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IMPROVED METHOD FOR THE PREPARATION OF OXADIAZOLES FROM DIACYL HYDRAZINES

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***N*-methylimidazole (NMI) is used as the base in the triflic anhydride (Tf_2O)–mediated formation of oxadiazoles from diacyl hydrazines. This reagent is superior to pyridine-derived bases in terms of cost and reaction profile.**

Keywords: Cyclization; dehydration; oxadiazoles

The oxadiazole ring is a frequently occurring motif in medicinal chemistry, exemplified by zibotentan (**1**, an Astra-Zeneca agent in phase 3 development for the treatment of prostate cancer)[1] and raltegravir (**2**, an HIV integrase inhibitor discovered by Merck) (Fig. 1).[2]

2,5-Disubstituted oxadiazoles are typically prepared from diacyl hydrazines by a cyclodehydration reaction. Traditionally, this has been carried out using powerful reagents such as $POCl_3$ or $SOCl_2$; however, it is possible to use a variety of other reagents: inorganic[3] and organic[4] acids and strong dehydrating agents such as P_2O_5,[5] P_2S_5,[6] and PCl_5.[7] The functional group tolerance of most of these reagents is often low, which has lead to efforts to identify milder conditions for this cyclization. Triphenylphosphine has been used in combination with a selection of other reagents to accomplish this transformation: CX_4 (X=Cl, Br, I),[8] hexachloroethane,[9] iodine,[10] diethylazodicarboxylate (DEAD),[11] and trichloroacetonitrile.[12] However, such successes must be qualified by the generation of large quantities of triphenylphosphine oxide as a by-product, while attempts to circumvent this problem by using a polymer-supported reagent must be limited to small scales because of the high cost of immobilized phosphine. Similar considerations undermine the otherwise attractive use of TsCl and 5 equivalents of polymer-supported phosphazene base *t*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP).[13] The Burgess reagent has been reported as an alternative,[14] but it is also limited because of its high cost. Other reported reagents ($ZrCl_4$[15] and $Pd(PPh_3)_4$[16]) are disadvantaged by low substrate scope and very high

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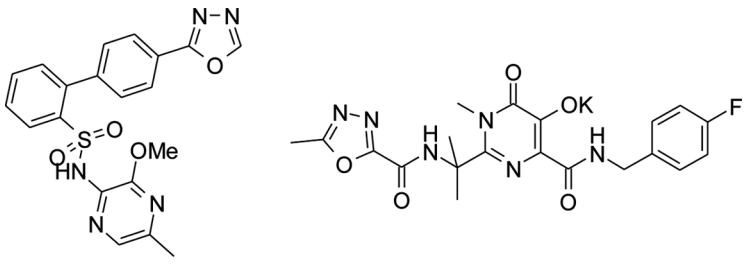
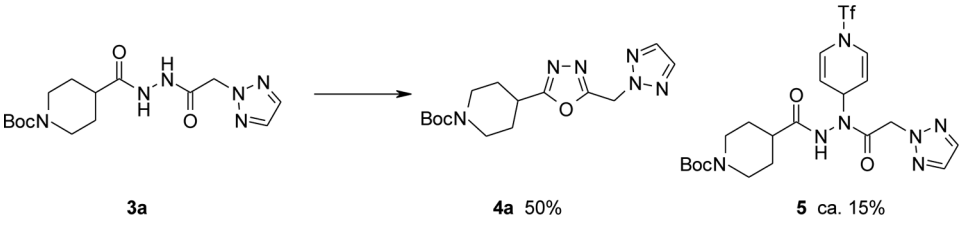


Figure 1. Drugs containing oxadiazole rings.

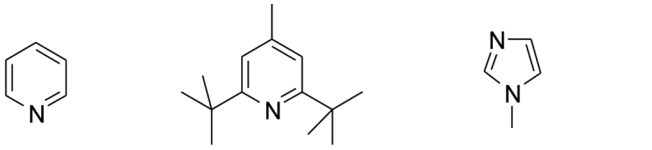
reaction temperatures, respectively. Hence, the search for mild, general conditions for this important cyclisation has continued. The use of hexamethyldisalazane (HMDS) and tetrabutyl ammonium fluoride (TBAF)[17] and an imidazolinium salt[18] has received scant further attention and were capricious in our hands. Perhaps the most promising approach to a general solution to the problem of preparing oxadiazoles of this nature is the combination of triflic anhydride (Tf_2O) and pyridine.[19] However, this reagent combination is not without its disadvantages. Most particularly, the highly electrophilic nature of the Tf_2O prompts attack by the pyridine base, which is then itself activated to nucleophilic attack at the 2- and 4-positions. Indeed, attempts in our laboratories to obtain oxadiazole **4a** from diacyl hydrazine **3a** led to only 50% isolated yield from a messy reaction mixture from which compound **5** could also readily be isolated (Scheme 1).

Such problems are commonplace with Tf_2O, which has caused many researchers to replace pyridine with alkyl-substituted derivatives, most commonly 2,6-di-*t*-butyl-4-methylpyridine. We were not attracted to this approach because of the high cost of this base and instead searched for a cheaper alternative. We postulated that N-methylimidazole (NMI) would provide similar nucleophilcity to pyridine but in an electron-rich ring, which would not be subject to mechanistic pathways leading to products analogous to **5**. We were gratified to find that this base was successful in the cyclodehydrative preparation of oxadiazoles, giving clean reaction profiles in every case. (Cheapest prices, derived from the 2009–2010 Aldrich catalogue, are shown in Scheme 2; from the same source the cheapest price of Tf_2O is £0.83 g^{-1}.)

The broad scope of these reaction conditions is demonstrated with the examples listed in Table 1. A range of functional and protecting groups survive

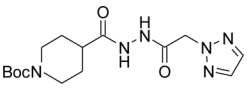
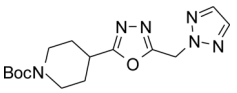
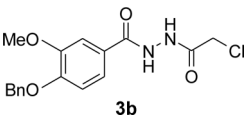
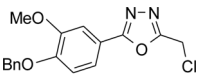
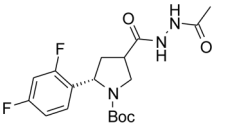
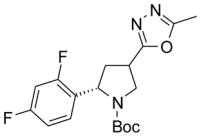
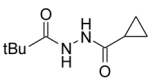
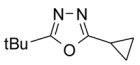
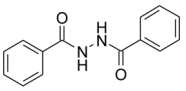
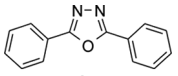
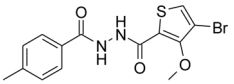
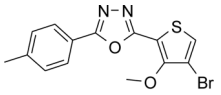
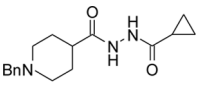
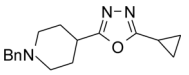


Scheme 1. Product and by-product from the reaction of **3a** with Tf_2O/pyridine.



Scheme 2. Price comparison of bases used in the Tf_2O cyclization of diacyl hydrazines.

Table 1. Substrate scope and yields

Starting material	Product	Time (h)	Yield[a]
 **3a**	 **4a**	3	68
 **3b**	 **4b**	1	72
 **3c**	 **4c**	3	61[b]
 **3d**	 **4d**	16	65
 **3e**	 **4e**	16	85
 **3f**	 **4f**	5	50
 **3g**	 **4g**	1.5	38

[a]Refers to isolated yield of pure material.

[b]Compound **3c** was a 1:1 mixture of (2S, 4 R)- and (2S, 4S)-diastereomers. Stereochemistry at C-2 was not affected by the reaction.

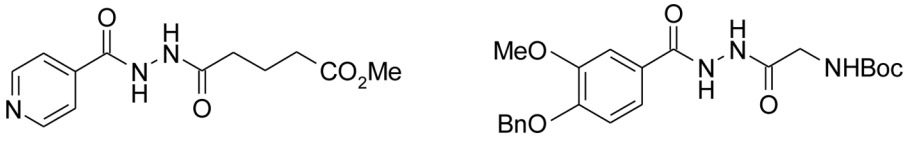


Figure 2. Diacyl hydrazines unreactive under our conditions.

the reaction unscathed. As well as the usual dialkyl (**3a, 3c, 3d**, and **3g**) and diaryl (**3e** and **3f**) examples, it is possible to accommodate aromatic (**3a** and **3f**) and aliphatic (**3c** and **3g**) heterocycles. Primary alkyl chlorides are stable to the reaction conditions (**3b**), as are nitrogen and oxygen atoms protected as the t-butyl carbamate (**3a** and **3c**) and benzyl ether (**3b**) respectively. We were particularly pleased to discover that diacyl hydrazine **3a**, which had been problematic with pyridine as base, reacted cleanly under these new conditions, giving an improved yield after only minor purification.

The reaction usually proceeds in a few hours at 0 °C or slightly below. It generally requires 1.5 equivalents of Tf_2O and 3 equivalents of NMI. Dichloromethane (DCM) was the solvent in all cases, though we have not yet attempted to change this for a more environmentally benign alternative. We have employed this protocol as successfully on scales of <100 mg and up to >100 g (compound **4a**).

This is not a general solution to the problem of finding mild conditions for oxadiazole formation, however. In addition to the poor yield obtained on cyclizing **3 g**, we were disappointed to find that diacyl hydrazines **3h** and **3i** proved unreactive under our conditions even when adding multiple equivalents of Tf_2O (Fig. 2).

REPRESENTATIVE EXPERIMENTAL PROCEDURE

Tf_2O (0.353 ml, 1.5 equivalents) was added to a solution of diacyl hydrazine **3b** (500 mg, 1.43 mmol) in DCM (5 ml) and NMI (0.365 ml, 3.2 equivalents) cooled in an ice-water bath, keeping the reaction temperature ≤ 0 °C. After 1 h, thin-layer chromatography suggested completion. The reaction mixture was washed with 2M HCl (10 ml) and then with saturated aqueous $NaHCO_3$ (10 ml). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The oily residue was triturated with Et_2O to give the oxadiazole **4b** (339 mg, 71%) as a cream-colored solid.

^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 3.98$ (s, 3H), 4.76 (s, 2H), 5.23 (s, 2H), 6.98 (d, $J = 8.2$ Hz, 1H), 7.33 (d, $J = 7.0$ Hz, 1H), 7.38 (t, $J = 7.4$ Hz, 2H), 7.45 (d, $J = 7.4$ Hz, 2H), 7.57 (dd, $J = 8.2$, 2 Hz, 1H), 7.60 (d, $J = 2$ Hz, 1H). LRMS (ESI) m/z 331/333 $[M + 1]^+$.

CONCLUSION

In conclusion, we have demonstrated an improved procedure for the preparation of oxadiazoles from diacyl hydrazines under mild conditions. This method is characterized by simple procedures, ease of isolation, good yields, and high tolerance of functional and protecting groups. We anticipate that the ability

of our protocol easily to install an oxadiazole ring in the center of a molecule will increase the popularity of this moiety in medicinal chemistry. Further research is necessary to identify a truly general set of conditions for this cyclization. It is also to be hoped the N-methylimidazole may serve as a cheap and effective alternative to 2,6-di-*t*-butyl-4-methylpyridine in other processes involving triflic anhydride, such as the preparation of triflates from lactams. Preliminary results from our laboratories suggest that this is indeed the case.

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