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Solid-phase synthesis of imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyrimidines☆

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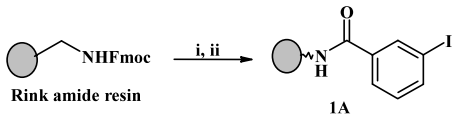
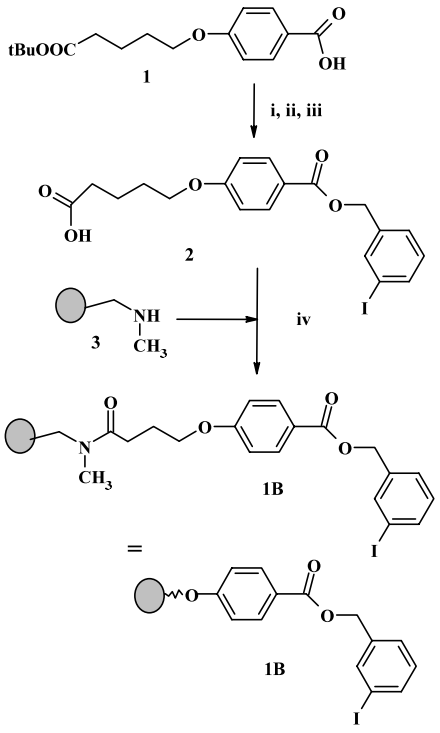
Abstract—The synthesis of imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine derivatives by condensation between an α-bromoketone bound to solid support and various 2-aminopyridine or 2-aminopyrimidine derivatives was described. Either an acid labile linker or a base labile linker was used in this study.

The possibility of synthesizing heterocyclic systems[1,2] and therefore pharmaceutically useful compounds utilizing solid-phase chemistry is by now well established. As far as we know, only two kinds of syntheses have been described in the literature allowing to obtain the imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine on solid support. The first one involved a multi-component reaction (MCR) with 2-aminopyridine or 2-aminopyrimidine, aldehyde and isonitrile.[3] The other used benzenesulfinate as a traceless linker.[4] Imidazopyridines have shown interesting pharmacological activity, such as antiviral,[5] antiulcer,[6] antibacterial,[7] antifungal,[8] herbicidal,[9] has been explored and more recently 2-arylimidazo[1,2-*a*] pyridines were described[10] as ligands for detecting β Amyloid (Aβ) plaques in the brain, which production is a pivotal event in the pathology of



Scheme 1. Synthesis of aromatic iodide bound to acid labile linker. *Reagents and conditions*: (i) piperidine/DMA (1/4) 30 min (×2); (ii) 3-iodobenzoic acid (4.4 equiv.), TBTU (4.4 equiv.), HOBt (2 equiv.), Et_3N (10 equiv.) DMAP (1 equiv.), 1,4-dioxane, 48 h.



Scheme 2. Synthesis of aromatic iodide bound to base labile linker. *Reagents and conditions*: (i) $Me_2C{=}C(NMe_2)Cl$ (1.1 equiv.), CH_2Cl_2, rt, 3 h; (ii) 3-iodobenzylalcohol (1 equiv.), DMAP (0.2 equiv.), Et_3N (11.5 equiv.), CH_2Cl_2, rt, 16 h, 90%; (iii) TFA/CH_2Cl_2 (1/3) 20 h, 98%; (iv) TBTU (4.4 equiv.), HOBt (2 equiv.), Et_3N (10 equiv.), DMAP (1 equiv.), 1,4-dioxane, 48 h.

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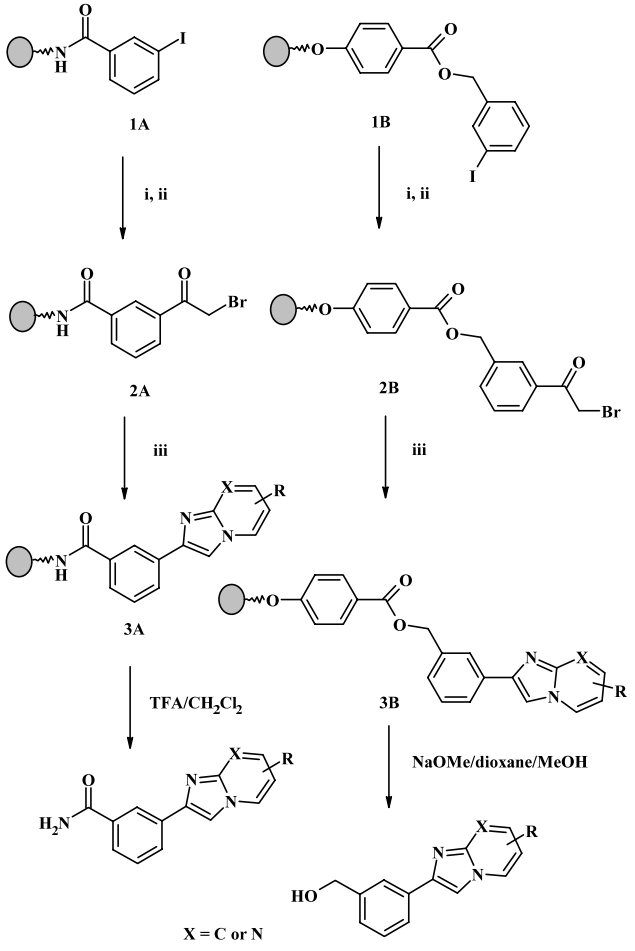
Alzheimer's disease. It was interesting to investigate this kind of chemistry on solid phase. Lately, we described[11] a new method from an α-bromoketone bound to solid support used for thiazole and aminothiazole analogs synthesis. In our continuing investigation to exploit the synthetic utility of this synthon, we report here a new imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyrimidines solid support synthesis.

The α-bromoketone was generated from an aromatic iodide bound to polystyrene to react with various 2-aminopyridines or 2-aminopyrimidines. This method is not limited by cleavage conditions because of compatibility with both acid and base labile linker. Aromatic iodide bound to polystyrene was readily obtained with both linker strategies as outlined in Scheme 1.

The aromatic iodide bound to acid labile Rink resin **1A** (Scheme 1) was prepared by standard peptidic coupling with 3-iodobenzoic acid. The linker **2** (Scheme 2) was synthesized from **1** by treatment with 1-chloro-*N*,*N*-dimethyl-2-methyl propenamine in dichloromethane followed by addition of 3-iodobenzyl alcohol in the presence of 4-dimethyl aminopyridine and triethylamine.

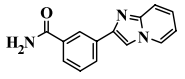
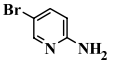
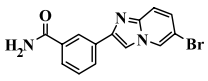
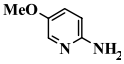
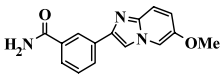
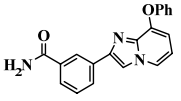
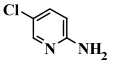
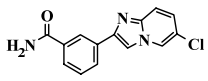
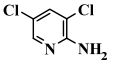
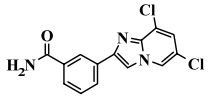
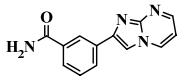
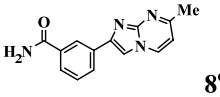


Scheme 3. Synthesis of imidazo[1,2-*a*]pyridines or imidazo[1,2-*a*]pyrimidines bound to solid support. *Reagents and conditions*: (i) tributyl(1-ethoxyvinyl)tin (2 equiv.), Ph_3As (0.4 equiv.), $Pd_2(dba)_3$ (2 equiv.), 1,4-dioxane, 50°C, 24 h (×2); (ii) NBS (2.5 equiv.) in THF/H_2O (4/1), 1 h; (iii) 2-aminopyridine (6 equiv.) or 2-aminopyrimidine derivatives, DMF, rt, 72 h or EtOH, 50°C, 48 h.

Subsequent deprotection of tertiobutyl ester by trifluoroacetic acid in dichloromethane gave expected compound **2** which can be bound to a commercially available *N*-methyl aminomethylated polystyrene **3**[12] to generate **1B**. The α-bromoketone resin **2A** and **2B** were synthesized starting from resin **1A** and **1B** (Scheme 3) by palladium mediated coupling, followed by treatment with *N*-bromosuccinimide according to already published method.[11]

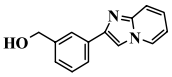
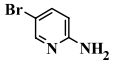
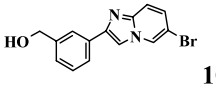
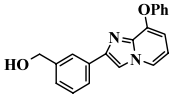
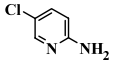
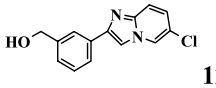
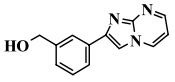
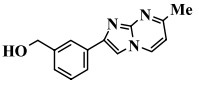
Imidazo[1,2-*a*]pyridines or imidazo[1,2-*a*]pyrimidines bound to solid support **3A** and **3B** were obtained by treatment of resin **2A** and **2B** with various 2-aminopyridines and 2-aminopyrimidines in *N*,*N*-dimethylformamide or ethanol at 50°C. Cleavage of the resin **3A** by trifluoroacetic acid and resin **3B** by transesterification with NaOMe in a mixture of methanol and 1,4-dioxane gave imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]-pyrimidines derivatives.

Table 1. Imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]-pyrimidines synthesized on acid labile linker

Reagents	Products	Solvent /time (h)	Yields [a,b] %
	 **1**	DMF/72 DMF/ (72+72)	79 80 (57)
	 **2**	EtOH/48	76 (62)
	 **3**	EtOH/48	77 (55)
	 **4**	DMF/72	80 (61)
	 **5**	DMF/72	79 (52)
	 **6**	DMF/72	50
	 **7**	EtOH/48	71 (51)
	 **8**[c]	DMF/72	80 (48)

[a] conversions are calculated from ^1H NMR of crude product after cleavage. [b] in brackets are the yields of isolated product after purification. [c] the structure of compound **8** is determined by NMR (NOESY experiment).

Table 2. Imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]-pyrimidines synthesized on base labile linker

Reagents	Products	Solvent /time (h)	Yields [a,b] %
	 **9**	DMF/72	100 (80)
	 **10**	EtOH/48	98 (73)
	 **11**	DMF/72	100 (83)
	 **12**	DMF/72	97 (62)
	 **13**	EtOH/48	100 (66)
	 **14**[c]	DMF/72	91 (54)

[a] conversions are calculated from ^{1}H NMR of crude product after cleavage. [b] in brackets are the yields of isolated product after purification. [c] the structure of compound **14** is determined by NMR (NOESY experiment).

It should be noted, that all reactions reported here were performed on a scale (typically 200–250 mg beads; 0.7 mmol/g or 0.87 mmol/g) allowing the isolation of at least 20 mg of crude product. In some cases, yields of products purified by flash chromatography were reported in parentheses. The structure of all compounds was established by ^{1}H, ^{13}C NMR and mass spectroscopy.

Six different imidazo[1,2-*a*]pyridines and two imidazo[1,2-*a*]pyrimidines were synthesized by this route on Rink amide resin (Table 1). Unfortunately, use of this solid support does not allow to obtain a total conversion (50–80% after six steps) even with a double coupling (twice 8 equivalents and 72 h).

Furthermore, four examples of imidazo[1,2-*a*]pyridines and two imidazo[1,2-*a*]pyrimidines were synthesized on the base labile resin (Table 2). In this case, both conversions and purities were excellent after six steps.

Although the reaction times are long in agreement with experiments performed in solution,[6] use of base labile linker is an efficient way to generate this class of compounds.

Supplementary material

Spectroscopic characterization (^{1}H, ^{13}C NMR and MS) for compounds **1**, **3**, **7**, **8**, **9**, **10**, **12**, **13** is available on-line.

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