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Diversity-oriented synthesis of *N,N*-dimethylamino-substituted azoles employing TBTU

Alexey Lukin,[a] Natalya Kalinchenkova,[a] Tatiana Vedekhina,[a] Nikolay Zhurilo,[a] and Mikhail Krasavin[b,*]

[a]*Lomonosov Institute of Fine Chemical Technologies, Moscow Technological University, 86 Vernadskogo Prospekt, Moscow, 117571 Russian Federation*

[b]*Saint Petersburg State University, Saint Petersburg, 199034 Russian Federation*

* Corresponding author.

Phone: +7 931 361 7872, fax: +7 812 428 6939, e-mail: mkrasavin@spbu.ru

URL: https://krasavin-group.org

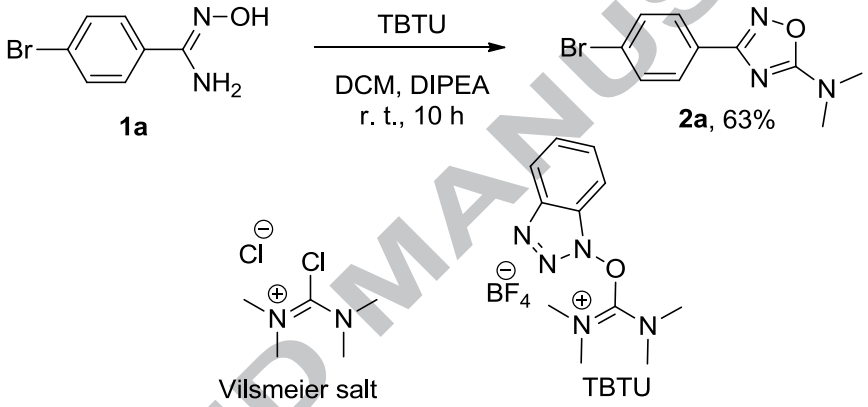
Abstract: A convenient, diversity-oriented approach for the transformation of readily available amidoximes, *o*-hydroxyarylamines, acyl hydrazines, carboximidohydrazides and thiohydrazides into their respective *N,N*-dimethylamino-substituted azoles is described. The method is particularly suitable for array chemistry application as it employs a stable, solid reagent TBTU.

Keywords: dimethylamino group; azoles; acylation; guanidine formation; diversity-oriented synthesis; fragment-based drug discovery.

Organic compounds that are based on privileged[1] heterocyclic cores, which possess increased solubility and low molecular weight, are of particular interest for fragment-based drug discovery (FBDD).[2] Indeed, privileged character increases the chances of identifying, *via* initial screening, the starting affinity points for further fragment evolution; high solubility allows testing the fragments at high enough concentration to detect binding to protein targets and low molecular weight provides sufficient room for fragment growth and subsequent medicinal chemistry optimization within the limits of druglikeness.[3] Various azole moieties are omnipresent in organic compounds endowed with diverse biological activities and are often included in fragment screening libraries.[4] As an alternative to the costly protein/ligand X-ray crystallography platform,[5] NMR-based approaches[6] have been employed as a time- and cost-efficient way to identify fragment hits, ever since the conceptual introduction of FBDD in 1996.[7] Methyl groups bound to a heteroatom, a (hetero)aromatic ring or a carbonyl group

that give a standalone, uncoupled signal in the ^{1}H NMR spectrum and thus facilitate NMR fragment screening, are desired structural elements in a fragment library.[8] *N,N*-Dimethylamino-substituted azoles combine the above-mentioned features (privileged core and 'NMR screening-friendly' methyl groups) with the solubilizing character of the nitrogen atom. Herein, we describe a new and convenient method for the preparation of such compounds, many of them fragment-like,[9] in a diversity-oriented fashion from readily available precursors and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU).

Scheme 1. Serendipitously discovered transformation of **1a** into **2a** and the structures of TBTU and Vilsmeier salt.

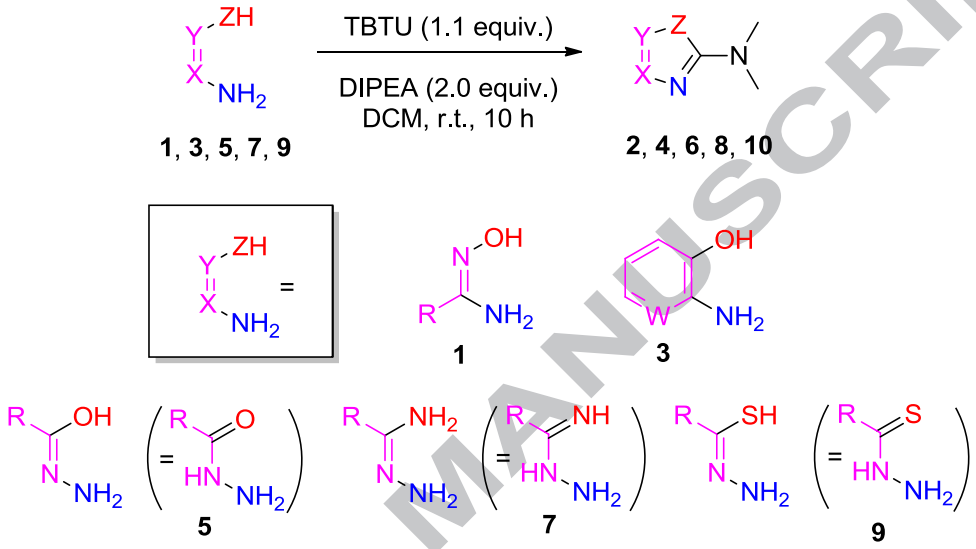


In the course of preparing an array of 1,2,4-oxadiazoles from amidoximes and carboxylic acids *via* TBTU activation as described in the literature,[10] the carboxylic acid coupling partner was not added to the reaction mixture by accident. This resulted in the conversion of amidoxime **1a** into 5-(dimethylamino)-1,2,4-oxadiazole **2a** which was isolated in 63% yield. This transformation is quite similar to the known cyclization of amidoximes to 1,2,4-oxadiazoles brought about by the action of Vilsmeier salt (Scheme 1).[11] Since Vilsmeier salt needs to be prepared prior to use[12] and cannot be stored and used as an off-the-shelf reagent, we viewed TBTU as being a potentially attractive alternative, particularly for small-scale parallel chemistry applications where the convenience of using a stable, solid reagent is likely to be of importance.[13] Considering that no such application of TBTU or its analogs (e. g., HATU or HBTU) had been described in the literature, we set off to investigate the substrate scope of the newly identified reaction.

Since the use of Vilsmeier salt has been applied to the synthesis of other azoles besides 5-(dimethylamino)-1,2,4-oxadiazoles such as **2a**, including various benzazoles,[14-15] we included *o*-hydroxyarylamines **3a-f** in the selection of substrates hoping to obtain the corresponding arene-fused 1,3-oxazoles **4a-f**. In addition, although no such reaction had been described in

the literature neither for Vilsmeier salt nor for TBTU or its analogs, we also attempted to transform acyl hydrazines **5a-d**, carboximidohydrazides **7a-b** and thiohydrazides **9a-d** into 1,3,4-oxadiazoles **6a-d**, 1,2,4-triazoles **8a-b** and 1,3,4-thiadiazoles **10a-d**, respectively (Scheme 2). As evident from the data presented in Table 1, the reaction with TBTU readily transformed all these substrates into the respective *N*,*N*-dimethylamino-substituted azoles.

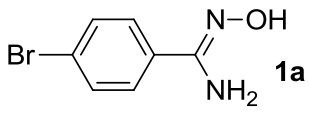
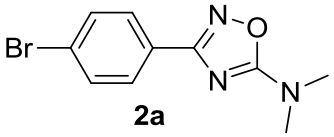
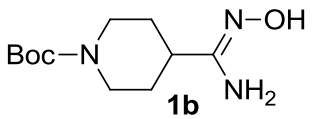
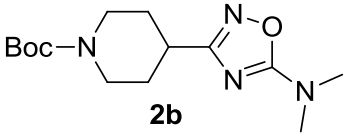
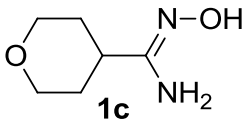
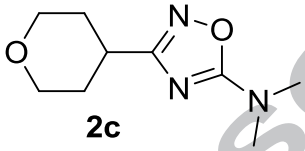
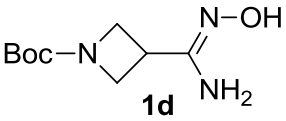
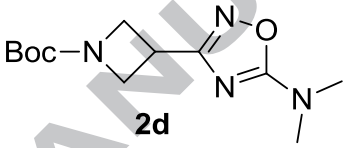
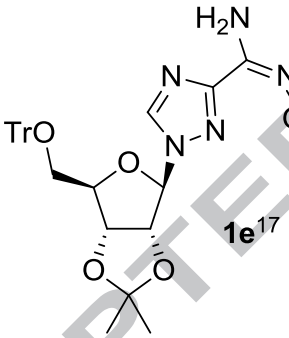
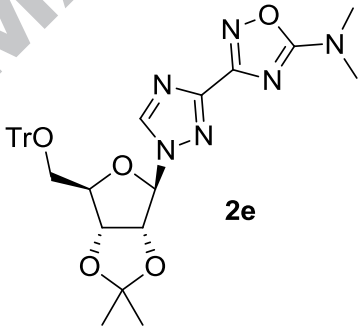
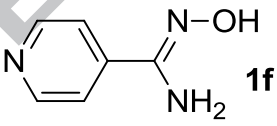
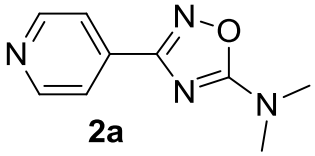
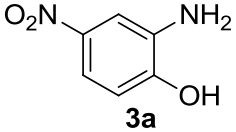
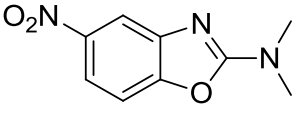
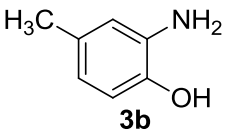
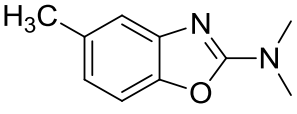
Scheme 2. Synthesis of *N*,*N*-dimethylamino-substituted azoles investigated in this work.

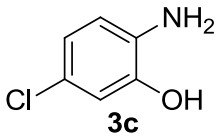
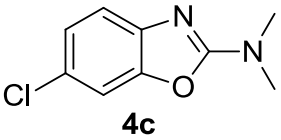
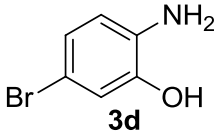
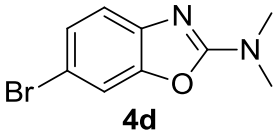
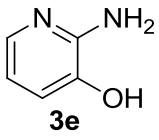
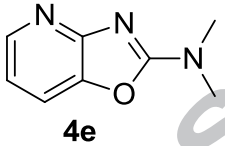
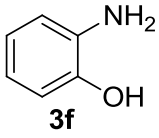
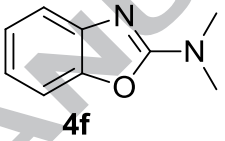
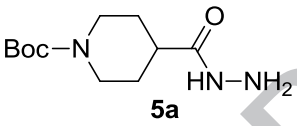
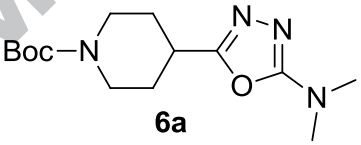
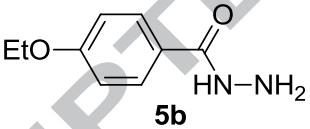
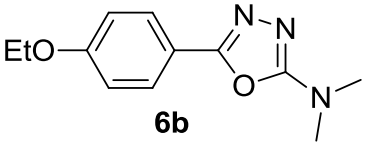
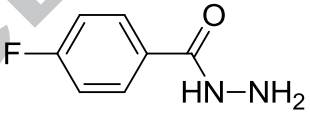
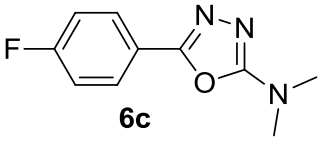
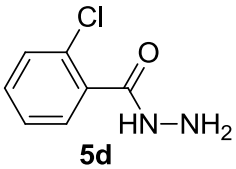
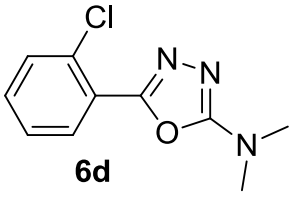
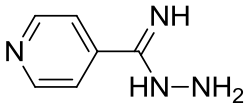
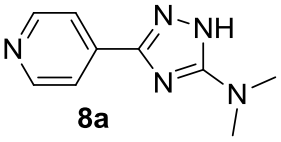


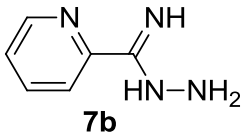
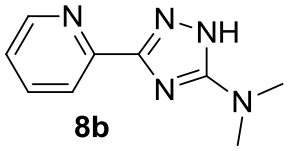
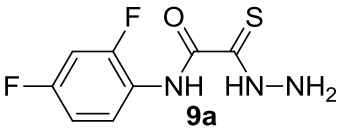
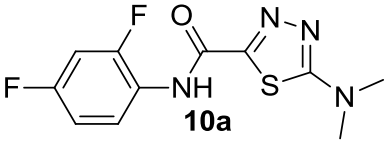
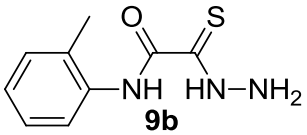
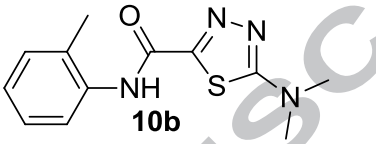
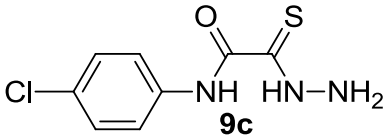
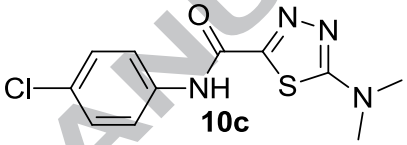
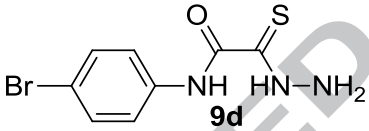
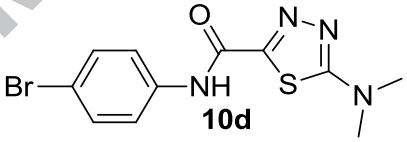
Prior to performing the substrate scope investigation, we briefly examined variations of the reaction time and temperature as well as the substrate-to-DIPEA and substrate-to-TBTU ratios and found the conditions shown in Scheme 2 to be optimal.[16] Except for the transformation of acyl hydrazines **5** into the respective 1,3,4-oxadiazoles **6** (Table 1, entries 13-16), which required heating the reaction mixture at reflux for 4 h, all reactions were performed at ambient temperature for 10 h. The isolated yields obtained after chromatographic purification of the azole product were moderate to very good. With respect to molecular weight, the majority of compounds obtained are rule-of-three compliant (MW < 300), which makes them suitable tools for FBDD.[9] The method was found to be compatible with a range of protecting groups such as Boc (Entries 2 and 4) as well as trityl and acetonide (Entry 5).

Table 1. Preparation of *N*,*N*-dimethylamino-substituted azoles **2**, **4**, **6**, **8** and **10**.

Entry	Substrate	Product	MW	Isolated yield (%)

1	 **1a**	 **2a**	267	63
2	 **1b**	 **2b**	296	69
3	 **1c**	 **2c**	197	43
4	 **1d**	 **2d**	268	27
5	 **1e**[17]	 **2e**	594	55
6	 **1f**	 **2a**	190	45
7	 **3a**	 **4a**	229	87
8	 **3b**	 **4b**	176	63

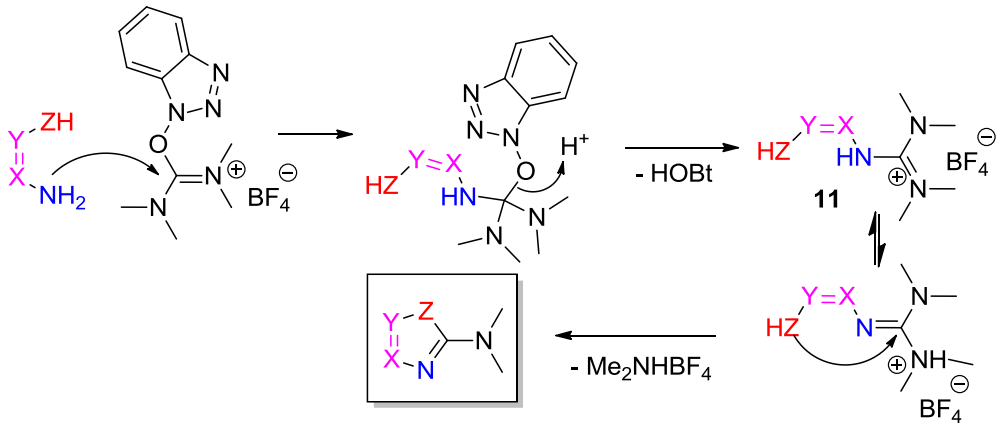
9	 **3c**	 **4c**	196	61
10	 **3d**	 **4d**	239	75
11	 **3e**	 **4e**	185	64
12	 **3f**	 **4f**	162	61
13[a]	 **5a**	 **6a**	296	20
14[a]	 **5b**	 **6b**	233	68
15[a]	 **5c**	 **6c**	207	70
16[a]	 **5d**	 **6d**	223	79
17	 **7a**	 **8a**	189	43

18	 **7b**	 **8b**	189	79
19	 **9a**	 **10a**	284	59
20	 **9b**	 **10b**	262	55
21	 **9c**	 **10c**	282	85
22	 **9d**	 **10d**	325	63

[a]Reaction was conducted at reflux for 4 h.

From the mechanistic perspective, it is likely that the reaction is initiated by the known[18] formation of guanidine intermediate **11** which undergoes intramolecular addition-elimination leading to formation of the azole ring (Scheme 3).

Scheme 3. Plausible mechanism for azole formation.



In summary, we have developed a convenient, diversity-oriented approach for the transformation of readily available amidoximes, *o*-hydroxyarylamines, acyl hydrazines, carboximidohydrazides and thiohydrazides into their respective *N*,*N*-dimethylamino-substituted azoles using a unified synthetic procedure. The method represents a practical alternative to the use of Vilsmeier salts. The transformation has been applied to acyl hydrazines, carboximidohydrazides and thiohydrazides for the first time. The majority of compounds obtained *via* this method are rule-of-three compliant and can be considered practical tools for fragment-based drug discovery, particularly by NMR-based techniques.

Acknowledgements

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References and notes

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16. General procedure for the synthesis of *N*,*N*-dimethylamino azoles **2**, **4**, **6**, **8** and **10** – The substrate (1.40 mmol) was dissolved in CH_2Cl_2 (10 mL) and treated with TBTU (1.54 mmol) with stirring. Diisopropylethylamine (DIPEA, 2.80 mmol) was added dropwise and the reaction was stirred at r. t. for 10 h (heated at reflux for 4 h in the case of substrates **5a-d**). The reaction mixture was washed with 5% aq. citric acid, 5% aq. K_2CO_3, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using 0→5% methanol in chloroform as eluent.

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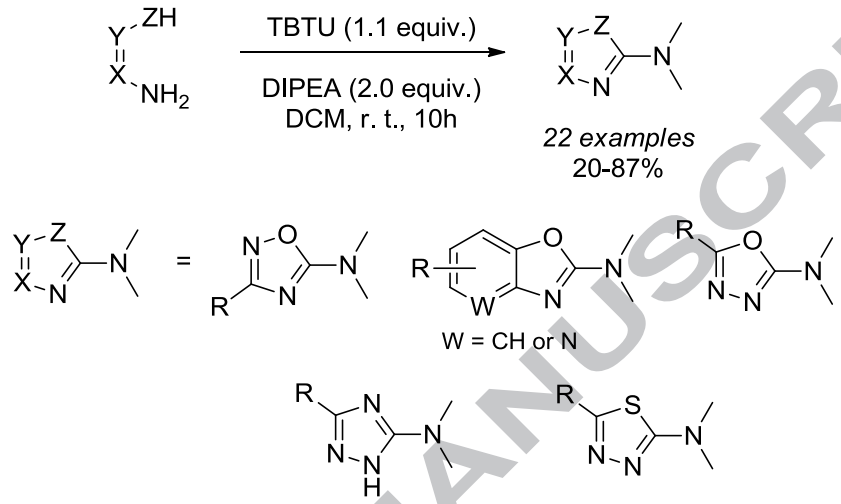
Diversity-oriented synthesis of *N,N*-dimethylamino-substituted azoles employing TBTU

Alexey Lukin, Natalya Kalinchenkova, Tatiana Vedekhina, Nikolay Zhurilo, and Mikhail Krasavin*



- TBTU was found to give 5-(dimethylamino)-1,2,4-oxadiazoles from amidoximes
- The transformation was found applicable to a variety of substrates
- The method offers a practical alternative to the use of Vilsmeier salt
- Compounds obtained can be considered tools for fragment-based drug discovery

19.