Tetrahedron Letters 59 (2018) 2732–2735

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Alexey Lukin [a], Natalya Kalinchenkova [a], Tatiana Vedekhina [a], Nikolay Zhurilo [a], 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

ARTICLE INFO

Article history:
Received 24 April 2018
Revised 23 May 2018
Accepted 25 May 2018
Available online 26 May 2018

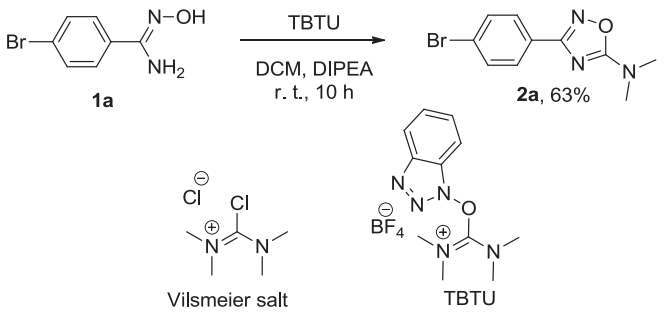
Keywords:
Dimethylamino group
Azoles
Acylation
Guanidine formation
Diversity-oriented synthesis
Fragment-based drug discovery

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.

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).

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]



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

* Corresponding author.
E-mail address: mkrasavin@spbu.ru (M. Krasavin).
URL: https://krasavin-group.org (M. Krasavin).

https://doi.org/10.1016/j.tetlet.2018.05.075
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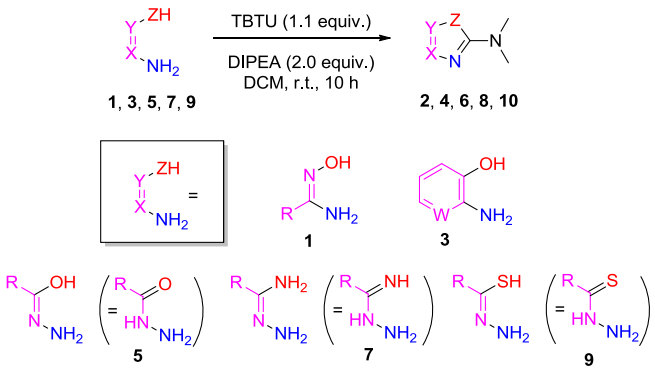
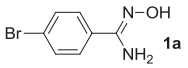
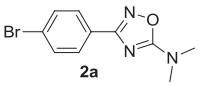
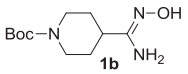
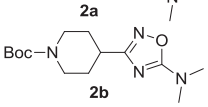
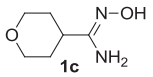
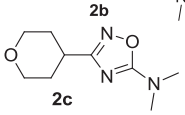
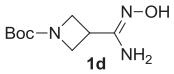
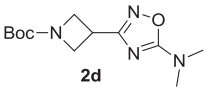
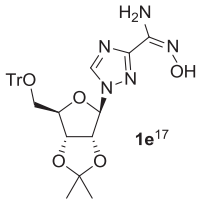
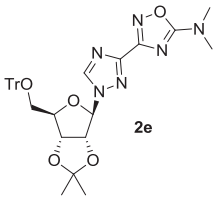
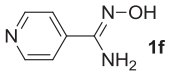
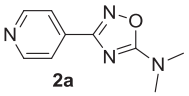
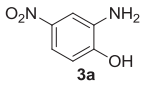
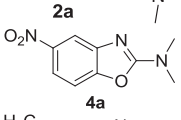
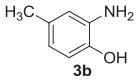
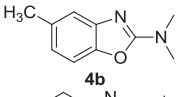
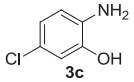
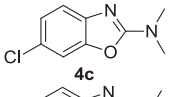
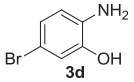
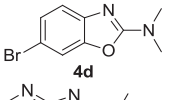
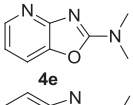
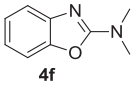


Scheme 2. Synthesis of *N,N*-dimethylamino-substituted azoles investigated in this work.

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.

Table 1
Preparation of *N,N*-dimethylamino-substituted azoles **2**, **4**, **6**, **8** and **10**. (See above-mentioned references for further information.)

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

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