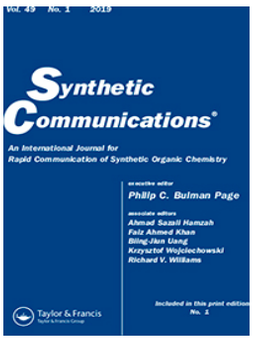

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A convenient one-pot synthesis of N-fused 1,2,4-triazoles via oxidative cyclization using chromium (VI) oxide

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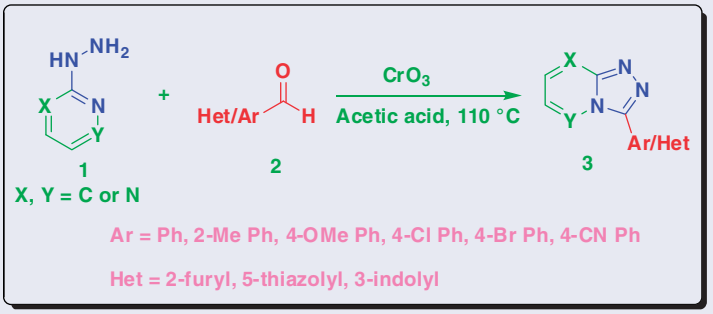
ABSTRACT

A facile one-pot synthesis of N-fused 1,2,4-triazoles from heterocyclic hydrazines and aldehydes is reported. The reaction is efficiently promoted by chromium (VI) oxide to afford the desired products mostly in high yields and in relatively short time. The high yield of the products and short reaction time are notable advantages of the developed protocol. This protocol is effective toward various substrates having different functionalities.

GRAPHICAL ABSTRACT



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KEYWORDS
Acetic acid; chromium (VI) oxide; 1,2,4-triazoles; [1,2,4]triazolo[4,3-a]pyridines; [1,2,4]triazolo[4,3-a]pyrazines

Introduction

Fused aromatic heterocycles are among the most important compound classes in drug discovery and also play a pivotal role in living organisms.[1,2] In particular, such scaffolds can be found as building blocks for DNA (guanine, adenine) but also in many approved drugs including sildenafil, zolpidem, and trazodone, as well as in medicinal chemistry studies[3–6] (i.e., tyrosine kinase c-Src inhibitors[7,8] or P38α inhibitors[8] [Figure 1]).

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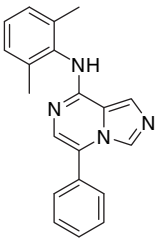
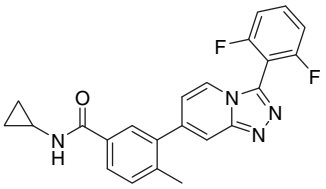
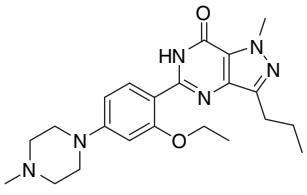


tyrosine kinase
c-Src inhibitor



P-38 a inhibitor



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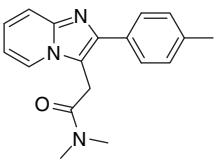
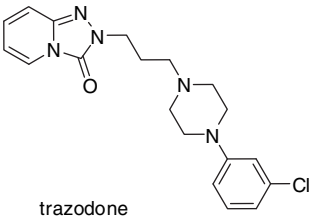


zolpidem

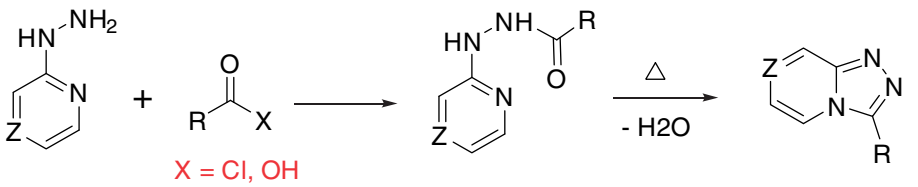


trazodone

1,2,4-Triazoles have elicited considerable interest among medicinal chemists because they are considered to be privileged structural constituents of many pharmaceutical agents as well as natural products. In particular, compounds containing N-fused 1,2,4-triazoles, such as triazolopyridine and triazolopyrazine substructures exhibit a wide spectrum of biological activity including antifungal,[9] antimicrobial,[10] antiviral,[11] anti-inflammatory,[12] antiasthmatic,[13] antiproliferative,[14] and hypotonic.[15] In addition, they have often been used as bioisosteres of esters and amides, and as dipeptidomimetics in a number of pharmacologically important molecules.[16] On the other hand, they also play important roles as ligands in organometallic compounds, as precursors for N-heterocyclic carbenes, as ionic liquids and as corrosion inhibitors.[17]

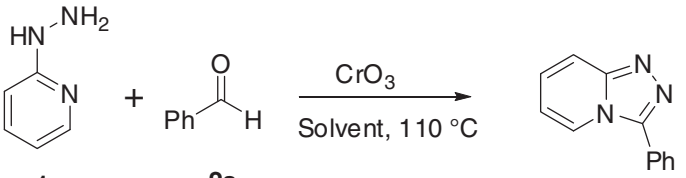
Due to their importance, many efficient methods have been developed to access N-fused 1,2,4-triazoles.[18] Among them, coupling of carboxylic acids or their derivatives with amidrazones, followed by cyclodehydration is the most common explored strategy (Scheme 1).[19] However, some of these protocols suffer from the limitations of harsh conditions, tedious synthetic procedures, time taking reactions and unsatisfactory yields. Hence, the development of milder and more general procedures to access N-fused 1,2,4-triazoles with high yields in short reaction time remains desirable.

The described oxidative cyclization has previously been reported for the preparation of triazoloquinoxalines.[20–26] Other methods reported in the literature for the



Scheme 1. General synthesis of N-fused 1,2,4-triazoles.

Table 1. Optimization of the reaction conditions.



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

Entry	Solvent	CrO3 (eq.)	Time	Yield (%)
1	Formic acid	0.5	1 h	71
2	AcOH	0.5	45 min	80
3	DMF	0.5	1.5 h	50
4	DMSO	0.5	1.5 h	60
5	HMPT	0.5	1 h	65
7	AcOH	1	30 min	90
8	AcOH	1.5	15 min	95
9	AcOH	2	10 min	81

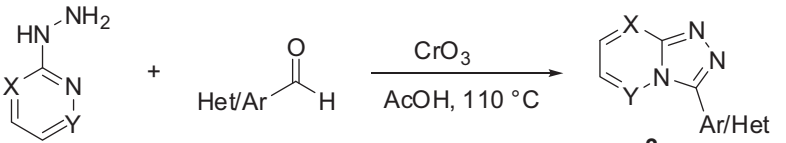
cyclization of the triazole ring usually require a combination of NBS and base,[27] refluxing orthoesters,[28,29] acids,[29,30] desulfurization of thiosemicarbazides,[31] or cyclization of hydrazides in polyphosphoric acid (PPA).[29] A couple of examples of oxidative cyclizations using chloramine-T have previously been reported.[32]

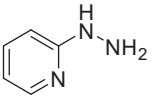
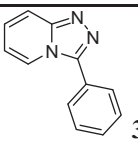
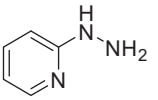
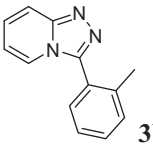
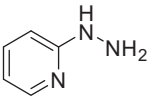
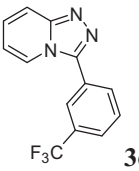
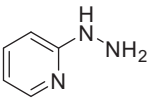
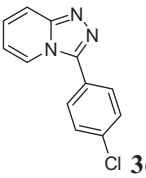
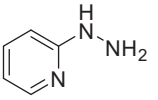
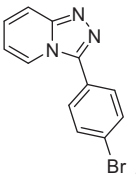
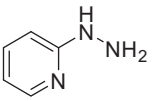
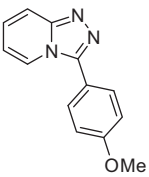
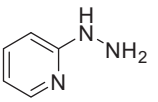
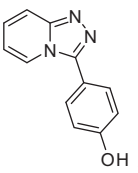
Chromium trioxide (CrO_3) is one of the most widely used of all oxidizing reagents in organic synthesis because of its commercial availability at low cost. Our continued interest in the development of useful synthetic methodologies prompted us to explore the feasibility of chromium trioxide (CrO_3) for the one-pot synthesis of N-fused 1,2,4-triazoles with high yields. However, it has not been investigated as a catalyst in the synthesis of 1,2,4-triazoles until now.

Result and discussion

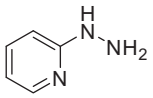
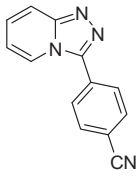
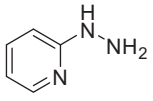
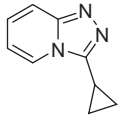
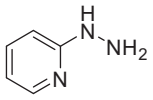
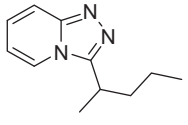
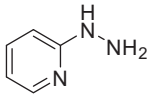
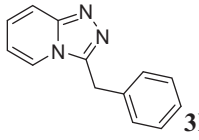
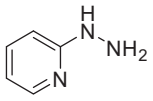
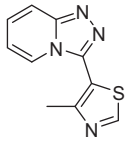
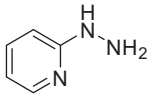
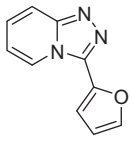
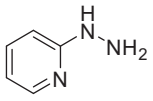
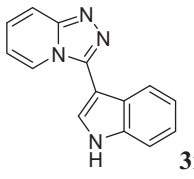
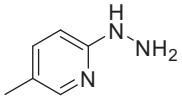
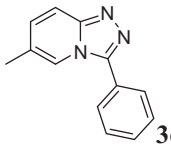
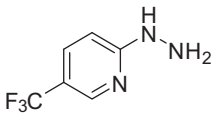
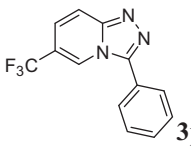
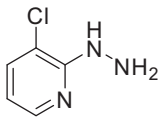
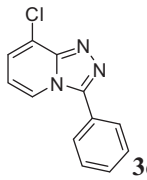
Our preliminary investigation began with the reaction of 2-hydrazinopyridine **(1a)** and benzaldehyde **(2a)** in the presence of CrO_3 (0.5 eq.) in formic acid at 110 °C temperature. We were delighted to observe the formation of the desired product **(3a)**, albeit in a low yield of 71% (Table 1, entry 1). Next, we optimized the reaction conditions in order to increase the yield. Thus, different solvents were screened and the results are summarized in Table 1. It was found that acetic acid was the most superior solvent in terms of the reaction time and yield of the product (Table 1, entry 2). Once, we had established a suitable solvent for the synthesis of N-fused 1,2,4-triazoles, we then focused on the quantity of CrO_3. An increase in the amount of CrO_3 (from 0.5 eq. to 1.5 eq.) not only decreased the reaction time from 1 h to 15 min, but also increased the product yield from 80% to 95% (Table 1, entry 8). Further increasing the quantity of CrO_3 (from 1.5 eq. to 2 eq.) led to a decrease in the yield to 81% (Table 1, entry 9). Therefore, we decided to perform the subsequent reactions of the heterocyclic hydrazines with different aldehydes in the presence of CrO_3 (1.5 eq.) in acetic acid at 110 °C. The effect of temperature on the reaction rate as well as on the yields of the products was also investigated. Faster reactions occurred on increasing the temperature but the

Table 2. Synthesis of various [1,2,4]triazolo[4,3-a]pyridines, [1,2,4]triazolo[4,3-a]pyrazines, and [1,2,4]triazolo[4,3-a]pyrimidines.

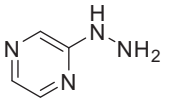
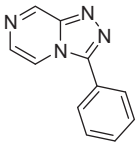
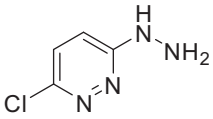
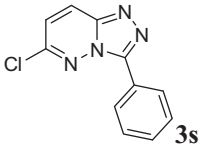
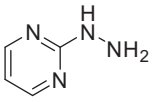
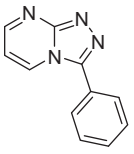


Entry	Het/Ar (2)	Hydrazine (1)	Product	Time (min)	Yield (%)
1	Ph **2a**		 **3a**	15	95
2	2-MeC$_6$H$_4$ **2b**		 **3b**	15	98
3	3-CF$_3$C$_6$H$_4$ **2c**		 **3c**	20	85
4	4-ClC$_6$H$_4$ **2d**		 **3d**	20	90
5	4-BrC$_6$H$_4$ **2e**		 **3e**	20	91
6	4-OMeC$_6$H$_4$ **2f**		 **3f**	15	98
7	4-OHC$_6$H$_4$ **2g**		 **3g**	15	90

(*continued*)

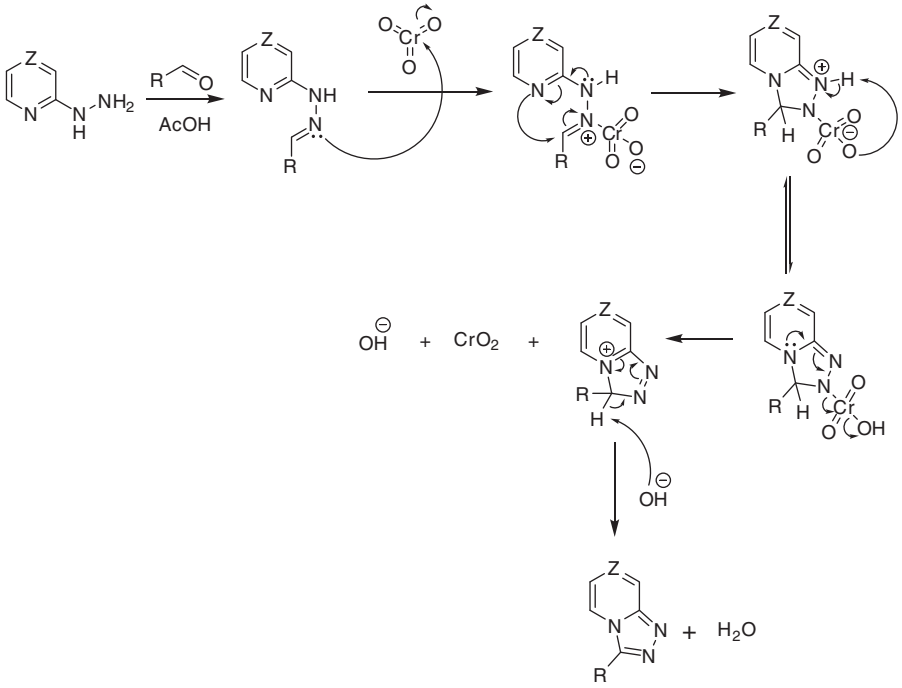
8	4-CNC_6H_4 **2h**		 **3h**	15	85
9	Cyclopropyl **2i**		 **3i**	15	88
10	Pentane-2-yl **2j**		 **3j**	15	86
11	$PhCH_2$ **2k**		 **3k**	20	85
12	4-Me thiazolyl **2l**		 **3l**	20	80
13	2-furyl **2m**		 **3m**	20	88
14	3-indolyl **2n**		 **3n**	25	82
15	Ph **2a**		 **3o**	20	83
16	Ph **2a**		 **3p**	25	78
17	Ph **2a**		 **3q**	25	85

(*continued*)

18	Ph **2a**		 **3r**	15	92
19	Ph **2a**		 **3s**	15	90
20	Ph **2a**		 **3t**	15	86

product yields were not satisfactory. The progress of the reactions was monitored by TLC analysis (using EtOAc–hexane as the eluent).

Mechanism:



With optimized conditions in hand, the scope of the reaction was investigated and the results are summarized in Table 2. As expected, all of the aldehydes employed gave the corresponding N-fused 1,2,4-triazoles in good to excellent yields. . Benzaldehydes with electron-donating groups such as *o*-tolualdehyde **(2b)** and *p*-anisaldehyde **(2f)** gave the desired products in very good yields (Table 2, entries 2 and 6). An aromatic aldehyde with an electronwithdrawing group, 3-trifluoromethyl benzaldehyde **(2c)**, 4-

chlorobenzaldehyde **(2d)** and 4-bromobenzaldehyde **(2e)** gave the corresponding triazole in 85% **(3c)**, 90% **(3d)**, and 91% **(3e)** yield (Table 2, entries 3, 4, and 5) respectively. The heteroaryl aldehyde, 5-formyl thiazole **(2l)**, 2-formylfuran **(2m)**, and 3-formyl indole **(2n)** reacted smoothly, affording the corresponding desired product **(3l)**, **(3m)**, and **(3n)** in good yield (Table 2, entries 9, 10, and 11), respectively. Pyrazine, pyridazine, and pyrimidine have also been successfully coupled with aldehydes affording the corresponding valuable cyclized products **(3r)**, **(3s)**, and **(3t)** in good yields. (For more information see supporting information files).

Conclusion

We have developed a short and efficient synthesis of N-fused 1,2,4-triazoles using a mild and straightforward one-pot oxidative cyclization method using chromium (VI) oxide which is a low cost commercially available reagent. A variety of substituents are tolerated allowing the synthesis of diverse products in good to excellent yields. The main advantage of this procedure is to access N-fused 1,2,4-triazoles with high yield and short reaction time. The newly developed synthetic route is believed to be valuable for the construction of building blocks but also for medicinal chemistry studies comprising N-fused 1,2,4-triazole moiety.

Experimental

General: All solvents and reagents were purchased from commercial sources and used without further purification. Melting points were determined on a Stuart SMP3 melting point apparatus without corrections. ^{1}H NMR and 13C NMR spectra were recorded on AV–500 Bruker using the solvents indicated with 500 MHz and 126 MHz, respectively. Elemental analyses were performed with a VarioEL analyzer. High-resolution mass spectra (HRMS) were performed on a Thermo Finnigan MAT95XP microspectrometer. Thin layer chromatography was performed on silica gel 60 F254 (Merck) TLC plates using hexane/EtOAc (6:4 v/v) as the mobile phase. Column chromatography was carried out using Merck silica gel (200–300 mesh) and hexane/EtOAc (6:4 v/v) as the eluent.

N-fused 1,2,4-triazole 3a-t; general procedure

A mixture of heterocyclic hydrazine **1** (1 mmol) and aldehyde **2** (1.2 mmol) in AcOH (10 mL) was stirred at ambient temperature for 5 min. Then to it was added chromium (VI) oxide (149.9 mg, 1.5 mmol) and refluxed in a pre-heated oil bath at 110 °C until the starting material was completely consumed (monitored by TLC, 10 min). The reaction mixture was quenched with sat. $NaHCO_3$ solution (30 ml) and extracted with EtOAc (50 ml). The organic layer was washed with water (40 ml), dried over Na_2SO_4 and evaporated. The resulting crude compound was purified by silica gel column chromatography (EtOAc/Hexane, 4:6 v/v), affording the pure N-fused 1,2,4-triazole **3**.

3 -Phenyl-[1,2,4]triazolo[4,3-a]pyridine (3a)[33]

Off-white solid; Yield: 84.9 mg (95%); Mp. 171–173 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (dt, $J = 7.0$, 1.2 Hz, 1H), 7.88–7.82 (m, 3H), 7.63–7.55 (m, 3H), 7.31 (ddd, $J = 9.3$, 6.5, 1.1 Hz, 1H), 6.89 (td, $J = 6.8$, 1.1 Hz, 1H); 13C NMR (126 MHz, $CDCl_3$): δ 150.3, 146.8, 130.3, 129.4, 128.3, 127.5, 126.5, 122.7, 116.6, 114.5; HRMS (EI, m/z) for $[M]^+$ calcd. 195.0796; Found: 195.0792; Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.80; H, 4.61; N, 21.48.

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