DOI: 10.1002/chem.200900169

Iron Salts in the Catalyzed Synthesis of 5-Substituted 1*H*-Tetrazoles

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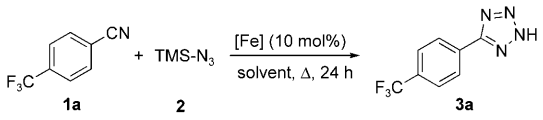
Tetrazoles are important heterocycles for explosives, photographic agents, and pharmaceuticals.[1] In the latter application, they can serve as metabolically stable surrogates of carboxylic acid groups.[2] Reactions between nitriles and azides lead to 5-substituted 1*H*-tetrazoles, and many synthetic approaches towards them have been developed.[3] For example, Sharpless and co-workers demonstrated that 1*H*-tetrazoles could be accessed through the addition of sodium azide to nitriles in the presence of 0.5 to 1.0 equivalents of Zn^{II} salts.[4] Later, Pizzo and co-workers showed that the metal salt could be replaced by tetrabutylammonium fluoride (TBAF; 0.5 equiv).[5] More recently, Yamamoto and co-workers catalyzed cycloadditions between nitriles and trimethylsilyl azide (TMS-N_3) with 2.5 mol% of Cu_2O, by performing the reaction in a 9:1 mixture of DMF and MeOH at 80 °C.[6] Copper proved to be a very efficient metal for this transformation. A one-pot multicomponent reaction was achieved by Kundu and co-workers, who applied a copper/iron combination as catalyst in water for the formation of triazoles.[7] In this case, iron was suggested to serve as modulator for the oxidation state of copper. All of these approaches reveal that the catalytic formation of tetrazoles is still challenging and that the area demands to be developed further.

Iron salts proved useful for several catalyzed reactions including cross-couplings, oxidations, and reductions.[8] Since iron is cheap, non-toxic, and environmentally friendly, its application has attracted much attention. Considering the rich activation mechanisms of iron salts we hypothesized that they could also be useful in click-type cycloadditions. The realization of this idea is demonstrated here.

For the initial metal source screening and the subsequent optimization of the reaction conditions *para*-trifluorotoluonitrile (**1a**) and trimethylsilyl azide (**2**) were selected as model substrates. Guided by Yamamoto's findings the reaction was first tried under his conditions using iron(II) acetate instead of copper(I) oxide (Table 1, entry 3). To our delight, the catalysis [with 10 mol% of $Fe(OAc)_2$] proceeded very well, affording tetrazole **3a** in 91% yield. In contrast to our previously reported reactions involving iron salts,[9] the addition of a ligand was unnecessary. Neither raising the temperature to 90 or 100 °C nor lowering it to 70 or 60 °C had any beneficial effect on the formation of **3a** (Table 1, entries 1, 2 and 3, 4, respectively). Control reactions per-

Table 1. Optimization of the catalyzed formation of tetrazole **3a**.[a]



1a **2** **3a**

Entry	Fe source[b]	Solvent	Temp. [°C]	Yield of **3a** [%][c]
1	$Fe(OAc)_2$	DMF/MeOH (9/1)	100	88 (47)
2	$Fe(OAc)_2$	DMF/MeOH (9/1)	90	89 (42)
3	$Fe(OAc)_2$	DMF/MeOH (9/1)	80	91 (37)
4	$Fe(OAc)_2$	DMF/MeOH (9/1)	70	59 (15)
5	$Fe(OAc)_2$	DMF/MeOH (9/1)	60	35 (5)
6	$FeCl_3$[d]	DMF/MeOH (9/1)	80	76
7	$FeCl_3.6H_2O$[e]	DMF/MeOH (9/1)	80	72
8	$Fe(ClO_4)_2$[f]	DMF/MeOH (9/1)	80	80
9	$FeBr_2$[g]	DMF/MeOH (9/1)	80	87
10	$Fe(NTf_2)_2$[f]	DMF/MeOH (9/1)	80	86
11	$Fe(OTf)_2$[f]	DMF/MeOH (9/1)	80	87
12	$Fe(OAc)_2$[h]	DMF/MeOH (9/1)	80	87
13	$Fe(OAc)_2$	DMF	80	56
14	$Fe(OAc)_2$	H_2O	80	0
15	$Fe(OAc)_2$	DME	80	0
16	$Fe(OAc)_2$	dioxane	80	traces
17	$Fe(OAc)_2$	toluene	80	0
18	$Fe(OAc)_2$	THF	80	0
19	$Fe(OAc)_2$	THF/water (9/1)	80	0

[a] Reaction conditions: **1a** (1.0 equiv), **2** (1.5 equiv), [Fe] (0.1 equiv), solvent (1 mL mmol^{-1} of **1a**), 24 h. [b] $Fe(OAc)_2$ (95%; Acros). [c] In parentheses, results from reactions performed in the absence of iron. [d] $FeCl_3$ (98%; Merck) [e] $FeCl_3.6H_2O$ (98%; Grüssing GmbH). [f] Iron source prepared according the literature. [g] $FeBr_2$ (98%; Aldrich). [h] $Fe(OAc)_2$ (99.995%; Aldrich).

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900169.

formed in the absence of the metal salt revealed that in all cases a substantial amount of product was formed in an uncatalyzed manner (Table 1, entries 1–5; data in parentheses). Commonly, however, the yields were at least double when the iron catalyst was applied.

A screening of various iron salts [in DMF/MeOH (9/1) at 80 °C] revealed that both the oxidation state of the iron as well as the counterion have only a minor effect on the catalysis. In all cases the yields of **3a** were in the 70–80% range (Table 1, entries 6–11). Solvents other than the DMF/MeOH mixture led to unsatisfying results (Table 1, entries 13–19).

To exclude that the observed catalysis was not resulting from trace impurities in the metal salt, iron sources with different purity grades obtained from various commercial providers were applied. In this context the experiment with $Fe(OAc)_2$ having a purity of 99.995% (Aldrich) proved most instructive, since it gave tetrazole **3a** in 87% yield (Table 1, entry 12). Atom absorption spectroscopy confirmed that neither that iron salt sample nor the subsequently applied $Fe(OAc)_2$ with a purity of 95% (Acros) contained copper (which is a common metal for catalyzed click reactions).

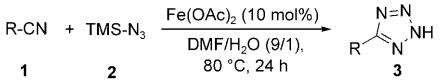
Next, the substrate scope was evaluated. As the entries in Table 2 reveal, the catalysis proceeded well for a wide variety of aryl nitriles, providing the corresponding tetrazoles in high yields. Both the type of substituent and the substitution pattern had a major effect on the yield. The best results were achieved with compounds bearing electron-withdrawing groups. For example, 4-nitrobenzonitrile and 3,5-dinitrobenzonitrile gave the corresponding tetrazoles **3e** and **3l** in 96 and >99% yield, respectively (Table 2, entries 5 and 12). Having the nitro group in the *ortho*-position hampered the tetrazole formation, and **3j** was only obtained in 67% yield (Table 2, entry 10). As to be expected from this trend, the yield of *ortho*-bromo-substituted tetrazole **3g** was very low (15%; Table 2, entry 7). Benzonitriles with halo and other electron-donating substituents in *meta* and *para* positions reacted well, providing the corresponding products in moderately good yield. Non-aromatic nitriles did not react (Table 2, entries 15 and 16). As before, $Fe(OAc)_2$ with purities of both 95 and 99.995% catalyzed the reaction well, with the former being slightly more effective in each case. Currently, we cannot say if this reactivity difference is due to the presence of unknown contaminants or a matter of metal salt consistencies leading to differences in catalyst accessibility.

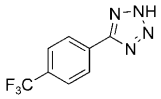
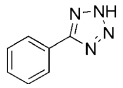
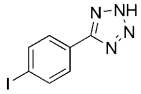
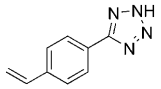
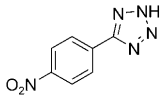
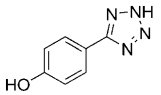
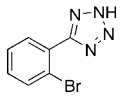
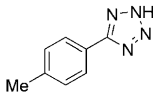
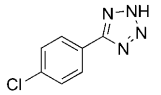
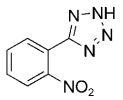
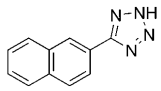
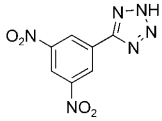
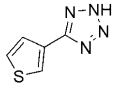
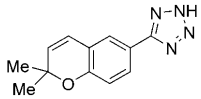
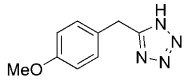
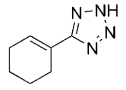
In conclusion, a catalyzed tetrazole synthesis that utilizes iron salts has been developed. Since the method avoids the use of toxic and expensive metals, is appears attractive for industrial and pharmaceutical applications.

Experimental Section

General procedure: A sealable tube equipped with a magnetic stir bar was charged with the aryl nitrile (1.0 equiv) and $Fe(OAc)_2$ (0.1 equiv). A rubber septum was used to cover the aperture of the tube, an argon atmosphere was established, and trimethylsilyl azide (1.5 equiv) and a 9:1

Table 2. Fe-catalyzed synthesis of 5-substituted 1*H*-tetrazoles.[a]



Entry	Product		Yield [%][b]
1		**3a**	91 (87)
2		**3b**	56 (22)
3		**3c**	68 (53)
4		**3d**	37 (11)
5		**3e**	96 (86)
6		**3f**	41 (7)
7		**3g**	15 (11)
8		**3h**	57 (42)
9		**3i**	70 (64)
10		**3j**	67 (48)
11		**3k**	58 (56)
12		**3l**	>99 (>99)
13		**3m**	74 (43)
14		**3n**	53 (49)
15		**3o**	0
16		**3p**	0

[a] Reaction conditions: R–CN (1.0 equiv), **2** (1.5 equiv), $Fe(OAc)_2$ (0.1 equiv, 95%; Acros), solvent (1 mL mmol^{-1} of R–CN), 80 °C, 24 h. [b] In parentheses, results from experiments performed with $Fe(OAc)_2$ of 99.995% purity (Aldrich).

DMF–MeOH solution (1 mL) were added by using a syringe. Then the rubber septum was replaced with a Teflon-coated screw cap, and the reaction vessel was heated at 80 °C. After stirring at this temperature for 24 h, the mixture was cooled to room temperature and diluted with ethyl acetate. The resulting solution was washed with 1 N HCl, dried over anhydrous Na_2SO_4, and concentrated. An aqueous solution of NaOH (0.25 N) was added to the residue, and the mixture was stirred for 30 min at room temperature. The resulting solution was washed with ethyl acetate, and then 1 N HCl was added until the pH value of the water layer became 1. The aqueous layer was extracted with ethyl acetate three times, and the combined organic layers were washed with 1 N HCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The identity and purity of the product was confirmed by ^1H and ^{13}C NMR spectroscopic analysis.

Acknowledgements

We are grateful to the Fonds der Chemischen Industrie for the financial support. We also thank Prof. Dr. R. Dronskowski and Mr. L. Stork (Institute for Inorganic Chemistry, RWTH Aachen University) for substrate analyses by atom absorption spectroscopy.

Keywords: azides · catalysis · cycloaddition reactions · heterocycles · iron · tetrazole

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Received: January 20, 2009
Published online: March 18, 2009

