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New facile and mild synthesis of 2-substituted oxazolopyridines

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Abstract—A new, two-step synthesis of oxazolopyridines is described. The synthesis involving amide formation between *o*-aminopyridinols and aliphatic or aromatic carboxylic acids followed by condensation with hexachloroethane/triphenylphosphine takes place at room temperature and thereby gives mild access to all regioisomeric, 2-substituted oxazolopyridines in good yields.

Benzoxazoles[1] and their derivatives[2] are widely found in natural products. Moreover, they find application in drug discovery as melatonin receptor agonists,[3] COX inhibitors,[4] anticancer agents,[5] 5-HT_3 receptor antagonists[6] and HIV-1 reverse transcriptase inhibitors.[7] Interestingly, the oxazolopyridine moiety is far less common in the literature although it might offer some advantages from a medicinal chemistry point of view. The pyridine fragment may provide better water solubility by offering an additional site for protonation and salt formation or it might enhance intermolecular interactions with a target protein by formation of an additional hydrogen bond. Interested in these potential benefits, we focused on the synthesis of 2-substituted oxazolopyridines during the course of one of our research programmes. A robust, generally applicable synthesis was required in order to access all of the pyridyl regioisomers.

The few routes to oxazolopyridines described in the literature are very similar to the numerous benzoxazole syntheses that have been reported.[8] Typically an *o*-aminopyridinol is condensed with a carboxylic acid or derivative thereof in the presence of a large excess of polyphosphoric acid at high temperatures.[9] Acid labile groups are not tolerated during the usual aqueous work up. Use of acid catalysis and lower reaction temperatures have been reported,[10,11] as has a base promoted cyclisation of an *o*-halogeno amido pyridine at very high temperature.[12] The reaction of *o*-aminopyridinols with aldehydes under oxidative conditions is also described.[13] Aside from the limitations of functional group tolerance with some of these routes, access to all of the possible oxazolopyridyl regioisomers has not been demonstrated with these methods.

In order to find a milder ring-closing method, we turned to known oxazole syntheses. The cyclodehydration of α-acyl-aminoketones, the Robinson–Gabriel synthesis,[14] offers good synthetic access towards substituted oxazoles.[15] Various extensions and modifications of this protocol have been described.[16] Most noteworthy in this regard is the work of Wipf who demonstrated that α-acylaminoaldehydes can be readily cyclodehydrated using a mixture of triphenylphosphine and iodine,[17] although this reagent system is known to have limited applicability.[18] With this in mind, we envisioned a two-step approach with initial amide formation followed by cyclodehydration using the milder combination of triphenylphosphine and hexachloroethane.[19]

The synthesis of the required *o*-aminopyridinols not commercially available was achieved following known literature procedures. 3-Aminopyridin-4-ol (**1a**) was obtained in excellent yield by catalytic hydrogenation of 3-nitropyridin-4-ol.[11] 4-Aminopyridin-3-ol (**1b**) was prepared by the method of Chu-Moyer and Berger starting from 4-aminopyridine.[20]

The amide formation was performed by *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU)-mediated coupling (Scheme 1) of a variety of carboxylic acids and the four regioisomeric *o*-aminopyridinols (**1a**–**d**).[21] With yields of 52–85% the reaction

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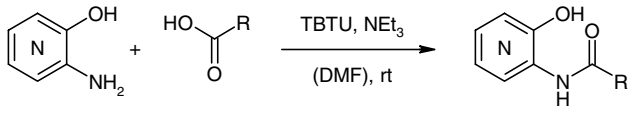


1a-d **2-8** **10a-g, 11-13**

Scheme 1. TBTU-mediated amide formation between *o*-amino-pyridinols **1a–d** and carboxylic acids derivatives **2–8**.

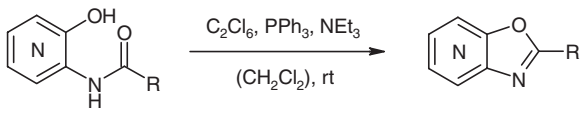
proceeded quite satisfactorily (Table 1), the only exception being entry 10 where no product could be isolated. An alternative synthesis of **13** employing isobutyryl chloride (9) proceeded in 75% yield (entry 11).

The key cyclisation step was achieved at room temperature in dichloromethane using the triphenylphoshine–hexachloroethane combination, with the triphenylphosphonium halide being formed prior to addition of the amide[22] (Scheme 2). Even under such mild conditions, all regioisomeric oxazolopyridines were obtained in moderate to high yields after purification (Table 2).

Table 1. Amide-formation between *o*-aminopyridinols **1a–d** and carboxylic acid derivatives **2–9**

Entry	*o*-Aminopyridinol	Carboxylic acid derivative	Product	Yield (%)
1[a]	**1a**	**2**	**10a**	70
2[a]	**1a**	**3**	**10b**	72
3[a]	**1a**	**4**	**10c**	72
4[a]	**1a**	**5**	**10d**	80
5[a]	**1a**	**6**	**10e**	67
6[a]	**1a**	**7**	**10f**	52
7[a]	**1a**	**8**	**10g**	58
8[a]	**1b**	**3**	**11**	64
9[a]	**1c**	**3**	**12**	85
10[a]	**1d**	**3**	**13**	0
11[b]	**1d**	**9**	**13**	75

[a] 1.2 equiv TBTU, 2.8 equiv NEt_3, in DMF at rt after 16 h using 1 equiv of carboxylic acid.
[b] 1 equiv NEt_3, in CH_2Cl_2 at rt after 16 h using 1 equiv of isobutyryl chloride.



10a-g, 11-13 **14a-g, 15-17**

Scheme 2. Oxazolopyridine synthesis by cyclodehydration of amides **10a–g**, **11–13**.

Table 2. Oxazolopyridine synthesis by cyclodehydration of amides **10a–g**, **11–13** with $PPh_3/C_2Cl_6/NEt_3$

Entry	Substrate	Product	Yield (%)
1	**10a**	**14a**	83[a]
2	**10b**	**14b**	91[a]
3	**10c**	**14c**	78[a]
4	**10d**	**14d**	93[a]
5	**10e**	**14e**	84[a] (95)[b]
6	**10f**	**14f**	73[a]
7	**10g**	**14g**	50[a] (71)[b]
8	**11**	**15**	41[a] (77)[b]
9	**12**	**16**	88[a]
10	**13**	**17**	41[a] (74)[b]

[a] Isolated yield, 2.5 equiv C_2Cl_6, 3 equiv PPh_3, 8 equiv NEt_3 in CH_2Cl_2 at rt after 1 h.

[b] Isolated yield, 2 equiv C_2Cl_6, 2 equiv polymer-bound PPh_3, 2.9 equiv piperidinomethylpolystyrene HL resin in CH_2Cl_2 at rt after 16 h.

Although not all amides **10a–g** and **11–13** were readily soluble in dichloromethane, the reactions were quite fast and ran to completion in only 1 h as monitored by TLC and HPLC–MS.

The reaction conditions tolerate a wide variety of substituents in the 2-position. For instance, 2-aryl oxazolopyridines are equally well accessed via this route (entry 5) as aliphatic derivatives (entries 1–4 and 8–10). Even a sterically bulky R group (entry 3) does not dramatically decrease the yield of desired product. Furthermore, it is noteworthy that the reaction conditions allow for the presence of acid labile protecting groups such as the Boc-group (entries 6 and 7) thereby circumventing problems with existing methods summarised herein.

In several examples, the moderate isolated yields of the oxazolopyridine originate from the difficult removal of triphenylphosphonium oxide (entries 7, 8 and 10). To facilitate purification of the products we used polymer-bound triphenylphosphine and piperidinomethyl-polystyrene HL resin. The reactions took place in good to excellent yields with a much easier work up (entries 5, 7, 8 and 10, brackets). The crude products obtained by concentration of the reaction mixtures after 16 h were purified by simple filtration through a short pad of silica.

In summary, we have developed a novel, very mild synthesis of 2-substituted oxazolopyridines, giving easy access to all pyridyl regioisomers. The synthesis from readily available carboxylic acids and *o*-aminopyridinols seems to be generally applicable and tolerant of a variety of functional groups, and is, to the best of our knowledge, the first time the triphenylphosphine–hexachloroethane reagent system has been used for the synthesis of oxazoloarenes. Moreover, the method described herein provides access to substituted oxazolopyridines not previously accessible via traditional procedures. The application of this method to the synthesis of benzoxazoles and other azabenzoxazoles such as oxazolopyrimidines is ongoing in our laboratories.

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21. Typical procedure: Add successively TBTU (770 mg, 2.4 mmol) and NEt_3 (566 mg, 786 μL, 5.6 mmol) to a solution of 3-amino-pyridin-3-ol (**1a**) (220 mg, 2.0 mmol) and pentanoic acid (**2**) (204 mg, 2.0 mmol) in 5 mL dry DMF and stir at room temperature for 16 h. Concentration of the reaction mixture in vacuo to remove most DMF and purification of the obtained residue by flash chromatography on silica gel (eluting with CH_2Cl_2→10% MeOH in CH_2Cl_2) yielded 270 mg (1.39 mmol, 70%) pentanoic acid (4-hydroxy-pyridin-3-yl)-amide (**10a**) as a white solid; ^{1}H NMR: (300 MHz, DMSO-d_6): δ (ppm) = 0.91 (t, ^3J = 7.3 Hz, 3H), 1.33 (m, 2H), 1.57 (m, 2H), 2.45 (t, ^3J = 7.4 Hz, 2H), 6.26 (d, ^3J = 7.1 Hz, 1H), 7.66 (dd, ^3J = 7.1 Hz, ^4J = 1.4 Hz, 1H), 8.72 (d, ^4J = 1.4 Hz, 1H), 8.97 (br s, 1H), 11.46 (br s, 1H); ^{13}C NMR: (75 MHz, DMSO-d_6): δ (ppm) = 13.9, 21.9, 27.5, 35.8, 112.9, 124.3, 129.1, 135.5, 170.1, 171.8.
22. Typical procedure: Add triphenylphosphine (1.09 g, 4.16 mmol) and NEt_3 (842 mg, 1.17 mL, 8.32 mmol) to a solution of hexachloroethane (820 mg, 3.46 mmol) in 10 mL CH_2Cl_2 and stir the resulting mixture at room temperature for 5 min. Add solid amide **10a** and stir at ambient temperature for 1 h. Add 50 mL CH_2Cl_2 and wash successively with 5 mL saturated NH_4Cl solution, 5 mL satd $NaHCO_3$ solution and 10 mL brine. Drying over Na_2SO_4, filtration and concentration of the organic phase gives a brown oil. Purification of the obtained residue by flash chromatography on silica gel (eluting with hexanes→80% *tert*-butylmethyl ether in hexanes) provided 203 mg (1.15 mmol, 83%) 2-butyl-oxazolo[4,5-*c*]pyridine (**11a**) as a white solid; mp: 42–43 °C; ^{1}H NMR: (300 MHz, $CDCl_3$): δ (ppm) = 0.96 (t, ^3J = 7.3 Hz, 3H), 1.45 (m, 2H), 1.87 (m, 2H), 2.95 (t, ^3J = 7.6 Hz, 2H), 7.43 (dd, ^3J = 5.5 Hz, ^4J = 1.0 Hz, 1H), 8.51 (d, ^3J = 5.5 Hz, 1H), 8.98 (br s, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ (ppm) = 13.6, 22.2, 28.2, 28.6, 106.2, 139.1, 142.3, 145.0, 155.9, 168.2; MS (EI, 70 eV): *m*/*z* (%) = 176 (7), 161 (3), 147 (27), 134 (100); ESI-HRMS: *m*/*z* calcd for ($C_{10}H_{12}N_2O$+H^+) = 177.1022, *m*/*z* found = 177.1023.