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A one-pot pseudo nine-component isocyanide-based reaction: synthesis of a new class of zinc 1,5-disubstituted 1*H*-tetrazol-5-yl coordination complexes

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ABSTRACT

A novel one-pot pseudo nine-component synthesis of zinc 1,5-disubstituted 1*H*-tetrazol-5-yl coordination complexes in good yields starting from simple and readily available substrates, including a 1,3-dicarbonyl compound, an isocyanide, *N*,*N*-dimethylformamide dimethyl acetal, sodium azide, and zinc chloride in methanol at ambient temperature, is described.

Recently a new area in tetrazole chemistry has been developed which overlaps at the border with inorganic chemistry. Tetrazoles which contain four electron-donating atoms in the five-membered ring are able to coordinate to metals through different nitrogen atoms *via* a covalent, ionic, or coordination bond which has led to diversity in metal-tetrazole derivatives (MTs).[1–3]

It is interesting to note, that to date, numerous metal-tetrazole coordination complexes have been synthesized. MTs are useful coordinate compounds and are used in a wide range of applications in many research fields. A key application of MTs is in organic synthesis where they are used as starting and intermediate compounds for the synthesis of *N*-substituted tetrazoles from various metal tetrazolates.[1–9] The ability of tetrazoles to form stable complexes with various metal ions is used widely in photoprocesses, corrosion protection of metals,[10–14] energetic compositions,[15] pyrotechnics,[16] semiconductor nanoparticles,[17] ultra-low-density nanostructured metal foams,[18] gas storage, and heterogeneous catalysis.[19] For example, iron(III) complexes **I** and **II** showed high efficiency as catalysts in the oxidation of olefins (Fig. 1).[20]

Methods for the synthesis of MTs can be divided into two strategies. The first involves the reaction of five-substituted tetrazoles with metal salts in the presence of bases, such as metal hydroxides,[5,21–25] alkoxides[26–29,6,30,31], or hydrides[5,32] to afford tetrazolates. The second route comprises heterocyclizations of azide ions and nitrile compounds with metal salts. Among heterocyclization reactions for the synthesis of tetrazoles, [3+2] cycloadditions of azides to nitriles in the presence of metal salts are the most significant.[1–3,33]

Zinc(II) is a common metal ion in the human body and is involved in various biological activities, such as cellular processes, including cell proliferation, reproduction, immune function, and defense against free radicals,[34] and plays an important role in both genetic stability and functionality.[35] Tetrazole metal derivatives exhibit various applications and demonstrate interesting coordination chemistry.[36]

Isocyanide-based multicomponent reactions (IMCRs) are powerful approaches to access numerous highly functionalized heterocyclic molecules from readily available starting materials. In continuation of our previous work on IMCRs,[37] and inspired by Ugi tetrazole reactions,[38] attempts have been made to develop a new route for the synthesis of zinc 1,5-disubstituted 1*H*-tetrazol-5-yl compounds. The products were prepared *via* a one-pot process involving a pseudo nine-component condensation reaction of various cyclic 1,3-dicarbonyl compounds **1**, DMF-DMA (**2**), isocyanides **3**, and sodium azide with zinc chloride in methanol without using any catalyst or activation methods (Scheme 1).

The advantage of the IMCR strategy was the ability to assemble the desired product in one step, in contrast to the classic method which requires the use of more than one step. In addition, this strategy was shown to be environmentally friendly and highly efficient in that there was no need for ligand synthesis.

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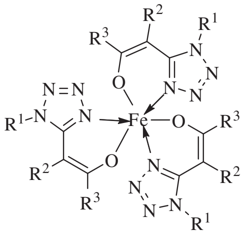


R^1 = ^{i}Bu, R^2 = CN, R^3 = OMe (**I**); R^1 = ^{t}Bu, R^2 = H, R^3= Ph (**II**)

Figure 1.

In a pilot experiment, dimedone (**1a**) and DMF-DMA (**2**) were stirred in the absence of solvent for 1 h at ambient temperature. After completion of the condensation reaction (monitored by TLC),[39] cyclohexylisocyanide (**3a**), sodium azide, and zinc chloride were added to the reaction vessel along with methanol as the solvent, and the contents stirred for 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the product **5a** was obtained in 83% yield.

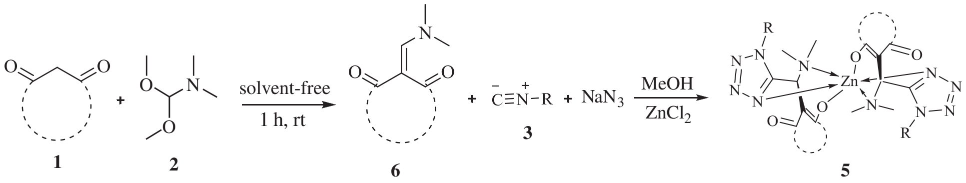
To evaluate the use of this interesting approach, a variety of cyclic and acyclic 1,3-dicarbonyl compounds and isocyanides were examined, however, we were only able to obtain five of these products. The results are summarized in Table 1.

The reaction proceeded very efficiently under mild reaction conditions at ambient temperature to produce the corresponding products **5a–e** in good yields (Fig. 2).

The structures of compounds **5a–e** were deduced from their IR, mass, ^{1}H and ^{13}C NMR spectral data. The structure of **5a** was also determined by single crystal X-ray analysis. The ORTEP diagram of **5a** shows that two of the four-component products coordinated to zinc and resulted in the formation an octahedral complex (Fig. 3).

It is conceivable that the initial event is the formation of intermediate **6** from condensation between the 1,3-dicarbonyl compound and DMF-DMA.[39] Then, on the basis of the well-established reaction of isocyanides with electron-deficient α,β-unsaturated carbonyl compounds,[40] compound **6** coordinates with Zn(II) and undergoes a Michael-type addition with the isocyanide to produce intermediate **8**. Next, nucleophilic attack of an azide ion on the nitrilium moiety followed by 1,5-dipolar cycloaddition produces intermediate **9**.[41,42] Intermediate **9** can then be converted into complex **10**. It is highly possible that this species coordinates to intermediate **6** which undergoes a second identical process. Finally, zinc retains its coordination to these ligands and produces octahedral complexes **5a–e** of zinc (Scheme 2).

In conclusion, from simple and readily available substrates under mild reaction conditions using an IMCR strategy, we have developed a pseudo nine-component isocyanide-based reaction



Scheme 1. Synthesis of zinc 1,5-disubstituted 1*H*-tetrazol-5-yl complexes **5a–e**.

Table 1
Synthesis of zinc 1,5-disubstituted 1*H*-tetrazol-5-yl coordination complexes **5a–e**

Entry	1,3-Dicarbonyl **1**	R	Product	Time (h)	Yield (%)
1	Dimedone	Cy	**5a**	7	83
2	1,3-Cyclohexanedione	Cy	**5b**	8	76
3	1,3-Cyclopentanedione	Cy	**5c**	7	80
4	Dimedone	1,1,3,3-Tetramethylbutyl	**5d**	7.5	79
5	1,3-Cyclopentanedione	^{t}Bu	**5e**	6.5	75

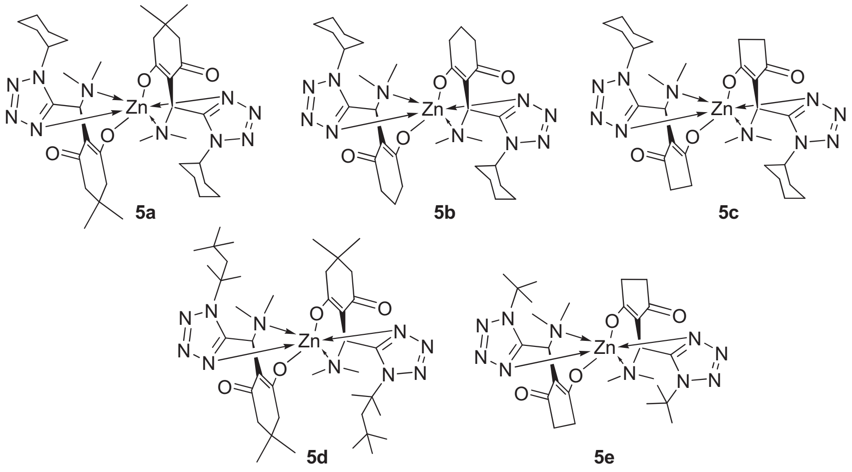


Figure 2. The structures of products **5a–e**.

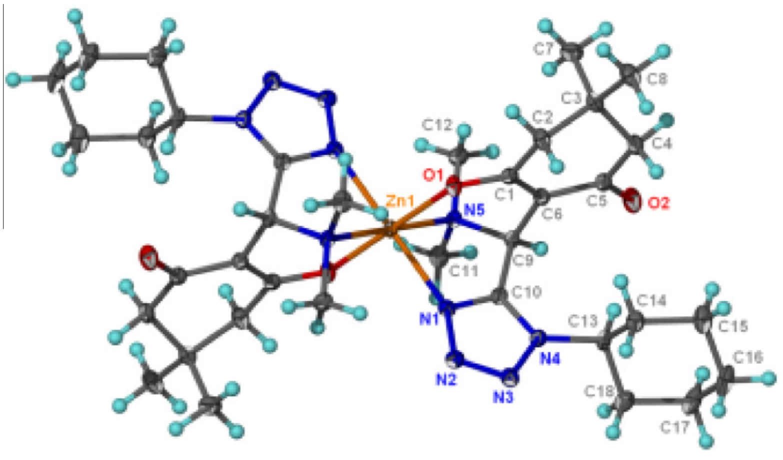
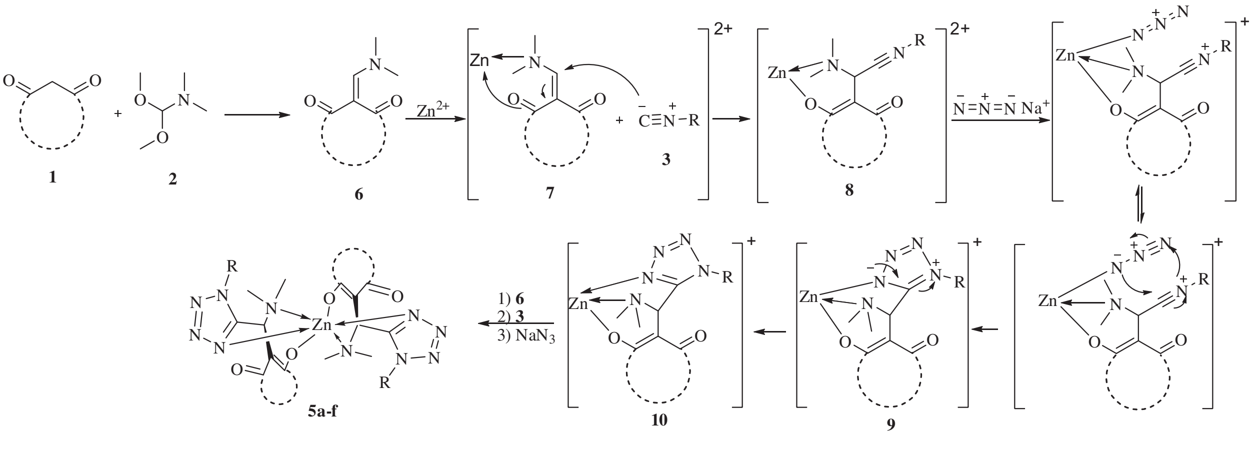


Figure 3. ORTEP diagram of **5a**.



Scheme 2. The proposed mechanism for the formation of complexes **5**.

to produce MTs. These reactions led to the formation of zinc 1,5-disubstituted 1*H*-tetrazol-5-yl coordination complexes under mild reaction conditions without using any catalyst or activation methods. The complexes were obtained in good yield, and product isolation was very straightforward. This approach may be useful to chemists seeking novel synthetic fragments with unique properties for medicinal chemistry programs. Further studies and synthetic applications of this chemistry are in progress in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.017.

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