

OPHA (Oxidation–Passerini–Hydrolysis–Alkylation) Strategy: a Four-Step, One-Pot Improvement of the Alkylative Passerini Reaction

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Supporting Information



ABSTRACT: Multicomponent reactions are often recognized for their efficiency and convergency, if compared with multistep organic synthesis. Nevertheless, we here demonstrate that a four-step-one-pot approach (named OPHA strategy for the initials of the four steps involved) is not only able to afford compounds that could not be obtained by an alkylative Passerini reaction but also capable of generating them with minimal loss of atoms and high operational simplicity, as in a typical multicomponent approach.

The Passerini three-component (P3C) reaction is one of the most important multicomponent reactions. This reaction is a three-component condensation of aldehydes, isocyanides, and carboxylic acids to give α -acyloxy amides in one step.¹

Various modifications of this reaction have already been developed, mainly involving replacement of the carboxylic acid. For example, trimethylsilyl azide,² phenols,³ thioacids,⁴ or silanol⁵ have been efficiently employed. Very recently, we reported that the carbonyl component can also be replaced by a ketene, and captodative olefins can be assembled through a photoactivated process.⁶ The use of a free aliphatic alcohol instead of a carboxylic acid has also been realized, as reported by Taguchi.⁷ The reaction is performed with the alcohol used as the solvent in the presence of a Lewis acid at 80 °C. The use of trimethyl orthoformate is found beneficial for the final outcome, and good results are obtained with aromatic or α , β -unsaturated aldehydes with the catalysis by lanthanoid(III) triflates.

This method, however, is limited in scope as the alcohol component is also the solvent of the reaction; therefore, construction of libraries of α -alkoxy amide derivatives is somehow prevented. In addition, a second addition of isocyanide, catalyst, and additive is required to improve the overall yield.

We recently became interested in the synthesis of compounds of general structure 1 and 2 to be subjected to intramolecular dipolar cycloaddition⁸ for the preparation of unprecedented triazolo-fused benzoxazepines 3 and benzoxazepinones 4, respectively. In particular, compound 3 seemed very promising for biological applications, lacking the easily hydrolizable lactone moiety (Scheme 1).

Searching for a straightforward method to prepare compound **1**, we envisaged that an alkylative Passerini reaction

Scheme 1. Synthesis of Triazolo-Fused Benzoxazepines and Benzoxazepinones



between an azidobenzaldehyde 5, and isocyanide, and a propargyl alcohol could serve the purpose (Scheme 2).

As the original method developed by Teguchi seemed rather inconvenient when dealing with valuable building blocks such







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as propargylic alcohols, we performed preliminary experiments with 2-azidobenzaldehyde **5***a*, *tert*-butyl isocyanide, and 2propanol. When the third component was employed as the solvent, following the procedure developed by Teguchi, compound **6** could be isolated in a modest 39% yield, and no improvement was achieved by replacing conventional heating with microwave. On the other hand, when the alcohol was used, even in large excess, in the presence of an alternative solvent such as THF or DMF, formation of the desired product was not observed (Scheme 3).

Scheme 3. First Attempts to an Alkylative Passerini Reaction with 2-Azidobenzaldehydes



In a second set of experiments, 2-propanol was replaced by propargyl alcohol and 2-azidobenzaldehyde by benzaldehyde. The results were even worse, as the product of the alkylative Passerini reaction could be isolated only in traces (7%), even employing the alcohol as the solvent. Although discouraged by these results, we attempted the synthesis of compound 1 by performing the reaction of **5a** with *tert*-butyl isocyanide and propargyl alcohol as the solvent. The desired product was not detected in the reaction mixture, while cyclic acetal 7, deriving from the combination of one molecule of **5a** and two molecules of the alcohol in an acetalyzation/cycloaddition sequence, was recovered as the major product, albeit with low purity (Scheme 4).

Scheme 4. Alkylative Passerini Reaction Does Not Afford the Expected Compound



Enticed by the chance to gain a combinatorial-friendly entry into benzoxazepines **3**, which to date have been solely prepared in a single example with methodologies unsuitable for parallel synthesis purposes,⁹ we therefore decided to search for other strategies. With the aim of assembling compound **1** in one pot from simple building blocks, a viable option was found in the design of a pathway encompassing an oxidative Passerini reaction,¹⁰ followed by ester hydrolysis and *O*-alkylation with propargyl bromides (Scheme 5). Such an approach could maintain the same advantages of an alkylative Passerini reaction

Scheme 5. Four-Step, One-Pot Alternative to the Alkylative Passerini Reaction



in terms of convergency and, in addition, could directly use 2azidobenzyl alcohols **9** as starting materials. Notably, azidobenzaldehydes **5** are not commercially available and are usually prepared by oxidation of the corresponding alcohols.¹¹

We envisioned, however, one criticism to this OPHA (oxidation–Passerini-hydrolysis–alkylation) strategy: that is the use of a sacrificial carboxylic acid that would not be incorporated in the final product, thus contradicting the principles of atom economy.¹² This was, however, only an apparent problem, as the carboxylic acid (acetic acid) would already be part of the reaction medium in case the oxidation of azidobenzyl alcohols was carried out with the TEMPO-bis(acetoxy)iodobenzene system.¹³

Intrigued by this straightforward approach, we initially studied the distinct steps individually. As the main concern was on the regioselectivity of the alkylation reaction, we prepared compound 8 by reacting 5-chloro-2-azidobenzalde-hyde **Sb** with cyclohexyl isocyanide and acetic acid, followed by basic hydrolysis of the ester bond. After column chromatography, the truncated Passerini adduct was obtained in quantitative yield. Conditions for the selective alkylation of the hydroxyl group were then investigated, and the best results were obtained under phase-transfer conditions, adapting a method reported by Lamberth¹⁴ and Li.¹⁵

When the reaction was performed with 2-hexynyl bromide, compound 1a was isolated in 81% yield, while when propargyl bromide was used instead, a mixture of compound 1b and cyclized adduct 3b was isolated in overall 84% yield (Scheme 6). This prompted us to investigate conditions for the 1,3-dipolar cycloaddition, which was found to proceed smoothly in toluene at 100 °C with the aid of microwave heating.¹⁶

As the conditions employed for the alkylation step could also be effectively applied to the hydrolysis of the Passerini adducts, compound 9, prepared in 82% yield reacting 2-azidobenzaldehyde 5a with *tert*-butyl isocyanide and acetic acid, was reacted under the same conditions developed previously, employing phenylpropargyl bromide as alkylating agent. The desired adduct 1c was isolated in 86% yield, thus demonstrating that hydrolysis and alkylation could be performed concurrently and that acetate ion, probably dissolved in the water phase, did not interfere as a nucleophile (Scheme 7).

In another experiment, S-chloro-2-azidobenzaldehyde **5b** was reacted in dichloromethane with acetic acid and cyclohexyl

Scheme 6. Alkylation of Truncated Passerini Adducts



Scheme 7. Hydrolysis and Alkylation of Passerini Adducts



isocyanide; upon consumption of the starting materials, the phase-transfer catalyst, the 30% NaOH solution, and phenyl-propargyl bromide were added,¹⁷ and after 24 h adduct 1d was isolated, upon chromatographic purification, in quantitative yield (Scheme 8).

Scheme 8. One-Pot Passerini Reaction, Hydrolysis, and Alkylation



Finally, the one-pot procedure starting from 2-azidobenzylalcohol **9** was attempted, this was dissolved in dichloromethane together with a catalytic amount of TEMPO and a stoichiometric amount of bis(acethoxy)iodobenzene.¹⁸ When the oxidation was complete, *tert*-butylisocyanide was added and formation of the Passerini adduct was monitored. Then, 3methoxyphenylpropargyl bromide was added together with the other reagents for the hydrolysis/alkylation step and adduct **1e** was obtained in 59% overall yield (Scheme 9). At this stage, it was found that a quick filtration of the crude material over a





short silica pad afforded a compound sufficiently pure for the subsequent cyclization step, which was performed according to the conditions described above.

The scope of this approach was investigated preparing a small set of benzoxazepines **3**, as illustrated in Table 1.

Table 1. Small Library of Benzoxazepines 3 Has Been Prepared According to the above-Described Methodology, Followed by a Cycloaddition Reaction



^{*a*}Overall isolated yield after OPHA and cycloaddition. ^{*b*}Yield of alkoxyamide 1. ^{*c*}Alkoxyamide was not isolated due to partial spontaneous cyclization.

In conclusion, a straightforward methodology able to overcome the limitations of the alkylative Passerini reaction has been developed; it is also capable of generating alkoxyamide derivatives 1 with minimal loss of atoms and high operational simplicity, as in a typical multicomponent approach, and its versatility has been demonstrated by the synthesis of a small library of benzoxazepines. Further applications of this novel OPHA strategy will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization, and copies of the ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Andrea Armirotti (Istituto Italiano di Tecnologia) and Lorenzo Sonaglia (Univeristà di Genova) for HRMS. We also acknowledge PRIN 2009 ("Synthetic Methodologies for Generation of Biologically Relevant Molecular Diversity"), University of Genova for financial support, and Lamberti SpA for a generous donation.

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