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An efficient Passerini tetrazole reaction (PT-3CR)†

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A sonication accelerated, catalyst free, simple, high yielding and efficient method for the Passerini-type three-component reaction (PT-3CR) has been developed. It comprises the reaction of an aldehyde/ketone, an isocyanide and a TMS-azide in methanol : water (1 : 1) as the solvent system. The use of sonication not only accelerated the rate of the reaction but also provided good to excellent quantitative yields. This reaction is applicable to a broad scope of aldehydes/ketones and isocyanides.

Introduction

Tetrazole scaffolds are extensively used in medicinal chemistry and in industries like agriculture, explosives and photography.[1] 1,5-Disubstituted tetrazoles are important ring systems, having applications as bio-active agents or in drugs like cilostazol, pentylenetetrazole, latamoxef, BMS-317180 and *cis*-amide bond isosteres in peptides (Fig. 1). This propels the need for efficient synthetic methods for tetrazoles.[2] Different reactions have been developed for the direct access to diverse 1,5-disubstituted tetrazoles, but three- and four-component reactions (MCR) are mostly preferred due to their convergent, atom-efficient and flexible nature.[3] Multi-component reactions are considered ideal syntheses, and that's why their use in synthetic chemistry is increasing tremendously.[4]

In 1921, a three-component reaction between carboxylic acids, oxo components and isocyanides for the synthesis of α-acyloxy amide was discovered by Passerini (P-3CR).[5,7c] In 1961, Ugi reported the synthesis of tetrazoles *via* a Passerini-type 3CR (PT-3CR) for the first time using HN_3 and $Al(N_3)_3$.[6] Even though the use of HN_3 or NaN_3 in Passerini reactions for the synthesis of tetrazoles was reported, the highly toxic and explosive nature of HN_3 and NaN_3 limit its application.[7] The use of $TMSN_3$ as a safe substitute for HN_3 was then introduced by Hulme.[8] However the use of $TMSN_3$ as an azide source in the PT-3CR resulted in a very low yield, and the TMS-ether was found as a major product instead. Similarly protected amino aldehydes in DCM also resulted in generally low yields[9] and the described reaction times were up to 96 hours.[9a] Reported PT-3CRs are not very suitable for aromatic aldehydes.[7] The use of different Lewis acids as catalysts, like $AlCl_3$, to activate aldehydes forms inseparable mixtures of the desired product with α-hydroxy-amide, with a maximum yield of 30%.[10] Zhu and co-workers used $TMSN_3$ as a test reaction component in the asymmetric PT-3CR; nevertheless, they could not avoid the formation of α-hydroxy-amide.[7b]

To the best of our knowledge, no efficient, diverse and high yielding PT-3CR reaction has yet been reported. We report herein a sonication-promoted catalyst free, $TMSN_3$-modified PT-3CR using methanol : water (1 : 1) as solvent with diverse scope and affording good to excellent yields.

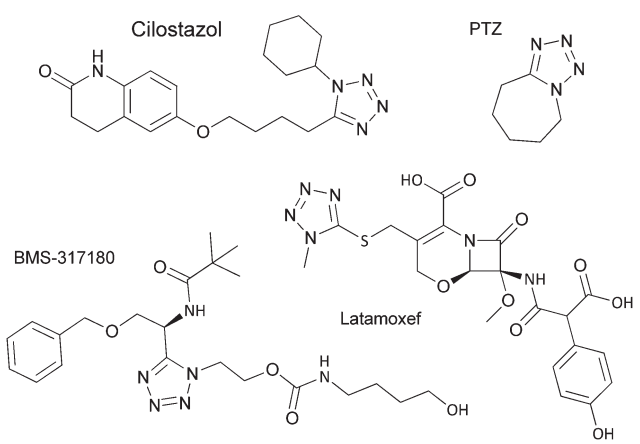

Fig. 1 Some bio-active agents/drugs containing the tetrazole moiety.

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Results and discussion

We started our investigation by using *tert*-butyl isocyanide, phenylacetaldehyde and $TMSN_3$ as starting materials (Table 1). We hypothesized that the use of fluoride ion sources like TBAF, CsF and KF could trigger $TMSN_3$ activation.[11] However, when the reaction was carried out with TBAF with different solvents like DCM or water, or in neat, the product was formed only in trace amounts (Table 1, entries 1–3). Surprisingly, using methanol as a solvent increased the isolated yield to 25%. Carrying out the reaction with alternative F-sources, such as KF in DCM or CsF in DCM, methanol and water, resulted only in small amounts of product formation.

The use of iodine, to trap TMS as TMSI, also failed to improve the reaction yield. 17% product formed when the reaction was carried out in water without any additive. TBAF in methanol : water (1 : 1) enhanced the yield up to 63%; however comparable yields were obtained when the reaction was carried out without TBAF in the same solvent system. Thus we concluded that the use of TBAF is not fruitful, whereas the solvent system has a major impact.

We foresaw that the accelerating effect of sonication could potentially speed up the reaction and increase yields. Ultrasound in general[12] and also in the context of MCR[12d] is often used in organic synthesis due to its advantages such as increasing the reaction efficacy while decreasing waste byproducts, short reaction times, cleaner reactions, easier experimental procedures and having low energy requirements. Recently, the popularity of sonication-assisted synthesis as a green synthetic approach has significantly increased and has resulted in a plethora of 'better' reactions.[13] Ultrasound in chemical reactions works *via* a physical phenomenon called acoustic cavitation, which forms, expands and collapses gaseous and vaporous cavities in an ultrasound irradiated liquid. The mechanical effect of cavitation destroys the attractive forces of molecules in the liquid phase and so accelerates reaction rates by facilitating mass transfer in the microenvironment.[13] To our delight, the use of sonication not only accelerated the reaction from 12 to two hours, but provided excellent quantitative yields using methanol : water (1 : 1) as the solvent system, noteworthily without the necessity of any previously used additive (Table 1, entry 14). We used a simple ultrasonic cleaning bath which is the most widely available and cheapest source of ultrasonic irradiation. A recent study has shown that both ultrasonic cleaning baths and ultrasonic probe systems are efficient in Passerini reactions.[14] The ultrasonic cleaning bath offers further advantages; for example, the reaction vessel can be put directly into the bath without any adaptation. This is in contrast to the ultrasonic probe system, which is more expensive and also requires special vessels, making it inconvenient to use.

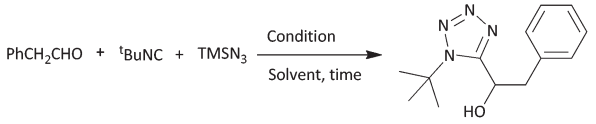
Lastly, reactions under sonication in DCM or in neat conditions provided smaller yields, of 34% and 31% respectively, and the formation of TMS-ether as a side product was observed. The use of pure water as the solvent under sonication conditions provided the product in 71% yield. The use of 1 equivalent of $TMSN_3$ avoids the danger of forming hydrazide from excess azide. This catalyst free reaction doesn't require any work-up.

With these optimized conditions in hand, we next examined the generality of this PT-3CR by reacting different aldehydes with different isocyanides (Table 2). Good to excellent yields were obtained with linear and branched aliphatic aldehydes. Aromatic aldehydes are also compatible substrates for this process (Table 2, entries 15–22). Electron donating (methoxy) and withdrawing groups (Cl, Br, NO_2) at different positions like *ortho*, *meta* and *para* are valid, providing moderate to good yields. Paraformaldehyde also reacts when pure water was used as the solvent. Reaction with one or six equivalents of paraformaldehyde in a methanol : water system only forms mono-substituted tetrazole. The reaction of benzyl isocyanide with aliphatic aldehydes gave excellent yields.

Isocyanides, easy to deprotect in acidic and basic conditions, are compatible with the developed methodology (Table 2, entries 2, 4 and 5). The functional group tolerance of the isocyanide (Table 2, entries 5–6 and 8–10), in this protocol provides multiple opportunities for various further chemical manipulations. For example, the compatibility of 1,1-diethoxy-2-isocyanoethane as the isocyanide component could be used in further reactions as aldehyde or halogen functional groups for coupling reactions.

We also explored the scope of ketones in the developed method (Table 2, entries 23 and 24). Cyclohexanone gives a

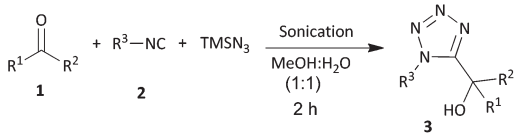
Table 1 Optimization of reaction conditions[a]

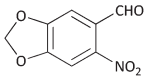


Entry	Catalyst	Solvent	Time (h)	Product yield[b] (%)
1	TBAF[c]	—	12	Trace
2	TBAF[d]	DCM	12	Trace
3	TBAF[c]	H_2O	12	Trace
4	TBAF[c]	MeOH	12	25
5	KF[e]	DCM	12	nd
6	CsF[f]	DCM	12	nd
7	CsF[f]	MeOH	12	nd
8	CsF[f]	H_2O	12	nd
9	I_2 [f]	DCM	12	nd
10	I_2 [f]	H_2O	12	nd
11		H_2O	12	17
12	TBAF[c]	MeOH : H_2O (1 : 1)	12	63
13		MeOH : H_2O (1 : 1)	12	64
14	**Sonication**	**MeOH : H_2O (1 : 1)**	**2**	**97**
15	Sonication[g]	—	3	31
16	Sonication	DCM	2	34
17	Sonication	H_2O	2	71

[a] The reaction was carried out with phenylacetaldehyde (1 mmol), *tert*-butyl isocyanide (1 mmol), and $TMSN_3$ (1 mmol) at room temperature. [b] Yield of isolated product. [c] 1 equivalent TBAF·3H_2O. [d] 1 equivalent TBAF in 1 M THF. [e] 1 equivalent KF. [f] 1 equivalent CsF. [g] Reaction carried out at 70 °C. nd = not determined.

Table 2 Substrate scope for the PT-3CR[a]

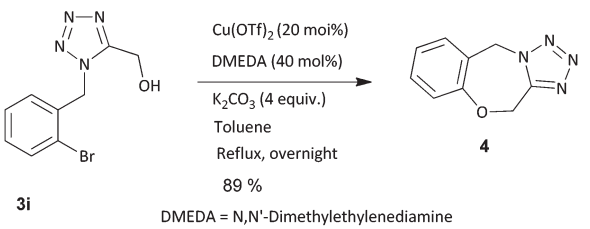


Entry	1	R^{3} [b]	Yield[c] (%)
Aldehydes			
1	C_6H_5–CH_2–CHO	C_6H_5–CH_2	96 (3a)
2	iPr-CHO	$(CH_3)_3$–C	98 (3b)
3	CH_3–$(CH_2)_2$–CHO	C_6H_5–CH_2	80 (3c)
4	C_6H_5–CH_2–CHO	^{t}Octyl	77 (3d)
5	iPr-CHO	CN–CH_2–CH_2	72 (3e)
6	C_6H_5–$(CH_2)_2$–CHO		53 (3f)
7	C_6H_5–$(CH_2)_2$–CHO	Cy	76 (3g)
8	C_6H_5–CH_2–CHO	2-BrC_6H_4–CH_2	77 (3h)
9	H–CHO[d]	2-BrC_6H_4–CH_2	42 (3i)
10	iPr-CHO	2-BrC_6H_4–CH_2	80 (3j)
11	C_6H_5–$(CH_2)_2$–CHO	$(CH_3)_3$–C	88 (3k)
12	CH_3–CH_2–CHO	C_6H_5–CH_2	91 (3l)
13	$(CH_3)_2$–CH–CH_2–CHO	C_6H_5–CH_2	92 (3m)
14	C_6H_5–CH_2–CHO	$(CH_3)_3$–C	97 (3n)
15	C_6H_5–CHO	$(CH_3)_3$–C	41 (3o)
16	2,6-$(Cl)_2C_6H_3$–CHO	C_6H_5–CH_2	71 (3p)
20	2,3-$(Cl)_2C_6H_3$–CHO	Cy	73 (3q)
17	2-MeO-5-BrC_6H_3–CHO	C_6H_5–CH_2–CH_2	46 (3r)
18	2-BrC_6H_4–CHO	Cy	60 (3s)
19	2-Cl-3,4-$(OCH_3)_2C_6H_2$–CHO	Cy	42 (3t)
21		Cy	39 (3u)
22	2,5-$(OCH_3)_2C_6H_3$–CHO	Cy	48 (3v)
Ketones			
23	Cyclohexanone	C_6H_5–CH_2	84 (3w)
24	1-Benzylpiperidin-4-one	C_6H_5–CH_2	46 (3x)

[a] The reaction was carried out with 1 mmol **1**, 1 mmol **2**, 1 mmol $TMSN_3$. [b] cy = cyclohexyl, octyl = 2-isocyano-2,4,4-trimethylpentane. [c] Yield of isolated product. [d] 6 equivalents of paraformaldehyde in water as solvent and at 60 °C. iPr = isopropyl.

good yield of 84%. The important building block piperidone is also compatible with the reaction.

Fused tetrazoles are important scaffolds as they possess a wide spectrum of activity and vast industrial applications. As functional groups bearing isocyanides are compatible in our developed method, we foresaw a quick and easy access to fused tetrazoles. According to our synthetic plan, the use of functionalized PT-3CR product for post modification would allow an anticipated cyclization process. (1-(2-Bromobenzyl)-1*H*-tetrazol-5-yl)methanol (**3i**), when refluxed with copper(II) triflate in the presence of base, formed 5,11-dihydrobenzo[*f*]-tetrazolo[5,1-*c*][1,4]oxazepine in 89% yield (Scheme 1).



Scheme 1 Synthesis of a fused tetrazole.

Conclusions

In conclusion, we have developed a novel, efficient, safe and general sonication assisted Passerini tetrazole reaction (PT-3CR) to access 5-(1-hydroxyalkyl)tetrazoles in good to excellent yields. The herein described Passerini tetrazole procedure provides multiple advantages over previously described procedures. The reaction does not use highly toxic and explosive staring materials like HN_3, $Al(N_3)_3$ or NaN_3. This catalyst free reaction avoids the use of any dangerous or adverse catalysts such as the Al–salen chiral complexes or $AlCl_3$. Sonifiaction was found to provide superior reaction conditions, resulting in high conversion and giving high yields of Passerini products and no TMS-ether side products, as often observed previously. Sonification is also well known to be compatible with upscaling procedures. The scope of the reaction could be dramatically extended, including aliphatic, aromatic aldehydes and also ketones. Due to the extended functional group compatibility of the reaction, many new scaffolds amenable by post-condensation reactions can be foreseen, as we have illustrated by the synthesis of a Cu-mediated fused tetrazole. Altogether, we believe that our procedure is superior to all previously reported Passerini tetrazole reactions and will be the method of choice for the future.

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