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Parallel synthesis of 1,2,4-oxadiazoles from carboxylic acids using an improved, uronium-based, activation

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Abstract—We describe the synthesis of 1,2,4-oxadiazoles from carboxylic acids and amidoximes using 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) as an activating agent of the carboxylic acid function for the *O*-acylation step. This method was used for the synthesis of a library of 24 1,2,4-oxadiazoles.

1. Introduction

1,2,4-Oxadiazoles have been described as good bioisosters of ester or amide in a variety of biological models. In the literature, 1,2,4-oxadiazoles are present in muscarinic agonists,[1] serotoninergic ($5\text{-}HT_3$) antagonists[2] and in dopamine (D_4) ligands.[3] Some compounds have also shown affinities for dopamine, serotonin and norepinephrine transporters.[4] The 1,2,4-oxadiazole ring system has also been used as an urea bioisoster in β_3 adrenergic receptor agonists.[5] Some articles have also reported the use of small heterocycles, among which 1,2,4-oxadiazoles, in the design of dipeptidomimetics.[6]

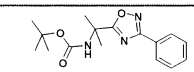
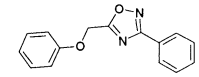
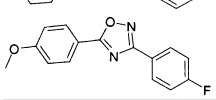
In general, synthesis of 1,2,4-oxadiazoles involves first the *O*-acylation step of an amidoxime by an activated carboxylic acid derivative, followed by cyclodehydration. Classically, the activated acid derivatives are esters,[2] acid chlorides,[5–7] symmetrical[6] or unsymmetrical[1] anhydrides and orthoesters.[8] A synthesis on solid support using esters has been also published.[9]

More recently, the use of carbodiimides like EDC,[3–10] DCC[10] and DIC[11] for the in situ activation of carboxylic acids has been reported. This method has even been used for solid-phase synthesis.[11] In the mean time, an original synthesis via palladium catalysis has been published.[12]

2. Results and discussion

We were interested in the synthesis of a library of 1,2,4-oxadiazoles from carboxylic acids and amidoximes from a single procedure, with good yields and purities. Though pyridine is classically used as a solvent, we used DMF which is more desirable for larger scale synthesis and as a solvent for a large variety of acids.[13]

Table 1.

		CDI Activation	TBTU Activation
Cpd #	Structure	Yield (%)	Yield (%)
1		21	62
2		67	92
3		51[(14)]	54

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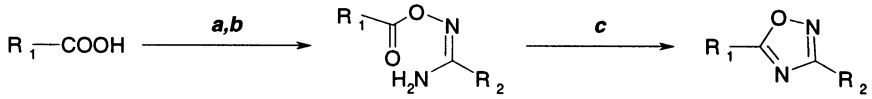


Scheme 1. (a) 1 equiv. TBTU, 0.2 equiv. HOBt, 5 equiv. DIPEA in DMF, 1 min, rt; (b) amidoxime, 1 h, rt; (c) DMF, 2 h, 110°C.[15]

Among the acids selected were some sterically hindered acids, for example 2-aminoisobutyric acid. It had been reported that DIC activation for this type of acid gave the expected 1,2,4-oxadiazoles in poor yields.[11] Moreover, carbodiimides are not of friendly use (allergenic) and are easily deactivated (unless HOBt is used) into *N*-acylureas. In an attempt to circumvent these problems, the use of *N*,*N*′-carbonyldiimidazole (CDI) for both the *O*-acylation step and the cyclodehydration steps has been recently reported.[14] The results obtained for three different acids, following this new protocol with CDI, are shown in Table 1. In our hands, the expected 1,2,4-oxadiazoles were obtained with poor to medium yields. Moreover, CDI has a variable shelf-life and is rapidly hydrolysed in DMF solution.

On the contrary, uronium salts are known to be easy to handle, to have quite fast coupling kinetics and to display hardly any losses of configuration during coupling. They are also known to enable efficient coupling of sterically hindered acids and to be soluble in DMF.

We thus developed the use of 2-(1*H*-benzotriazole-1 - yl) - 1,1,3,3 - tetramethyluronium tetrafluoroborate (TBTU) for the synthesis of 1,2,4-oxadiazoles (Scheme 1).

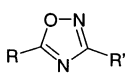
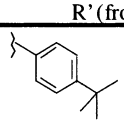
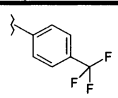
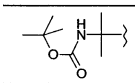
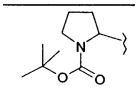
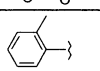
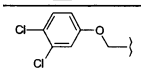
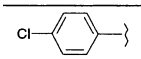
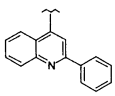
The *O*-acylation of amidoximes proceeds in DMF with 1 equivalent of TBTU, in the presence of 0.2 equiv. of HOBt to accelerate coupling and 5 equivalents of *N*,*N*′-diisopropylethylamine (DIPEA). HOBt can easily be removed from the mixture by a simple washing with water. To achieve cyclization, the reaction mixture is heated at 110°C for 2 h. This method gave moderate to excellent results for the three acids previously tested with CDI (Table 1).[16]

We thus used this versatile procedure for the parallel synthesis of a library of 24 1,2,4-oxadiazoles.[16] As in the preliminary results, very good yields and purities were obtained even for sterically hindered acids such as Aib or *o*-toluyl acid (Table 2). This method did succeed with a variety of different acids and amidoximes. In addition, it allows a very short activation step in comparison to the use of CDI. It thus prevents deactivation of the activated intermediate before the addition of the amidoxime.

3. Conclusions

A versatile method using uronium activation has been developed for the solution-phase synthesis of 1,2,4-oxa-

Table 2.

	R′ (from the amidoxime)							
								
R (from the acid)	Cpd #	Yield [a] (Purity [b])	Cpd #	Yield [a] (Purity [b])	Cpd #	Yield [a] (Purity [b])	Cpd #	Yield [a] (Purity [b])
	**1**	67 (97)	**4**	85 (90)	**5**	83 (91)	**6**	70 (90)
	**7**	71 (97)	**8**	66 (98)	**9**	69 (95)	**10**	79 (98)
	**11**	84 (96)	**12**	85 (93)	**13**	96 (92)	**14**	78 (93)
	**15**	75 (99)	**16**	69 (99)	**17**	78 (99)	**18**	74 (94)
	**19**	66 (96)	**20**	79 (97)	**21**	80 (98)	**22**	67 (99)
	**23**	86 (90)	**24**	87 (91)	**25**	79 (99)	**26**	77 (96)

[a] (%) Purified products.
[b] (%Area) Evaluated by HPLC.

diazoles. This method gives the title compounds with good yields and purities for all the acids tested. It can be applied to sterically hindered acids and to acids whose activated intermediate is not stable. This versatile protocol could easily be applied to the synthesis of 1,2,4-oxadiazoles in deep-well plates.

Acknowledgements

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15. Amidoximes are obtained from nitriles by reaction with $NH_2OH{\cdot}HCl$ in EtOH (reflux, 6 h) with 1 equiv. DIPEA.
16. All compounds were obtained as powders. Characterization via: NMR (Bruker DRX-300 MHz); LC/MS (Micromass Platform LCZ APCI and Diode Array LC Detection at 200–400 nM); melting points (Büchi B-450). (**1**): mp = 135–137°C; ^{1}H NMR (DMSO-d_6) δ 1.44 (s, 9H), 1.71 (s, 6H), 7.61–7.67 (m, 3H), 8.07–8.10 (m, 2H); MS = 304.4 (MH^+). (**2**): mp = 71–76°C; ^{1}H NMR (DMSO-d_6) δ 5.56 (s, 2H), 6.99 (t, 1H), 7.07 (d, 2H), 7.31 (t, 2H), 7.50–7.57 (m, 3H), 7.98–8.01 (m, 2H); MS = 253.3 (MH^+). (**3**): mp = 145–148°C; ^{1}H NMR (DMSO-d_6) δ 3.95 (s, 3H), 7.26 (d, 2H), 7.50 (t, 2H), 8.17–8.23 (m, 4H); MS = 271.3 (MH^+). (**4**): mp = 125–128°C; ^{1}H NMR (DMSO-d_6) δ 1.39 (br s, 9H), 1.70 (s, 6H), 7.65 (d, 2H), 8.00 (d, 2H); MS = 360.5 (MH^+). (**5**): mp = 97.0–101.9; ^{1}H NMR (DMSO-d_6) δ 1.44 (s, 9H), 1.71 (s, 6H), 7.61–7.67 (m, 3H), 8.07–8.10 (m, 2H); MS = 372.4 (MH^+). (**6**): mp = 122–125°C; ^{1}H NMR (DMSO-d_6) δ 1.44 (s, 9H), 1.71 (s, 6H), 7.69 (dd, 1H), 8.43 (d, 1H), 8.86 (d, 1H), 9.24 (s, 1H); MS = 305.4 (MH^+). (**7**): mp = 109–114°C; ^{1}H NMR (DMSO-d_6) δ 1.10 (s, 5.5H), 1.31 (s, 3.5H), 1.87–2.00 (m, 3H), 2.20–2.42 (m, 1H), 3.33–3.48 (m, 2H), 5.00–5.07 (m, 1H), 7.48–7.51 (m, 3H), 7.91–7.97 (m, 2H); MS = 316.4 (MH^+). (**8**): mp = 68–73°C; ^{1}H NMR (DMSO-d_6) δ 1.09 (s, 5.5H), 1.21 (s, 9H), 1.31 (s, 3.5H), 1.87–1.99 (m, 3H), 2.21–2.32 (m, 1H), 3.30–3.44 (m, 2H), 4.97–5.05 (m, 1H), 7.48 (d, 2H), 7.84 (d, 2H); MS = 372.5 (MH^+). (**9**): mp = 147–151°C; ^{1}H NMR (DMSO-d_6) δ 1.25 (s, 4.5H), 1.34 (s, 4.5H), 1.77–1.99 (m, 3H), 2.19–2.30 (m, 1H), 3.25–3.36 (m, 2H), 4.33–4.37 (m, 1H), 7.76 (d, 2H), 7.87 (d, 2H); MS = 384.4 (MH^+). (**10**): mp = 50–54°C; ^{1}H NMR (DMSO-d_6) δ 1.79 (s, 5H), 1.98 (s, 4H), 2.56–2.77 (m, 3H), 2.92–3.05 (m, 1H), 3.99–4.17 (m, 2H), 5.62–5.68 (m, 1H), 8.07 (dd, 1H), 8.89 (d, 1H), 9.29 (d, 1H), 9.76 (s, 1H); MS = 317.4 (MH^+). (**11**): mp = 49–50°C; ^{1}H NMR (DMSO-d_6) δ 2.60 (s, 3H), 7.34–7.51 (m, 7H), 7.99–8.01 (m, 2H); MS = 237.3 (MH^+). (**12**): mp = 41–44°C; ^{1}H NMR (DMSO-d_6) δ 1.21 (s, 9H), 2.60 (s, 3H), 7.27–7.38 (m, 2H), 7.47–7.54 (m, 3H), 7.91 (d, 2H), 7.99 (d, 2H); MS = 293.4 (MH^+). (**13**): mp = 100–104°C; ^{1}H NMR (DMSO-d_6) δ 2.48 (s, 3H), 7.20–7.32 (m, 3H), 7.39–7.50 (m, 1H), 7.76–7.82 (m, 2H), 7.93–7.98 (m, 2H); MS = 303.4 ($M-H^+$). (**14**): mp = 146–151°C; ^{1}H NMR (DMSO-d_6) δ 2.52 (s, 3H), 7.29–7.34 (m, 2H), 7.45–7.52 (m, 2H), 7.99 (dd, 1H), 8.12 (dt, 1H), 8.69 (d, 1H), 8.92 (s, 1H); MS = 238.4 (MH^+). (**15**): mp = 108–113°C; ^{1}H NMR (DMSO-d_6) δ 5.76 (s, 2H), 7.23 (dd, 1H), 7.56 (d, 1H), 7.63–7.71 (m, 4H), 8.11 (dd, 1H); MS = 320.2 ($M-H^+$). (**16**): mp = 130–134°C; ^{1}H NMR (DMSO-d_6) δ 1.39 (s, 9H), 5.75 (s, 2H), 7.23 (dd, 1H), 7.56 (d, 1H), 7.66 (d, 1H), 7.68 (d, 2H), 8.03 (d, 2H); MS = 376.3 ($M-H^+$). (**17**): mp = 139–141°C; ^{1}H NMR (DMSO-d_6) δ 5.75 (s, 2H), 7.23 (dd, 1H), 7.56 (d, 1H), 7.67 (d, 1H), 8.03 (d, 2H), 8.30 (d, 2H); MS = 388.2 ($M-H^+$). (**18**): mp = 120–126°C; ^{1}H NMR (DMSO-d_6) δ 5.75 (s, 2H), 7.23 (dd, 1H), 7.56 (d, 1H), 7.67 (d, 1H), 7.71 (dd, 1H), 8.45 (dt, 1H), 8.89 (d, 1H), 9.26 (s, 1H); MS = 323.2 (MH^+). (**19**): mp = 117–121°C; ^{1}H NMR (DMSO-d_6) δ 7.68 (m, 3H), 7.82 (d, 2H), 8.16–8.19 (m, 2H), 8.28 (d, 2H); MS = 255.7 ($M-H^+$). (**20**): mp = 96–99°C; ^{1}H NMR (DMSO-d_6) δ 1.40 (s, 9H), 7.68 (d, 2H), 7.79 (d, 2H), 8.08 (d, 2H), 8.25 (d, 2H); MS = 313.8 (MH^+). (**21**): mp = 121–125°C; ^{1}H NMR (DMSO-d_6) δ 7.81 (d, 2H), 8.04 (d, 2H), 8.27 (d, 2H), 8.35 (d, 2H); MS = 323.7 ($M-H^+$). (**22**): mp = 133–138°C; ^{1}H NMR (DMSO-d_6) δ 7.72 (dd, 1H), 7.82 (d, 2H), 8.28 (d, 2H), 8.50 (d, 1H), 8.90 (d, 1H), 9.32 (s, 1H); MS = 258.7 (MH^+).

(**23**): mp = 144–147°C; ^{1}H NMR (DMSO-d_6) δ 7.49–7.60 (m, 6H), 7.74 (t, 1H), 7.86 (t, 1H), 8.22–8.39 (m, 4H), 8.72 (s, 1H), 9.18 (d, 1H); MS = 350.4 (MH^+). (**24**): mp = 120–123°C; ^{1}H NMR (DMSO-d_6) δ 1.40 (s, 9H), 7.51–7.60 (m, 5H), 7.73 (ddd, 1H), 7.85 (ddd, 1H), 8.20 (d, 2H), 8.29 (dd, 2H), 8.69 (s, 1H), 9.18 (d, 1H); MS = 406.5 (MH^+). (**25**): mp = 155–157°C; ^{1}H NMR (DMSO-d_6) δ 7.54–7.62 (m, 3H), 7.79 (t, 1H), 7.88–7.95 (m, 3H), 8.21 (t, 1H), 8.33 (d, 2H), 8.41 (d, 2H), 8.75 (s, 1H), 9.08 (s, 1H); MS = 418.4 (MH^+). (**26**): mp = 163–167°C; ^{1}H NMR ($CDCl_3$) δ 7.50–7.59 (m, 4H), 7.77 (ddd, 1H), 7.86 (ddd, 1H), 8.25–8.31 (m, 3H), 8.54 (dt, 1H).