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Three-component condensations of aldehydes with *N*-methoxycarboxamides

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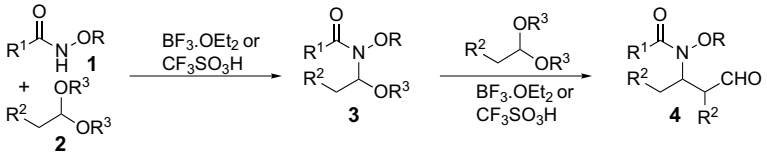
Abstract—The first condensations of *N*-methoxycarboxamides (component A) with aliphatic acetals (component B) are described. Depending upon the conditions, the hemiaminal type products (AB) can usually be isolated. Conducting the condensations with 2 equiv of acetal affords β-(*N*-methoxy)amido aldehydes (type ABB products). A condensation using anisole (component C) afforded a product of type ABC.

Condensations of amides with carbonyl compounds can provide access to a wide variety of compounds, many highly functionalised and difficult to prepare by other means.[1,2] In the typical case, an amidoalkylating species is generated which then reacts with a third molecule acting as a nucleophile, leading necessarily to a multicomponent product.[3,4] Much less general than the corresponding aminoalkylations (e.g., Mannich processes),[5,6] amidoalkylation at carbon frequently involves the condensation of an active methylene compound other than an aldehyde with an imine (Schiff's base) derived from an aromatic aldehyde. In 1988, our group described the preparation of β-amido aldehydes by means of a three-component condensation involving an amide and two molecules of an aliphatic aldehyde.[7] Those reactions extend the scope of *C*-amidoalkylations and do not involve isolation of the amidoalkylating species prior to reaction with the *C*-nucleophile, as is otherwise often the case.

In view of the importance of hydroxamic acids in medicinal chemistry, especially as inhibitors of matrix metalloproteinases[8] and of histone deacetylase,[9] it seemed very desirable to develop a reaction that involved a multicomponent condensation of a hydroxamic acid, or a derivative, with carbonyl compounds and especially aldehydes or their equivalents, thereby forming a functionalised compound with likely enzyme inhibitory potency and also capable of being readily diversified. However, condensations of hydroxamic acids or their derivatives with aliphatic carbonyl compounds have been little described; reactions with aliphatic aldehydes are very scarce,[10] and to our knowledge no such multicomponent process involving carbon–carbon bond formation has been described previously. Herein we report novel condensations of *N*-methoxycarboxamides with acetals to give, via hemiaminal type intermediates **3**, the multicomponent products, β-(*N*-methoxy)amido aldehydes **4** (Scheme 1).



Scheme 1.

Keywords: Hydroxamic acid derivatives; Acetals; Condensation; Multicomponent reaction.
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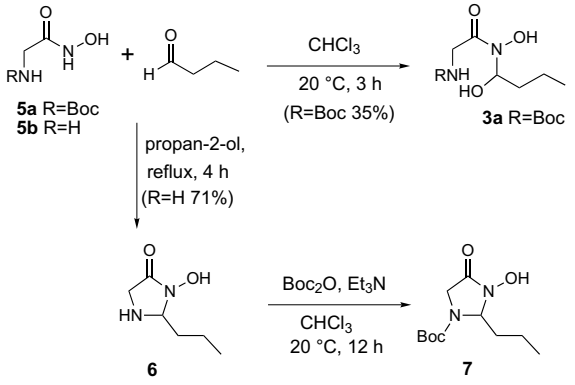
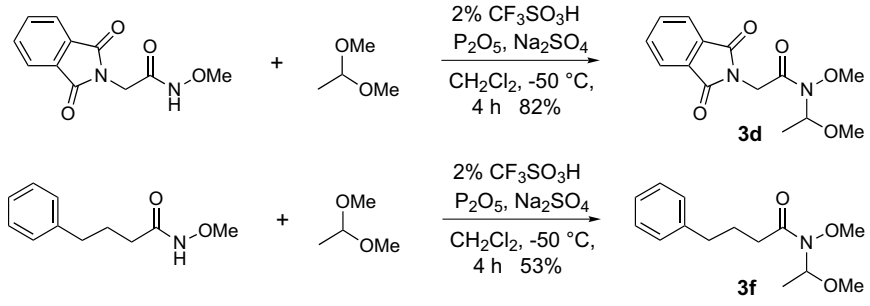
The starting point for this investigation was the condensation of hydroxamic acid **5b** with *n*-butyraldehyde. In propan-2-ol at reflux, condensation with ring-closure occurred to give **6**, analogous to other imidazolidine-4-ones.[11] By introducing an electron-withdrawing group at the amine nitrogen atom, electrophilic attack was hoped to be induced exclusively on the hydroxamic acid nitrogen atom. Gratifyingly, the Boc-protected hydroxamic acid **5a** afforded the hemiaminal **3a** at 20 °C, which exhibited a signal at 80.8 ppm in the ^{13}C NMR spectrum for the hemiaminal carbon atom (in contrast to the corresponding signal at 72.1 ppm for the cyclised product **7**) (Scheme 2).



Scheme 2.

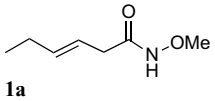
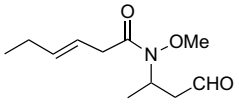
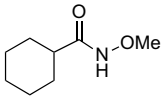
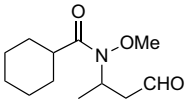
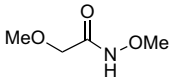
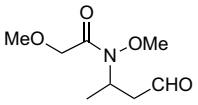
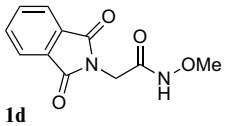
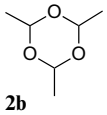
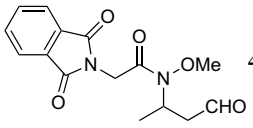
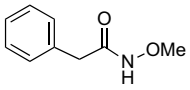
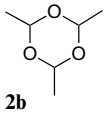
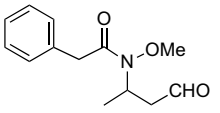
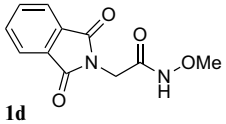
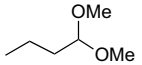
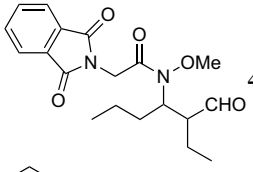
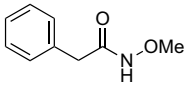
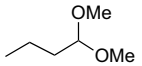
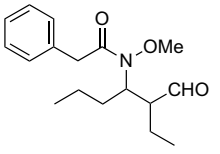
However, several attempted condensations using other hydroxamic acids and aldehydes, with or without acid catalysts, did not lead to satisfactory yields, either of hemiaminals or related products. The use of acetals as the aldehyde equivalents was then explored, and after considerable investigation it was found that trifluoromethanesulfonic acid (2% in dichloromethane) in a rigorously dry medium effected the condensation of *N*-methoxycarboxamides with acetals to give *N*-(α-methoxyalkyl)-*N*-methoxycarboxamides such as **3d** and **3f** (Scheme 3).[12] To our knowledge, α-oxy-substituted carboxamides bearing an *N*-alkoxy (or *N*-hydroxy) group such as **3** have not been described previously, and in related condensations involving amides the corresponding *N*-(α-hydroxyalkyl)carboxamides were not detected. In order to achieve the required goal of a three-component condensation, it was realised from previous work[7] that careful selection of reactants and conditions was likely to be important. In three-component condensations of amides with aldehydes[7] it was found in some instances that the use of the symmetrical trioxane was preferable to the corresponding aldehyde, in part because of the tendency of the latter to form aldol side-products derived from self-condensation. Encouragingly, an exploratory reaction using **3d** showed that replacement of acetaldehyde dimethyl acetal with a 1,3,5-trioxane enabled the reaction to proceed further, giving the β-(*N*-methoxy)amido aldehyde **4d** (Table 1).

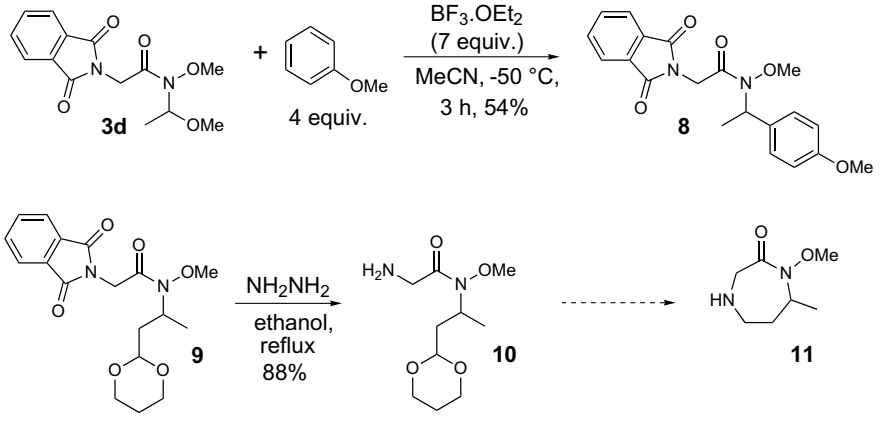
Further studies showed that in some cases the ABB product was better obtained from the symmetrical trioxane, in others from the corresponding dimethyl acetal; in the present study no clear trend was discerned, although the use of the dimethyl acetal appears to be more general. Investigation of the condensing agent showed that, in many cases, $BF_3{\cdot}OEt_2$ (in acetonitrile) was found to be more satisfactory than trifluoromethanesulfonic acid for the preparation of the β-(*N*-methoxy)amido aldehydes **4**.[13] The mildness of the procedure is consistent with other functionality including isolated double bonds (Table 1, entry 1), imides (entries 4 and 6) and ethers (entry 3). The sequential nature of the reaction, as well as proceeding via an electrophilic species derived from the intermediate *N*-(α-methoxyalkyl)-*N*-methoxycarboxamides **3** was further demonstrated by treatment of **3d** with anisole in the presence of excess $BF_3{\cdot}OEt_2$ (Scheme 4) whereupon the multicomponent product **8** was obtained. Manipulation of the functionality in the multicomponent adducts **4** was examined by protection of the aldehyde group of **4d** as the acetal **9** (ethylene glycol, toluene, *p*-TsOH, 80 °C, 90%) followed by deprotection with hydrazine to give the highly functionalised amine **10**. Although a reductive cyclisation using palladium on carbon did not afford **11** in satisfactory yield, it should be possible to synthesise *N*-heterocycles containing pharmacophore regions through the use of products **4** of this novel multicomponent process involving the condensation of *O*-alkylated hydroxamic acids with acetals. Additionally, the aldehyde group of the β-(*N*-methoxy)amido aldehydes **4** could participate in another multicomponent reaction such as a reductive amination, thereby enabling the rapid assembly of diversely functionalised compounds.



Scheme 3.

Table 1. Condensation of *N*-methoxycarboxamides with acetals using $BF_3{\cdot}OEt_2$ in MeCN at −40 °C or 2% CF_3SO_3H v/v in CH_2Cl_2 with P_2O_5 (5 equiv) and Na_2SO_4 (5 equiv) at −50 °C

Entry	*N*-Methoxycarboxamide	Acetal	Reagent	Product (%)
1	 **1a**	 **2a**	$BF_3{\cdot}OEt_2$	 **4a** (78)
2	 **1b**	 **2a**	$BF_3{\cdot}OEt_2$	 **4b** (48)
3	 **1c**	 **2a**	$BF_3{\cdot}OEt_2$	 **4c** (68)
4	 **1d**	 **2b**	CF_3SO_3H, P_2O_5, Na_2SO_4	 **4d** (53)
5	 **1e**	 **2b**	$BF_3{\cdot}OEt_2$	 **4e** (52)
6	 **1d**	 **2c**	$BF_3{\cdot}OEt_2$	 **4f** (33)
7	 **1e**	 **2c**	$BF_3{\cdot}OEt_2$	 **4g** (35)



Scheme 4.

Acknowledgements

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References and notes

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12. *N*-Methoxycarboxamides were prepared by stirring a mixture of a carboxylic acid (1 equiv), ethyl chloroformate (1.2 equiv) and *N*-methylmorpholine (1.3 equiv) in diethyl ether at 0 °C for 15 min. Filtration gave a solution that was added to a solution of *O*-methylhydroxylamine in methanol and the mixture stirred at 20 °C, the reaction being usually complete within 1 h. After work-up the material was purified by chromatography on silica using ethyl acetate 60–80 °C petroleum ether or ethyl acetate–toluene as eluent. The solution of hydroxylamine in methanol was prepared by adding *O*-methylhydroxylamine hydrochloride (1.5 equiv) in methanol to a stirred solution of potassium hydroxide (1.5 equiv) in methanol at 0 °C, stirring for 15 min and filtration.
13. Preparation of *N*-methoxy-*N*-(1-methyl-3-oxopropyl)acetamide (**4a**). To a solution of *(E)*-hex-3-enoic acid hydroxyamide (0.10 g, 0.78 mmol) in dry acetonitrile (3.5 mL) cooled to −35 °C was added borontrifluoride diethyl etherate (0.55 mL, 4.5 mmol). Acetaldehyde dimethyl acetal (0.28 mL, 2.3 mmol) was then added dropwise and the mixture stirred for 24 h at −35 °C. The solution was allowed to warm to 0 °C and neutralised with saturated aqueous sodium hydrogen carbonate solution. The organic layer was washed first with water then with brine, dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (1:9 ethyl acetate:toluene) to give **4a** (0.13 g, 78%; 6:1 aldehyde:diol hydrate form) as a colourless oil. For **4a**: IR ν_{max} (cm^{-1}) (KBr disc) 1700 (CO), 1670 (NCO), 1635 (C=C); ^{1}H NMR (300 MHz) δ 9.60 (1H, t, J = 2 Hz), 5.56 (2H, m), 4.80 (1H, m), 3.72 (3H, s), 3.33 (1H, d, J = 10.5 Hz), 3.28 (1H, d, J = 10.5 Hz), 2.81 (1H, ddd, J = 12.5, 8.5, 2 Hz), 2.63 (1H, ddd, J = 12.5, 6, 1.5 Hz), 2.03 (2H, m), 1.30 (3H, d, J = 7 Hz), 0.96 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz) δ 200.1, 173.2, 136.2, 121.0, 64.7, 55.8, 47.8, 36.9, 25.6, 18.1, 13.5. LRMS *m/z* (EI) 214 (M+1; 10), 117 (35), 69 (87), 59 (100). HRMS: calcd for $C_{11}H_{19}NO_3$+H 214.1143, found 214.1141. For the hydrate of **4a**: ^{1}H NMR (300 MHz) δ 5.66 (2H, m), 4.80 (1H, m), 3.82 (3H, s), 3.33 (1H, d, J = 10.5 Hz), 3.21 (1H, m), 3.28 (1H, d, J = 10.5 Hz), 2.03 (2H, m), 2.81 (1H, m), 2.63 (1H, m), 1.11 (3H, d, J = 6.3 Hz), 0.96 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz) δ 173.2, 136.3, 121.1, 102.5, 65.3, 56.1, 49.5, 38.6, 25.6, 18.7, 13.5.