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LETTER

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Novel Application of α-Azido Aldehydes in Multicomponent Reactions: Synthesis of Triazolo-Fused Dihydrooxazinones via a Passerini Reaction−Dipolar Cycloaddition Strategy

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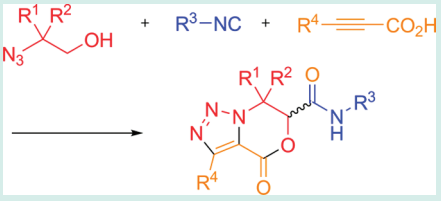
Supporting Information

ABSTRACT: α-Azido aldehydes can be employed in Passerini reactions with isocyanides and various propiolic acids to afford the three-component adducts in moderate to good yields. These compounds undergo a straightforward azide-alkyne dipolar cycloaddition to furnish triazolo-fused dihydrooxazinones.

KEYWORDS: α-azido aldehydes, multicomponent reactions, triazolo-fused dihydrooxazinones, Passerini reaction

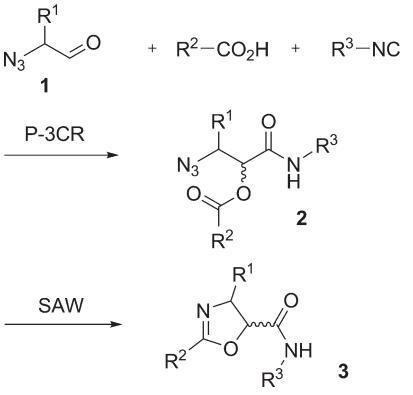


Isocyanides play a dual role as both a nucleophile and electrophile, allowing interesting multicomponent reactions to be carried out, including the classic Passerini[1] and Ugi[2] condensations and the more recent transformations involving the use of alkynes.[3] While the Ugi reaction has been widely exploited in pharmaceutical chemistry to prepare biologically relevant molecules and libraries, the Passerini condensation has encountered less success, that can be ascribed to two main factors. The first being that only three diversity inputs can be introduced, thus limiting for example the application of intramolecular versions to prepare heterocycles, while the second relates to the formation, during the reaction, of an ester functionality that is usually not very appealing in pharmaceutical chemistry due to its lability in physiological media.

In the past, we have tried to overcome this limitation by introducing the so-called PADAM strategy[4] that, starting from a classic Passerini adduct, affords a *β*-acylaminoamide by acyl migration, thus transforming the ester group into a more valuable amide functionality. This strategy has been applied by us[5] and others[6] to prepare acyclic peptidomimetics in a very straightforward manner. More recently we have also applied the same approach to prepare pyrazinone derivatives,[7] through a cyclization/aromatization step following the PADAM protocol. With the same intent of preparing heterocyclic structures, we have also replaced the amine deprotection and acyl migration steps with a Staudinger−Aza Wittig (SAW) cyclization to oxazolines **3** (Scheme 1).[8] This latter strategy has been made possible by employing an innovative class of building blocks in the Passerini reaction, namely α-azidoaldehydes **1**. The intrinsic instability of these compounds has been overcome by generating them in situ modifying the Passerini−Zhu protocol.[9]

Having gained a straightforward access to compounds of general formula **2**, we questioned whether the azido group could be exploited in postcondensations transformations other than the SAW reaction. Organic azides have recently encountered

Scheme 1. Passerini Reaction Applied to the Synthesis of Oxazolines



great success as substrates for click reactions, however in our opinion compounds of general formula **4**, deriving from cycloaddition of **2** with a terminal alkyne (Scheme 2), would suffer from the same limitations of the Passerini adducts, due to the presence of an ester functionality. On the other hand, by installing the alkyne functionality onto the acid component of the multicomponent reaction, would have produced, after the cycloaddition, a more precious lactone **5** and moreover a unique 6,7-dihydro-*4H*-[1,2,3]triazolo[5,1-c][1,4]oxazin-4-one, never reported before in the literature.

Although from a theoretical point of view the approach seemed simple and straightforward, we were aware of possible limitations and difficulties. More precisely, we questioned whether

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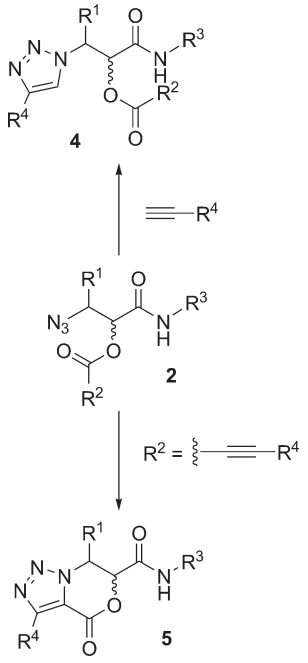
Scheme 2. Possible Exploitations of the Azide Functionality



it would be possible to apply the same microwave-assisted Passerini−Zhu protocol used for the synthesis of oxazolines, since the reactivity of isocyanides with alkynes is well documented even at room temperature. In addition, while copper-mediated dipolar cycloadditions of terminal alkynes with azides proceed smoothly at room temperature, the thermal cycloaddition of internal alkynes is often troublesome and requires harsher conditions.

In view of these considerations, we first decided to prepare compound **2**{*1,1,1*} to study the cycloaddition reaction (Scheme 3). However, we feared that propiolic acid **9**{*1*} could be instable in the presence of IBX, thus we reacted, under the standard Passerini−Zhu conditions, azidoalcohol **6**{*1*} and *t*-butyl isocyanide **7**{*1*} with trifluoroacetic acid,[10] planning to isolate α-hydroxyamide **8** to be subsequently esterified with propiolic acid **9**{*1*}. Unfortunately trifluoroacetic acid was found to be not compatible with the reaction conditions, product **8** being isolated only in traces. On the other hand, when we preliminary oxidized the azidoalcohol **6**{*1*} to the corresponding aldehyde under microwave heating, filtered the reaction mixture, added isocyanide and TFA and finally performed the MCR at room temperature, the final α-hydroxyamide **8** was obtained in satisfactory 58% isolated yield. With the deacylated Passerini adduct in hand we then reacted it with **9**{*1*} in the presence of DCC and catalytic DMAP at −78 °C to afford ester **2**{*1,1,1*}, although in only 32% yield. Moreover, compound **2**{*1,1,1*} was found to be unstable in the dry state, giving many side products probably deriving from intermolecular cycloaddition reactions.

Having demonstrated that the Passerini−Zhu protocol could be performed in two steps without isolating the aldehyde, we then attempted the same strategy employing propiolic acid **9**{*1*} itself instead of TFA. Although crude compound **2**{*1,1,1*} was contaminated by several side products, the overall 30% isolated yield was an improvement compared to the previous methodology. In addition, cycloadduct **5**{*1,1,1*} could be isolated by refluxing a concentrated solution of **2**{*1,1,1*} (deriving from chromatographic purification without evaporation of the solvents to dryness) in toluene, although in only 10% overall yield from **6**{*1*} (Scheme 3). Conversion was complete within two hours but, again, many side products probably deriving from intermolecular reactions were detected.

At this stage it was clear that the synthetic strategy could be feasible, but that propiolic acid was probably not the ideal alkyne to study the reactions more in detail.

To this purpose, we used trimethylsilyl propynoic acid **9**{*2*} instead and attempted to use it directly in a Passerini−Zhu reaction. To our surprise the major compound was not the Passerini product but cycloadduct **5**{*1,1,2*}, isolated in 20% yield: indeed under the microwave heating conditions the Passerini adduct reacted further to give the dipolar cycloaddition. Moreover, also compound **5**{*1,1,1*} was isolated from the reaction mixture in 6% yield, probably deriving from desilylation of the Passerini intermediate (indeed desilylation of the cycloadduct was less likely, since heating **5**{*1,1,2*} under the same reaction conditions did not afford **5**{*1,1,1*}). Interestingly both **5**{*1,1,2*} and **5**{*1,1,1*} were not obtained as nearly 1:1 mixtures of diasteroisomers, as usually occurs because of the poor stereoselection of the Passerini reaction, but with one of the two diasteroisomers predominating (∼3:1).

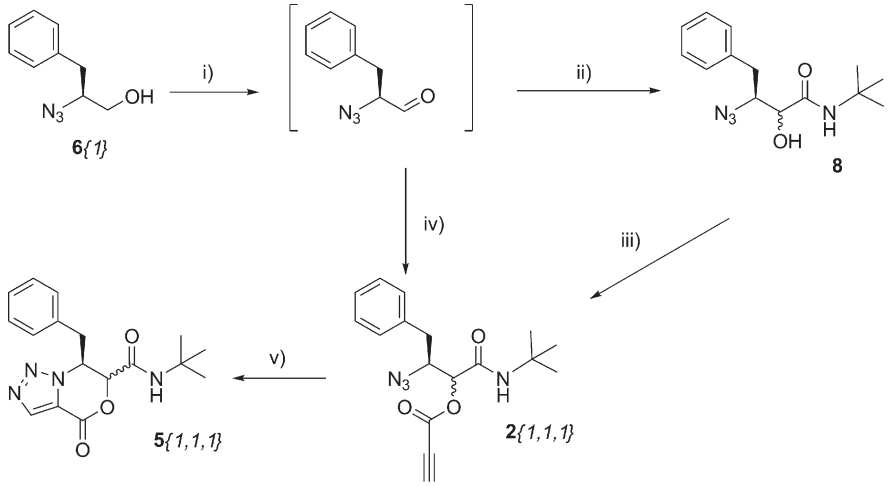
Once more, preforming the aldehyde, filtering IBX side products and adding the isocyanide and the alkyne at room temperature proved to be superior. In this case the Passerini adduct could be isolated in 40% yield and subsequent intramolecular cycloaddition in refluxing toluene, although slower, afforded solely **5**{*1,1,2*} in 79% yield as an equimolar mixture of diastereoisomers.

On the other hand, when we tried other propynoic acids, less reactive than **9**{*2*} toward cycloaddition, the Passerini adducts could be isolated after a classic Passerini−Zhu protocol under microwave heating, adding all the reagents at once. Indeed, when an alkyl or aryl group was present onto the C-3 of the alkyne the intramolecular cycloaddition was much slower and required 3−4 days in refluxing toluene to go to completion.

Compound **2**{*1,1,3*} was then chosen for further optimization of the cycloaddition reaction and the results are reported in Table 1. Despite our expectations, the use of ionic liquids,[11] with or without Cu(I) activation, under conventional or microwave heating, proved to be ineffective and usually complete decomposition of the starting material was observed. On the other hand DMF (entry 3) proved to be superior to other conventional solvents and the reaction under microwave heating was complete within 20 min, affording the desired cycloadduct in 70% isolated yield. Toluene, although being the most common solvent employed for this kind of reactions was not very efficient under microwave conditions because of its low heating capacity: on the other hand, when a few drops of DMSO were added, the reaction proceeded to completion within one hour, although the yield was lower (57%) than with DMF.

With these results in hand we then moved to prepare a small library of triazoloxazinones to investigate the scope of the reaction (Scheme 4 and Table 2). Both one-pot microwave oxidation/Passerini condensation process and preliminary oxidation of the azidoalcohol with subsequent MCR at room temperature were exploited. Where possible, the one-pot procedure was preferred for its operative simplicity, but in some cases the latter approach turned out to be necessary because of the instability of some alkynes and/or Passerini adducts under harsh

Scheme 3[a]



[a] Reagents and conditions: (i) IBX, THF, 100 °C (MW, 150 W); (ii) 7{1}, TFA, THF, rt, 58%; (iii) 9{1}, DCC, DMAP, DCM, −78 °C to rt, 32%; (iv) 7{1}, 9{1}, THF, rt, 30%; (v) toluene, reflux, 10%.

Table 1

entry	solvent	reaction conditions	time	yield
1	PhMe an.	reflux	3 days	48%
2	Dioxane an.	MW (120 °C, 200 W)	2 h	43%
3	DMF an.	MW (150 °C, 200 W)	20 min	70%
4	DMF an.	MW (200 °C, 200 W)	1 min	62%
5	*t*BuOH/H_2O	MW (130 °C, 100 W)	1 h	43%
6	PhMe an./DMSO	MW (140 °C, 200 W)	1 h	57%
7	C_8DABCO$^+$N(CN)$_2^-$	110 °C	overnight	/
8	AMMOENG 110	80 °C	overnight	/
9	PhMe an.	CuI, DIPEA, r.t.	overnight	/
10	PhMe an.	CuI, DIPEA, 80 °C	overnight	19%
11	C_8DABCO$^+$N(CN)$_2^-$	CuI, DIPEA, r.t.	overnight	/
12	C_8DABCO$^+$N(CN)$_2^-$	CuI, DIPEA, 80 °C	overnight	/
13	AMMOENG 110	CuI, DIPEA, r.t.	overnight	/
14	AMMOENG 110	CuI, DIPEA, 80 °C	overnight	/
15	*t*BuOH/H_2O	$CuSO_4 \cdot 5H_2O$, Na ascorbate, 80 °C	7 h	/

conditions. In particular, trimethylsilylpropynoic acid 9{2} and 3-nitrophenylpropynoic acid 9{5} were not compatible with the one-pot protocol (entries 2 and 9), the latter furnishing a plethora of side products and no trace of the desired Passerini adduct. It must be noted that the presence of the alkyne moiety in the carboxylic acid seems to worsen the yields compared to classic Passerini reactions, ranging from 23 to 53%. Furthermore adducts **2**, although showing a single TLC spot, were in some cases not very pure according to NMR spectra.

Nevertheless, we were pleased to find that impurities did not interfere with the following cyclization step, nor generated side products contaminating the final triazoles. Yields ranged from moderate to good (43−79%), and this strategy was particularly suitable for the synthesis of a larger library in a combinatorial format. In fact, reactions were in most of the cases quite clean and their extractive workup and chromatographic purification experimentally easy. Moreover, completion times remained short even upon variation of the substituents present on the starting materials. To our great delight, finally, separation of the two diastereoisomers (always in nearly 1:1 ratio) was possible upon column chromatography. Assignment of the absolute configuration was made on the basis of the *J* coupling constant between *H*-6 and *H*-7, consistently around 3.5 Hz in the case of the cis, less polar, diastereoisomer and around 1.5 Hz in the case of the trans, more polar, diastereoisomer. These coupling constants were in accordance with those theoretically determined on model compounds.

In conclusion, we have demonstrated that a novel class of triazolo-fused oxazinones can be efficiently assembled in two steps from readily available building blocks using a Passerini−Zhu/cycloaddition protocol. These results, together with the previously reported synthesis of oxazolines, demonstrate the utility of novel α-azidoaldehyde building blocks and the versatility of the Passerini multicomponent reaction to assemble heterocyclic compounds. We are currently investigating the

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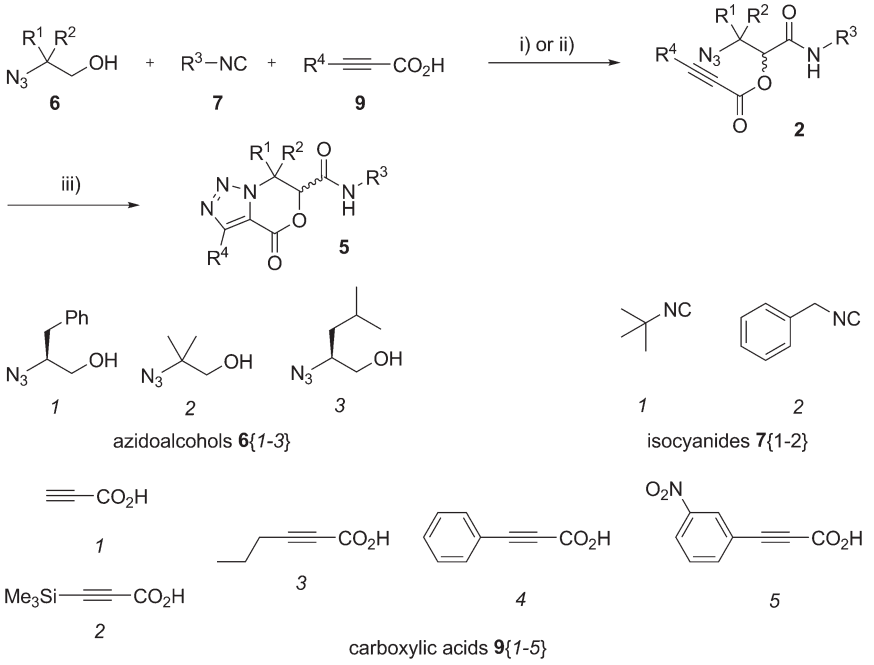
Scheme 4[a]



[a] Reagents and Conditions: (i) IBX, THF, 100 °C (MW, 150 W), then **7**, **9**, THF, rt; (ii) **7**, **9**, IBX, THF, 100 °C (MW, 150 W); (iii) DMF, 150 °C (MW, 150 W). Chemsets are shown in the bottom part.

Table 2

entry	6	7	9	yield 2	preformed aldehyde	yield 5
1	*1*	*1*	2	40%	yes	79%
2	*1*	*1*	2		no	20%
3	*1*	*1*	3	53%	no	70%
4	*1*	*1*	4	38%	no	70%
5	*1*	*1*	5	49%	yes	44%
6	2	*1*	3	36%	no	63%
7	2	*1*	4	38%	no	35%
8	2	*1*	5	35%	yes	60%
9	2	*1*	5		no	
10	2	2	2	37%	yes	57%
11	2	2	5	47%	yes	29%
12	3	*1*	2	31%	yes	43%
13	3	*1*	3	43%	no	77%
14	3	*1*	4	24%	no	58%

biological properties of this novel class of compounds, the results being reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. General procedures and full characterization of compounds **2** and **5**. Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **5**.This material is available free of charge via the Internet at http://pubs.acs.org.

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