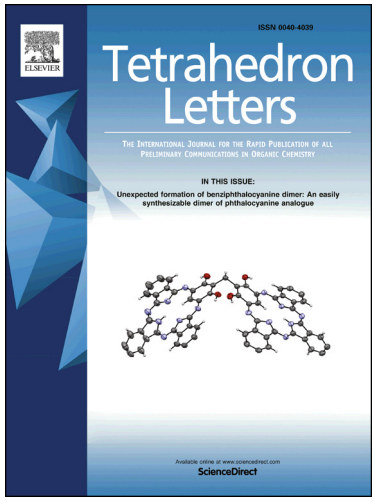

The Use of 2-Hydroxymethyl Benzoic Acid as an Effective Water Surrogate in the Passerini Reaction: a Straightforward Access to α-Hydroxyamides.

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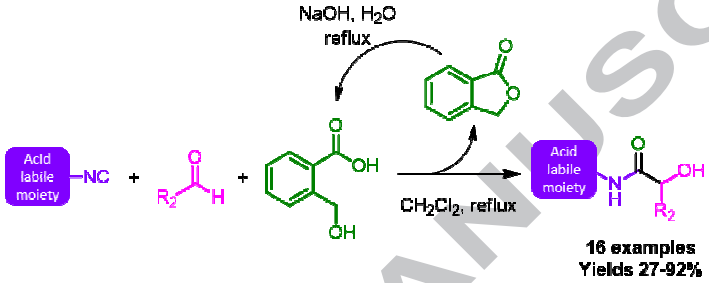
Marta Serafini,[a] Alessia Griglio,[a] Elena Oberto,[a] Tracey Pirali,[a]* and Gian Cesare Tron[a]



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The Use of 2-Hydroxymethyl Benzoic Acid as an Effective Water Surrogate in the Passerini Reaction: a Straightforward Access to α-Hydroxyamides.

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ABSTRACT

Dozens of strategies have been described for the synthesis of α-hydroxyamides over the years, but they share common drawbacks in terms of generality and tolerability, especially to acid labile functionalities. Here we report a truncated Passerini reaction suitable for the easy and mild preparation of functionalized α-hydroxyamides. In particular, this procedure is tolerant to acid sensitive protecting groups, which remain intact during the multicomponent reaction.

The role of α-hydroxyamides in organic and medicinal chemistry is well appreciated and recognized by chemists, both as building blocks for the synthesis of biologically active compounds and as pharmacophoric groups. To cite some examples, this scaffold is displayed by HIV protease inhibitor **1**,[1] bicalutamide **2**,[2] an antineoplastic drug used in the treatment of prostatic cancer, the anti-convulsivant themisone **3**,[3] the bradykinin antagonist **4**[4] and roxatidine **5**,[5] an antagonist of histamine H_2 receptor (Figure 1).

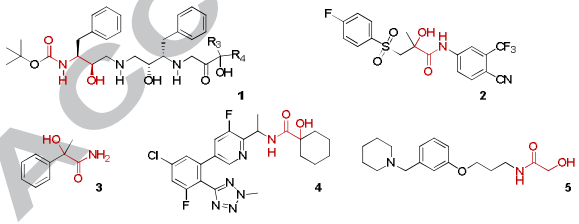

Figure 1. Selected Examples of Biologically Active α-Hydroxyamides.

A classic approach to prepare α-hydroxyamides is the condensation reaction between protected α-hydroxy acid derivatives and amines in the presence of coupling agents.[6]

This strategy is however restricted by the commercial availability of hydroxy acids or by their ease of preparation. Notwithstanding, the possibility to prepare α-hydroxyamides using the "truncated" Passerini reaction, in which water replaces the carboxylic acid, was reported for the first time only in 1966 by Müller.[7] The use of a Brønsted (e.g. HCl) or a Lewis acid (e.g. BF_3 * Et_2O) is necessary to by-pass the dual problem associated with the presence of water instead of a carboxylic acid: i) the lack of activation of the carbonyl group and ii) the poor nucleophilicity of water. Unfortunately, this reaction resulted to be poor in scope: mineral acids work only with more hydrolytically resistant isocyanides (tertiary and secondary), while in the presence of BF_3 the attack of isocyanides to the formed nitrilium ion, leading to oligomerization products, was reported. Only in 1983 with the seminal work of Seebach[8] an approach which avoided the formation of oligomerization by-products was disclosed. In practice, Seebach proposed the use of titanium tetrachloride to avoid the double isocyanide insertion. As subsequently demonstrated by Floriani,[9] the role of $TiCl_4$ was to form an acid-base Lewis adduct with both carbonyl moiety and isocyanide, followed by the attack of chlorine ion to the isocyanides to form an iminochloride preventing the further attack of another isocyanide. The iminochloride is then hydrolyzed to α-hydroxyamides during the work-up.

Again, the Seebach protocol revealed to be poor in scope, working well only with unfunctionalized or poorly functionalized substrates and with primary and secondary

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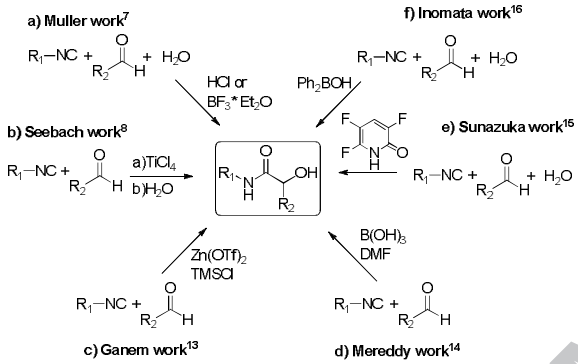
isocyanides. Indeed, with tertiary isocyanides the nitrogen dealkylation prevailed forming cyanohydrines as the main product.[10] In 2003, Denmark reported the use of $SiCl_4$ as Lewis acid in the presence of a chiral bisphosphoramide to give α-hydroxyamides with an excellent enantiomeric excess.[11] On the other hand, the success of this reaction was strictly dependent on the nature of isocyanide, working well only with *tert*-butyl and phenylisocyanide. For these reasons, over the course of years, many authors continued to synthesize α-hydroxyamides using a classical Passerini reaction, followed by basic hydrolysis of the ester moiety.[12] Very recently, other authors reported the one pot synthesis of α-hydroxyamides using different activating agents such as $Zn(OTf)_2$/TMSCl,[13] boric acid,[14] 3,5,6-trifluoro-2-pyridone,[15] borinic acids[16] and phenyl phosphinic acid[17] (Scheme 1).



Scheme 1. Previous Approaches to the Synthesis of α-Hydroxyamides.

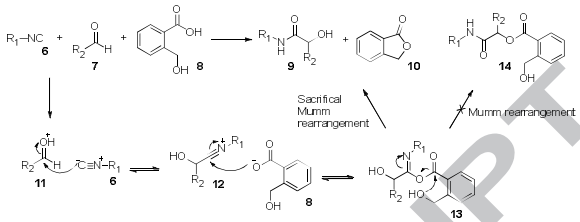
All these new strategies have demonstrated to be valuable, affording the desired α-hydroxyamides under very mild reaction conditions,[18] but failed to demonstrate their utility with functionalized isocyanides susceptible to degradation.

Keeping in mind the strategy reported for the synthesis of α-hydroxyamides via a truncated Passerini reaction, during a medicinal chemistry project, we needed to synthesize a library of α-hydroxyamides bearing TBDMS protected hydroxyl groups. At the beginning, we opted to explore the already reported methodologies, (e.g. $TiCl_4$, HCl, boric acid, phenyl phosphinic acid, and 3,5,6-trifluoro-2-pyridone) but under any circumstances we were not able to isolate the desired compound. In particular, we always observed the loss of the *tert*-butyldimethylsilyl protecting groups, along with the degradation of the starting material.

With the pressing request of this compound, we decided to explore a novel strategy to afford α-hydroxyamides by a one-pot reaction exploiting 2-hydroxymethyl benzoic acid **8**. This component, as reported in previous literature, is able to undergo a sacrificial Mumm rearrangement via an intramolecular cyclization to afford a pseudo-molecule of water in the Ugi reaction.[19]

Scheme 2. Plausible Reaction Mechanism for the Formation of α-Hydroxyamides **9**.

With our delight, when we performed the truncated



Passerini reaction with isocyanide **6a**, formaldehyde **7a** and 2-hydroxymethyl benzoic acid **8** in dichloromethane at reflux, we were able to obtain compound **9a** in 76% of yield.

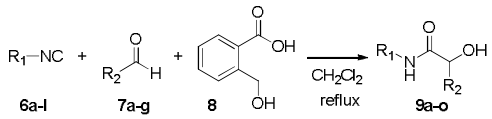
A proposed mechanism of the reaction is outlined in Scheme 2. After the nucleophilic addition of the isocyanide to the aldehyde, the 2-hydroxymethyl benzoic acid intercepts the nitrilium ion **12** to form intermediate **13**. At this point, the reaction does not follow a classical Mumm rearrangement, but undergoes an intramolecular cyclization, leading to compound **9** and phtalide **10**.[20]

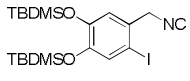
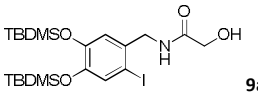
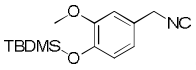
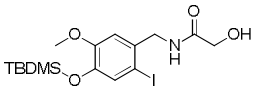
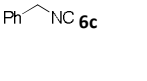
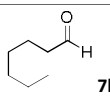
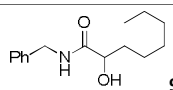
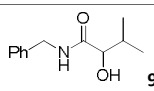
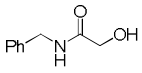
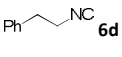
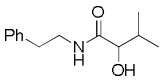
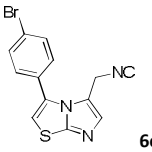
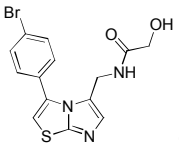
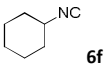
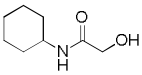
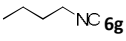
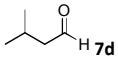
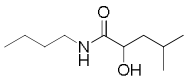
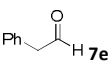
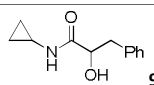
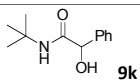
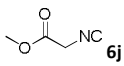
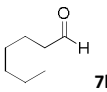
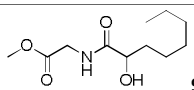
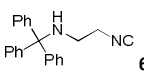
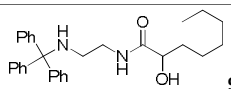
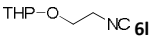
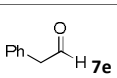
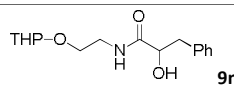
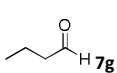
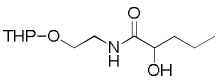
The scope of the reaction was next examined, using both different isocyanides and various aldehydes in order to prove its versatility. As shown in Table 1, primary (**6d, 6e, 6g, 6j, 6k** and **6l**), secondary (**6f** and **6h**) and benzylic isocyanides (**6a, 6b** and **6c**) react well in the MCR, leading to the corresponding products in high yields. On the contrary, aromatic isocyanides, such as 4-methoxyphenyl isocyanide, are unable to react in the MCR, leading to complex mixtures with no recovery of the desired product. Moreover, aliphatic (**7b, 7c, 7d** and **7g**) and benzylic aldehydes (**7e**) as well as formaldehyde (**7a**) were able to react in the MCR, affording α-hydroxyamides in good yields. On the other hand, benzaldehyde (**7f**) reacts slowly, affording the corresponding product (**9k**) in low yield.

When we performed the reaction with ketones, the results were not so encouraging. Despite our efforts using different ketones such as acetone, 2-butanone, cyclohexanone and acetophenone, and different reaction conditions (e.g. temperature from 40 °C to 60 °C and 1,2-dichloroethane as solvent), we have never been able to access the expected truncate Passerini compound. On the contrary, in two cases we isolated the corresponding Passerini products with relevant yields, suggesting that the sterically hindered *alpha* position was an obstacle for the sacrificial rearrangement.

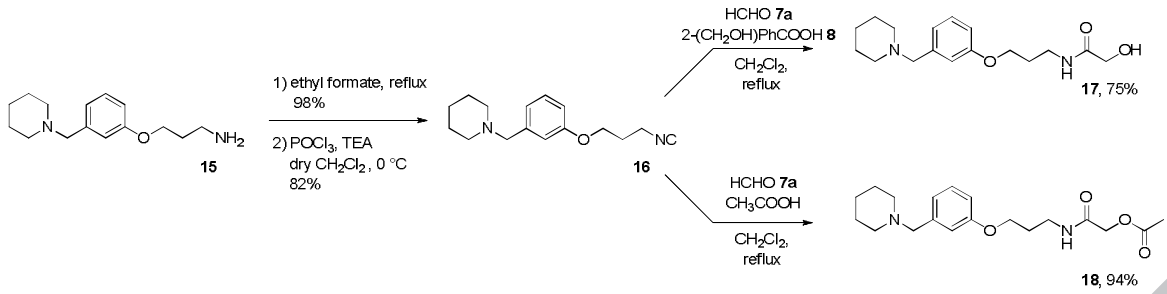
Finally, we explored the use of functionalized isocyanides bearing acid sensitive protecting groups. Methyl ester, trityl as well as dihydropyranyl and the aforementioned *tert*-butyldimethylsilyl were used as protecting groups in order to prove the retention of these functionalities during the truncated Passerini reaction. In all cases, we were able to access the desired compounds (**9a-b** and **9l-o**) with no loss of the protecting moieties.

Table 1. Substrate Scope of the MCR involving Isocyanides **6**, Aldehydes **7** and 2-Hydroxymethyl benzoic acid **8**[a].



Entry	Isocyanide	Aldehyde	Product	Yield%
1	 **6a**	HCHO **7a**	 **9a**	76%
2	 **6b**		 **9b**	70%
3	 **6c**	 **7b**	 **9c**	92%
4		 **7c**	 **9d**	80%
5		HCHO **7a**	 **9e**	70%
6	 **6d**	 **7c**	 **9f**	83%
7	 **6e**	HCHO **7a**	 **9g**	77%
8	 **6f**		 **9h**	90%
9	 **6g**	 **7d**	 **9i**	84%
10	 **6h**	 **7e**	 **9j**	51%
11	 **6i**	 **7f**	 **9k**	27%
12	 **6j**	 **7b**	 **9l**	59%
13	 **6k**		 **9m**	72%
14	 **6l**	 **7e**	 **9n**	65%
15		 **7g**	 **9o**	86%

[a]Reaction conditions: Isocyanide **6** (1 eq, 0.90 mmol), aldehyde **7** (1 eq, 0.90 mmol), 2-hydroxymethyl benzoic acid **8** (1 eq, 0.90 mmol), CH_2Cl_2 (7 mL) at reflux overnight. In case of formaldehyde **7a**, 4 equivalent were required to complete the reaction.



Scheme 3. Synthesis of Roxatidine **17** and Roxatidine Acetate **18**.

To demonstrate the synthetic utility of our approach, we performed the synthesis of roxatidine, a histamine H_2 receptor antagonist used in the treatment of gastric ulcers and gastro-esophageal reflux disease.[5] Following the synthetic route reported in literature,[21] we synthetized intermediate **15** and, after formylation and dehydration, isocyanide **16** was afforded in high yield. With this compound in our hands, we performed both the 2-hydroxymethyl benzoic acid mediated reaction and a traditional Passerini reaction with acetic acid and formaldehyde, obtaining both roxatidine **17** and roxatidine acetate **18** with 75 and 94% of yield, respectively (Scheme 3).

In conclusion, we reported a novel truncated Passerini reaction suitable for the synthesis a large array of functionalized α-hydroxyamides. Notably, our methodology is compatible with acid sensitive group that are not tolerated under previous reported reaction conditions. Finally, our synthetic strategy was applied to a novel route for the synthesis of roxatidine with high yield.

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References and notes

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Supplementary Material

Experimental procedure, spectroscopic data, copies of ^{1}H and ^{13}C spectra (PDF).

- One pot synthesis of α-hydroxyamides

- 2-Hydroxymethyl benzoic acid behaves as an effective water surrogate

- Reaction conditions suitable for acid sensitive protecting groups