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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 anticonvulsivant themisone **3**,[3] the bradykinin antagonist **4**[4] and roxatidine **5**,[5] an antagonist of histamine H_2 receptor (Fig. 1).

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. F_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

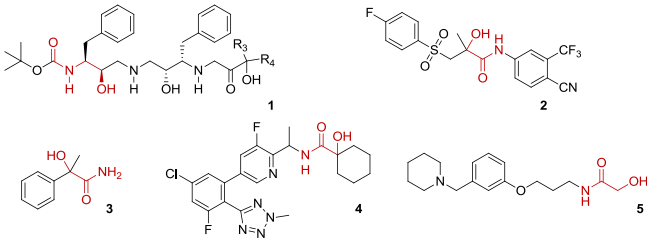
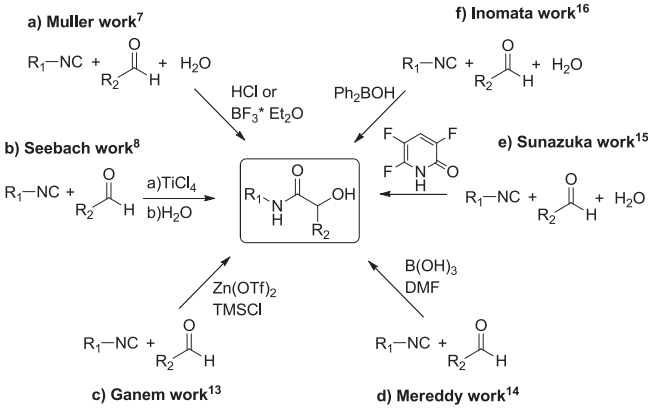


Fig. 1. Selected Examples of Biologically Active α-Hydroxyamides.



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

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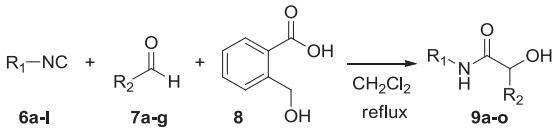
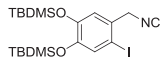
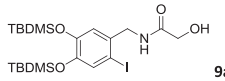
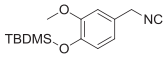
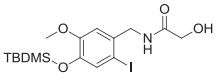
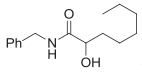
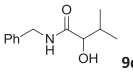
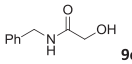
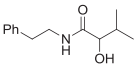
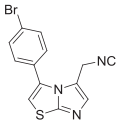
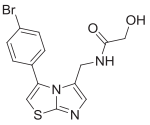
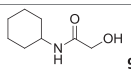
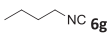
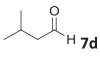
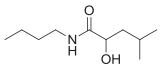
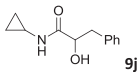
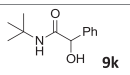
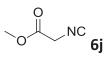
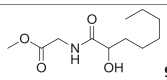
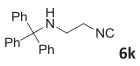
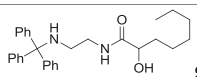
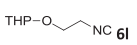
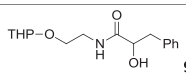
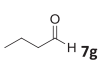
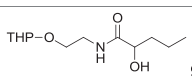
0040-4039/

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.