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A fast route for the synthesis of tetrazolyl oximes by a novel multicomponent reaction between *Z*-chlorooximes, isocyanides and trimethylsilyl azide

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ABSTRACT

A library of twenty variously decorated 1,5-disubstituted-(1*H*-tetrazol-5-yl)methanone oximes was prepared in one single synthetic step exploiting the combination of (*Z*)-chlorooximes, isocyanides and trimethylsilyl azide. The formal [3+1] cycloaddition between isocyanides and nitrile *N*-oxides with respect to the [3+1] cycloaddition between isocyanides and azides prevails, while the direct attack of azide onto nitrile *N*-oxides remains competitive. Finally, an intramolecular cyclization of a (1*H*-tetrazol-5-yl)methanone oxime to a benzoisoxazole tetrazole is reported for the first time.

Over the last decades, isocyanide-based multicomponent reactions (IMCRs) have demonstrated to be viable short-cuts for the rapid assembly of medium-complexity molecular skeletons usually accessible via two-component chemistry through a multistep approach.[1] Indeed, mixing three or four components in the same vessel can alter the typical course of a two-component reaction, as the third and/or the fourth component may be able to intercept unstable intermediates channeling the transformation toward different outcomes. A multicomponent approach is particularly viable and welcomed even when the reaction yield appeared to be moderate. Indeed, as recently highlighted, the synthetic efficiency of a MCR with moderate yield (35%) is by far higher than a three steps synthesis with yield higher than 70% for each step.[2]

In continuation with our research for the discovery of novel multicomponent reactions[3] we envisaged the possibility to set up a novel multicomponent transformation for the synthesis of tetrazolyl oximes, a class of very potent fungicides exemplified by compounds of general formula **1** (Fig. 1).[4] Usually, tetrazolyl oximes are synthesized from the corresponding 5-aroyl-1-aryltetrazoles **4** by condensation with hydroxylamine giving a mixture of *Z* and *E* isomers.[5]

As only the *Z* geometrical isomer has fungicide activity, several patents tried to solve the problem of the oxime regioselectivity.[6]

Different synthetic procedures for the synthesis of intermediates **4** have been reported so far. For example, a thermal [3+2] cycloaddition between acyl cyanides (**2**) and organic azides (**3**) have been described (Scheme 1).[7]

Anyway, the reaction fails with aromatic azides preventing the formation of 5-aroyl-1-aryltetrazoles (**4**). Reaction between nitrones (**6**) or α-ketoimidoylchlorides (**7**) and hydrazoic acid have also been reported although they were very poor in scope (Scheme 1).[8,9] Furthermore, the use of hydrazoic acid, an unstable, extremely explosive, and very toxic liquid, raises concerns about its use on industrial scale. An alternative and convergent approach for the obtainment of 5-aroyl-1-aryltetrazole derivatives was based on the use of an Ugi reaction between an aldehyde or a ketone (**8**), an amine (**9**), an isocyanide (**10**) and a source of azide (**11**). In this case, the Ugi-azide reaction affords derivative **12** (Scheme 1) in very good yields. However, further elaborations were needed to give 5-aroyltetrazoles (**4**).[10]

Understanding the difficulties associated with the synthesis of 5-aroyl-1-aryltetrazoles and the problems associated with the formation of the single *Z*-isomer of oxime, and in connection with our

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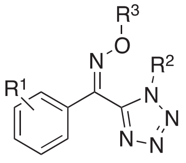
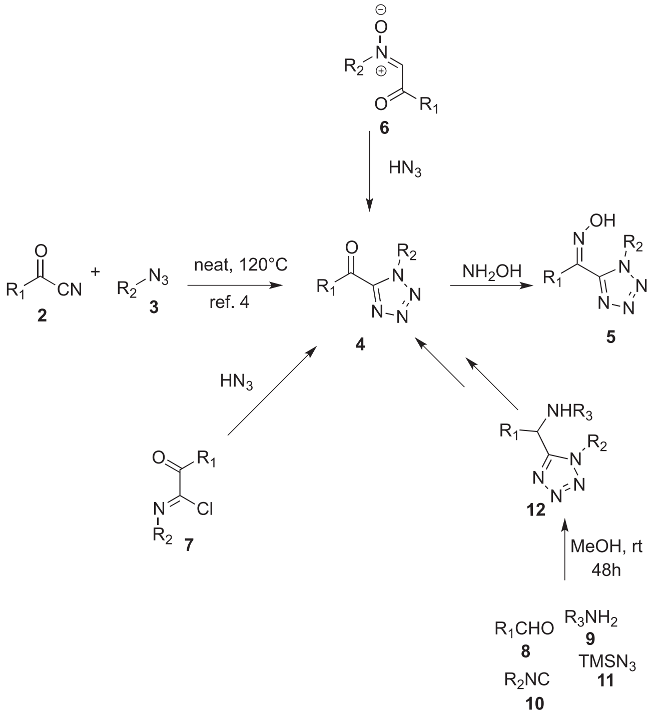
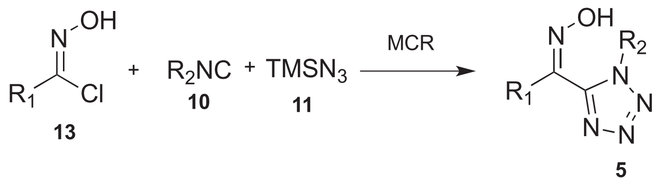


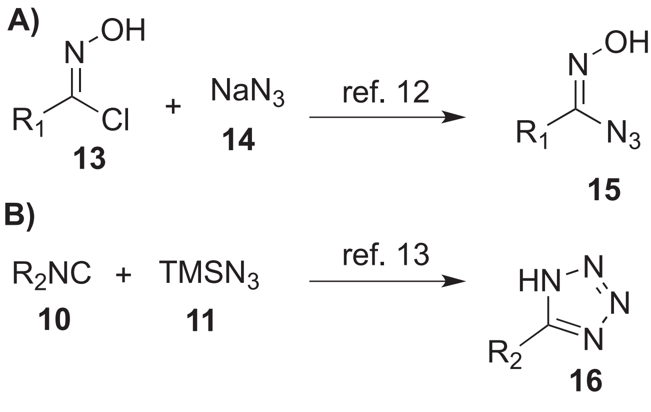
Fig. 1. General formula of tetrazolyl oximes endowed with fungicide activity.



Scheme 1. Literature reported syntheses of the 5-oxo-tetrazole precursors.



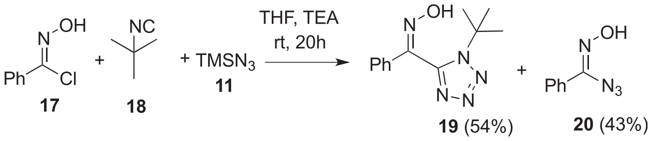
Scheme 2. Multicomponent reaction of *Z*-chlorooximes, isocyanides and trimethylsilyl azide.



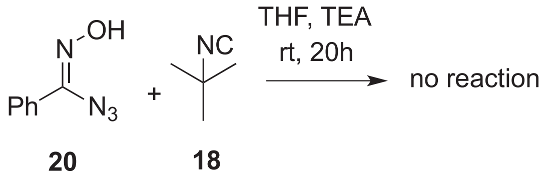
Scheme 3. Reported reactions of azide with *Z*-chlorooximes and isocyanides.

studies on the use of nitrile *N*-oxides in isocyanide-mediated multicomponent reactions,[11] we became intrigued in testing the one-pot reaction between *Z*-chlorooximes (**13**), isocyanides (**10**) and trimethylsilyl azide (**11**), in order to obtain *Z*-1,5-disubstituted-(1*H*-tetrazol-5-yl)methanone oximes (**5**) in one single chemical operation as exemplified in Scheme 2.

We have previously demonstrated that nitrile-*N*-oxides preferentially react with isocyanides in the presence of a third nucleophile independently from its nucleophilic strength, as the formal [3+1] cycloaddition reaction between isocyanides and nitrile *N*-oxides is energetically favorable.[11] In this case, anyway, the situation was even more puzzling as the third component, the azide, can behave both as strong nucleophile and reactive dipo-



Scheme 4. Test reaction affording tetrazole **19** and hydroxymoyl azide **20**.



Scheme 5. Attempted reaction between hydroxymoyl azide **20** and *t*-butylisocyanide **18**.

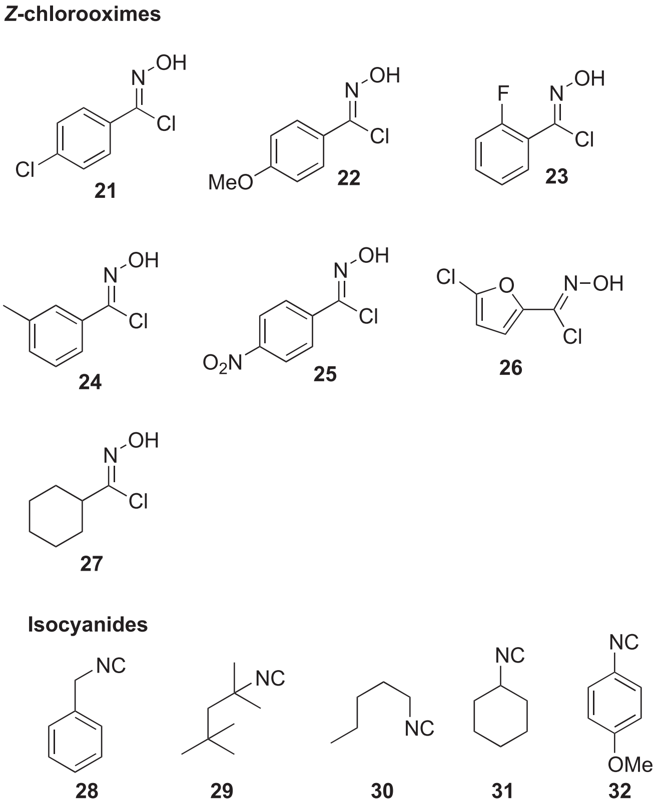


Fig. 2. Starting materials used for the synthesis of a library of 1,5-disubstituted-(1*H*-tetrazol-5-yl)methanone oximes.