In our ongoing program on acid-catalyzed trimerization of 2-formylpyrrole acetals directed towards the synthesis of a new type of ring system heterocyclic compound, we required various 2-formylpyrrole acetal as substrates.

First, we prepared 2-formylpyrrole acetal *via* reaction of 2-formylpyrrole compound with alcohol in the presence of *para*-toluenesulfonic acid [10]. However in most cases, 2-formylpyrrole acetals were obtained in low or moderate yields with the formation of considerable amount of other unidentified product as by-product requiring cumbersome separation, and only in few cases, desired 2-formylpyrrole acetal was prepared in high yield.

* Corresponding author.
** Corresponding author.
E-mail address: yanzh@ncu.edu.cn (Z.H. Yan).

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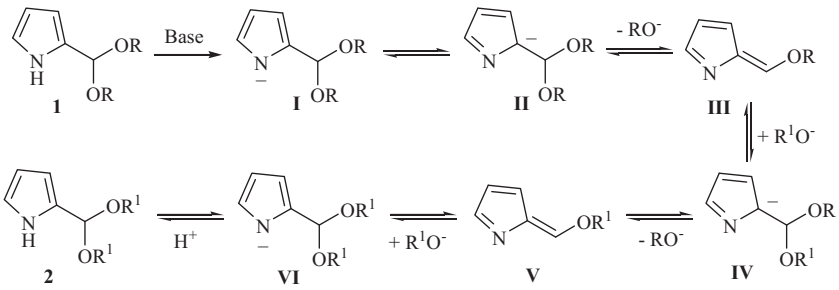
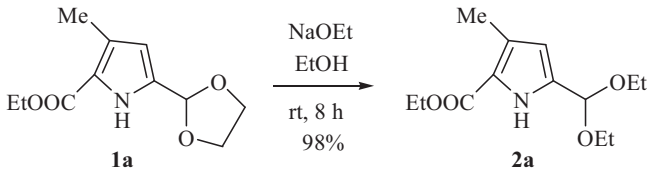


Fig. 1. Hypothesized process for transacetalization of 2-formylpyrrole acetal.



Scheme 1. Transacetalization of **1a** with sodium ethoxide.

In order to develop a general and robust protocol for the preparation of 2-formylpyrrole acetals, we turned our attention to transacetalization method. However, the use of reported conditions involving lewis acid still gives the unidentified by-products. It has been reported that nitrogen-unprotected pyrrole is prone to forming highly reactive azafulvene species [11,12] which can be attacked by a nucleophile to form a substituted pyrrole. Based on this specific reactivity of pyrrole compounds, we hypothesized that the reaction of 2-formylpyrrole acetal with a strong base (for example, sodium alkoxide) will lead to species **I** (Fig. 1), followed by subsequent attack of a nucleophile (for example, alkoxide anion) on 2-methylene carbon would give a transacetalization product **2**.

To test hypothesis, we treated **1a** with various bases in alcohols. We were pleased to find that the reaction with sodium ethoxide in EtOH at room temperature proceeded to give the corresponding transacetalization product **2a** in 98% isolated yield (Scheme 1). Reaction time can be reduced to 2 h under reflux temperature.

This preliminary result encouraged us. To the best of our knowledge, this kind of transacetalization of 2-formylpyrrole acetal through reaction with sodium alkoxide has not yet been reported. In order to investigate the scope and generality of transacetalization of 2-formylpyrrole acetal with sodium alkoxide, we screened a variety of 2-formylpyrrole acetal substrates. Herein we want to report our results.

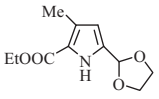
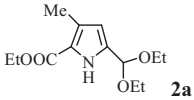
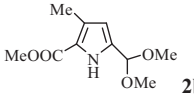
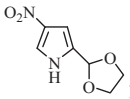
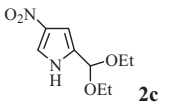
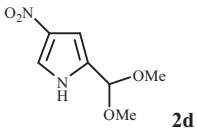
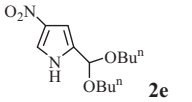
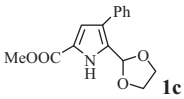
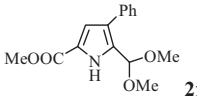
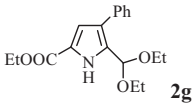
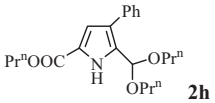
It is important to note that 2-formylpyrrole acetals without electron-withdrawing group on pyrrole ring are usually unstable, so we here selected some stable 2-formylpyrrole acetals with electron-withdrawing group on pyrrole ring as substrates to investigate the scope and generality of transacetalization.

Acetals derived from a number of 2-formylpyrrole can undergo efficient transacetalization under these newly developed conditions. It is worth noting that methanol, ethanol, propanol and butanol are all compatible. In these reactions, sodium alkoxides were made *in situ* by reaction of metallic sodium with alcohol prior to the addition of a substrate, and functioned as both a base and a nucleophilic anion. Not surprisingly, the transesterification of ester groups in the substrates also took place with the concurrent transacetalization of the acetal group (entries 2, 7, 8, 9, and 10 in Table 1).

Considering the relatively slow formation of sodium alkoxides resulting from the reactions of metallic sodium and secondary alcohols and tertiary alcohols, at this stage, sodium alkoxides of secondary alcohols and tertiary alcohols were not yet tested for the transacetalization.

Electron-rich 2-pyrrolecarbaldehyde ethylene diol acetal and 4-bromo-2-pyrrolecarbaldehyde ethylene diol acetal (both substrates are all very unstable. In the presence of traces of moisture or protic solvent, they quickly decomposed and were converted to their parent compounds 2-pyrrolecarbaldehyde and 4-bromo-2-pyrrolecarbaldehyde) were also used as substrates for the reaction with sodium methoxide in methanol. From TLC, we observed the similar phenomina indicating that the transacetalization also went well. Likewise, due to the unstability of the

Table 1
Transacetalization of 2-formylpyrrole acetals with sodium alkoxide in alcohol at reflux.[a]

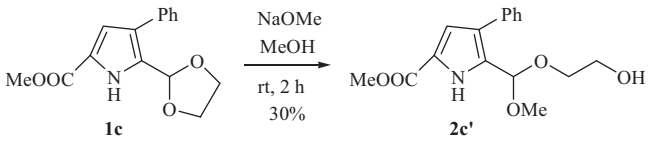
Entry	Substrate	Sodium alkoxide	Product	Yield[b] (%)
1	 **1a**	NaOEt	 **2a**	98
2	**1a**	NaOMe	 **2b**	99
3	 **1b**	NaOEt	 **2c**	96
4	**1b**	NaOMe	 **2d**	98
5	**1b**	$NaOBu^n$	 **2e**	97
6	 **1c**	NaOMe	 **2f**	99
7	**1c**	NaOEt	 **2g**	99
8	**1c**	$NaOPr^n$	 **2h**	97
9	**2g**	NaOMe	**2f**	99
10	**2h**	NaOMe	**2f**	99

[a] General conditions: a solution of **1** (0.5 mmol) and NaOR (3.0 mmol, was made *in situ* by addition of 3.0 mmol of sodium metal in ROH till it disappeared) in 10 mL of ROH was heated at refluxed for 2 h.
[b] Isolated yield.

products 2-pyrrolecarbaldehyde methanol acetal and 4-bromo-2-pyrrolecarbaldehyde methanol acetal, we cannot obtain their ^1H and ^{13}C NMR spectra.

A number of mechanistic information has also been obtained. First, an intermediate **2c′** was isolated by quenching the reaction at early stage. Monitoring by ^1H NMR, **2c′** was also shown to be converted to the product **2f** under the standard conditions (Scheme 2). Second, nitrogen-methylated products of **1a–1c** and acetal derived from benzaldehyde did not undergo transacetalization. These combined observations are consistent with the proposed mechanism (see Fig. 1).

In conclusion, nitrogen-unprotected 2-formylpyrrole acetals can react with sodium alkoxide in alcohol at reflux temperature smoothly to give the corresponding transacetalization products in nearly quantitative yields. This mild and highly efficient procedure will find usefulness for the preparation of acid sensitive 2-formylpyrrole acetals.



Scheme 2. The preparation of **2c′**.

Acknowledgments

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