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Synthesis of New *N*-Substituted Imidazo [1,2-a] Pyridine -2-Acetamides

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ABSTRACT:

In this paper, we present a new synthesis of *N*-substituted imidazo[1,2-*a*]pyridine-2-acetamides in high yields. The reaction conditions were investigated and optimized conditions were successfully applied to synthesis a wide variety of ethyl imidazo[1,2-*a*]pyridin-2-yl-acetate and *N*-substituted imidazo[1,2-*a*]pyridine-2-acetamide derivatives.

Keywords: *imidazo[1,2-a]pyridin-2-yl-acetates, imidazo[1,2-a]pyridines, N-substituted imidazo[1,2-a]pyridine-2-acetamides.*

Imidazo[1,2-*a*]pyridines are a class of heterocyclic compounds of both chemical[i] and pharmaceutical interests[ii]. Various studies have shown that certain compounds derived from imidazo[1,2-*a*]pyridines possess numerous and varied biological activities[2]. In addition, imidazo[1,2-*a*]pyridine derivatives are essential constituents of commercially available drugs such as Zolpidem, Alpidem and Saripidem[iii] (Figure 1).

Since 1988, Zolpidem has been available from Sanofi-Aventis under the specialty designation STILNOX®. The interest in the discovery of Zolpidem[3] lies in the development of a hypnotic agent with advantages over benzodiazepines[iv]. In contrast, Alpidem or ANANXYL® and Saripidem (figure 1) are anxiolytic drugs on the market with good affinities for benzodiazepine receptors BZ1 and BZ3[v] but not widely used.

On the other hand, Martini's team[vi] reported that 2-arylpyrazolo[1,5-a]pyrimidin-3-yl-acetamides, compounds **II** (Figure 1), had good affinity as ligands for the peripheral benzodiazepine receptor (PBR).

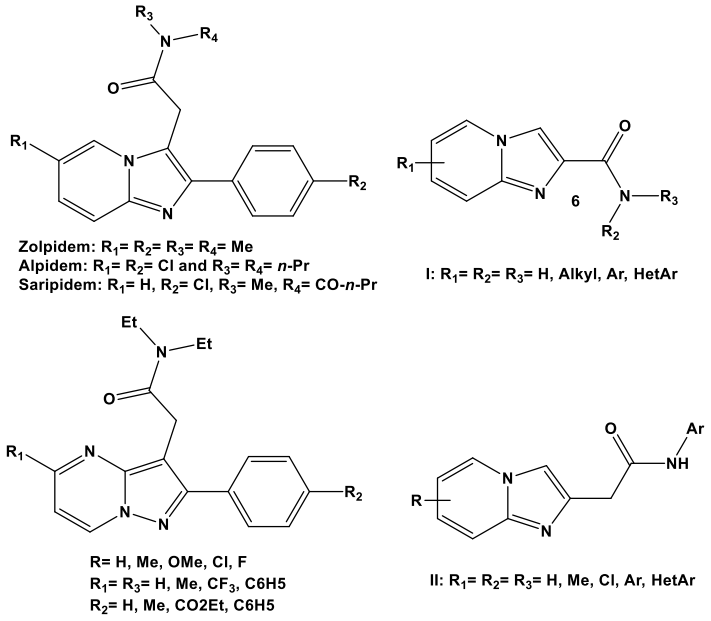
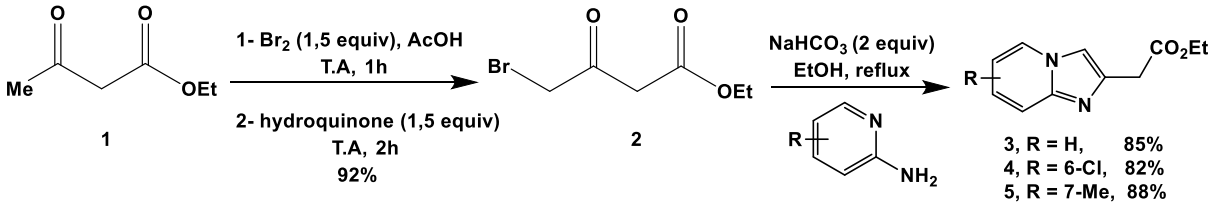


Figure 1: Representative bioactive targets derived from imidazo[1,2-*a*]pyridines and pyrazolo[1,5-*a*]pyrimidines

Other groups have proved the utility of various imidazo[1,2-a]pyridine-2-carboxamide **I** compounds in the treatment or prevention of diseases involving the Nurr-1 nuclear receptor[vii]. These molecules have been shown to be good antituberculosis agents with low cytotoxicity[viii] (Figure 1).

Interestingly, all these compounds show a strong analogy with *N*-substituted imidazo[1,2-*a*]pyridin-2-yl-acetamides **II** (Figure 1). For this reason, we have been interested in the synthesis of analogs of these molecules in order to generate various imidazo[1,2-*a*]pyridine compounds with an acetamide group in position 2. The method reported herein opens up a modular access to *N*-substituted imidazo[1,2-*a*]pyridin-2-yl-acetamides **II**.

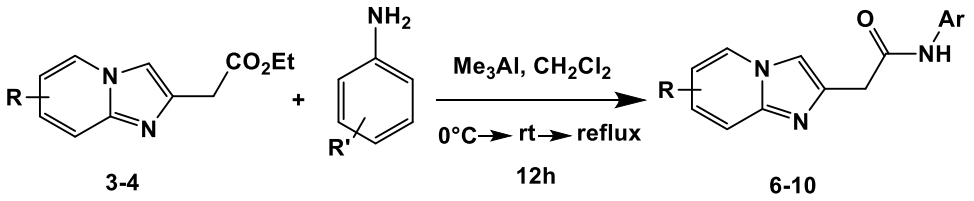
Initially, we synthesized ethyl 4-bromoacetoacetate **2** (Scheme 1), a brominated intermediate obtained by brominating ethyl acetoacetate **1** with bromine in acetic acid at room temperature for one hour, followed by the addition of 1,4-hydroquinone in the same pot for two hours at room temperature[ix] (Scheme 1). This sequence leads selectively to the desired α-bromoketone compound **2** in 92% yield (Scheme 1). Having the *a*-bromoketone **2** in hand, we next examined cyclization with 2-aminopyridines. The reaction was carried out in the presence of $NaHCO_3$ (2 equiv) in EtOH at reflux. The ethyl imidazo[1,2-*a*]pyridin-2-yl-acetate derivatives **3-5** were isolated in excellent yields (Scheme 1).

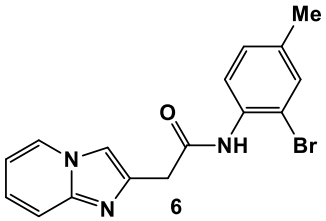
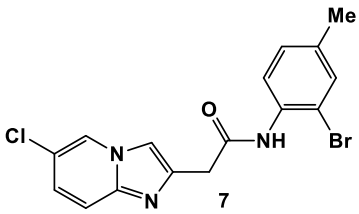
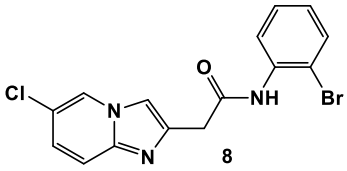


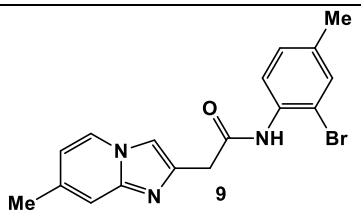
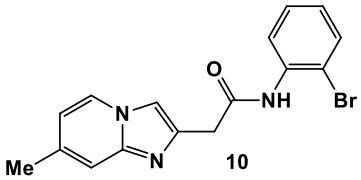
Scheme 1. *Synthesis of ethyl imidazo[1,2-a]pyridin-2-yl-acetates*

The synthesis of *N*-substituted imidazo[1,2-a]pyridin-2-yl-acetamides **II** was carried out by treatment of ethyl imidazo[1,2-*a*]pyridin-2-yl-acetate derivatives **3**, **4**, and **5**, with various aniline derivatives in the presence of trimethylaluminium (Me_3Al) under reflux in dichloromethane[x] to afford the original amide **6–10** in good yields (entries 1–5, Table 1).

Table 1: *Synthesis of N-substituted-imidazo[1,2-a]pyridin-2-yl-acetamides*



Entry	Ethyl imidazo[1,2-a]pyridin-2-yl-acetate	*N*-Imidazo[1,2-a]pyridin-2-yl-acetamides	Yield
1	**3**	 **6**	88%
2	**4**	 **7**	87%
3	**4**	 **8**	85%

4	**5**	 **9**	91%
5	**5**	 **10**	83%

In conclusion, we have developed an effective synthetic route for our further efforts to advance synthetically accessible *N*-substituted-imidazo[1,2-a]pyridine-2-yl-acetamides. Other studies are in progress to apply this method to the design of powerful bioactive molecules.

Experimental section

All reagents were purchased from Sigma–Aldrich, Acros Organics, and Alfa Aesar and used without further purification. Melting points were determined with a Buchi SMP20 melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR were recorded on a Bruker Avance DPX 250 spectrometer (250.19 MHz ^{1}H, 62.89 MHz ^{13}C) and DPX-400 spectrometer (400 MHz 1 H, 100.6 MHz 13C) using TMS as the internal standard, multiplicities were determined by the DEPT 135 sequence. All commercial solvents were used without further purification. Column chromatography was carried out using Silica gel 60N (spherical, neutral, 40–63 mm, Merck). TLC was carried out on Merck silica gel 60F254 percolated plates and visualized with UV light.

N-substituted imidazo[1,2-a]pyridin-2-yl-acetamide (6); General procedure

Under N_2 atmosphere at –5–0 °C, Me_3Al (2 M soln in toluene, 2 equiv) was added to a soln of 2-bromoaniline (1.5 equiv) in anhyd CH_2Cl_2 (20 ml) was added dropwise at –5°C, and the mixture was stirred for 30 min at this temperature. The mixture was then slowly warmed to 0°C over 30 min, and a soln of **3** (1 g, 1 equiv) in anhyd CH_2Cl_2 (10 ml) was added dropwise. The mixture was stirred for 4–6 h at reflux, and then carefully quenched with 1 N aq HCl (10 ml) at 0°C. The mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc– PE) to give the desired product **6** to **10**.

***N*-(2-Bromo-4-methylphenyl)-imidazo[1,2-*a*]pyridin-2-yl-acetamide 6.** RMN ^{1}H ($CDCl_3$, 400 MHz): δ 2.25 (s, 3H), 3.92 (s, 2H), 6.81 (m, 1H), 7.07 (dd, *J* = 1, 5.2 Hz, 1H), 7.21 (m, 1H), 7.31 (s, 1H), 7.52 (s, 1H), 7.59 (d, *J* = 5.5 Hz, 1H), 8.1 (m, 1H), 8.21 (d, *J* = 5.2 Hz, 1H), 9.74 (s, 1H, NH). RMN ^{13}C ($CDCl_3$, 100.6 MHz): δ 20.6, 37.8, 110.9, 112.8, 113.5, 117,3, 122.2, 125.4, 125.9, 128.8, 132.8, 134.0, 135.1, 140.4, 145.7, 168.0. SM (IS): *m/z* = 345 [M + 1].

***N*-(2-Bromo-4-methylphenyl)-6-chloroimidazo[1,2-*a*]pyridin-2-yl-acetamide 7.** RMN ^{1}H ($CDCl_3$, 400 MHz): δ 2.25 (s, 3H), 3.91 (s, 2H), 7.06 (dd, *J* = 0.6, 5.2 Hz, 1H), 7.16 (dd, *J* = 1.2, 6.0 Hz, 1H), 7.29 (m, 1H), 7.52 (m, 2H), 8.13 (d, *J* = 0.7 Hz, 1H), 8.19 (d, *J* = 5.2 Hz, 1H), 9.60 (s, 1H, NH). RMN ^{13}C ($CDCl_3$, 100.6 MHz): δ 20.5, 37.6, 111.3, 113.4, 117,4, 120.8, 122.1, 123.6, 126.6, 128.7, 132.7, 133.7, 135.1, 141.3, 143.8, 167.5. SM (IS): *m/z* = 379 [M + 1].

***N*-(2-Bromophenyl)-6-chloroimidazo[1,2-*a*]pyridin-2-yl-acetamide 8.** RMN ^{1}H ($CDCl_3$, 400 MHz): δ 3.93 (s, 2H), 6.93 (m, 1H), 7.19 (dd, *J* = 1.2, 5.7 Hz, 1H), 7.25-7.31 (m, 1H), 7.48-7.56 (m, 3H), 8.16 (d, *J* = 0.7 Hz, 1H), 8.36 (dd, *J* = 0.7, 5.0 Hz, 1H), 9.70 (s, 1H, NH). RMN ^{13}C ($CDCl_3$, 100.6 MHz): δ 37.8, 111.3, 113.5, 117,6, 121.0, 122.2, 123.7, 125.2, 126.8, 128.2, 132.5, 136.4, 141.4, 144.0, 167.7. SM (IS): *m/z* = 365 [M + 1].

***N*-(2-Bromo-4-methylphenyl)-7-methylimidazo[1,2-*a*]pyridin-2-yl-acetamide 9.** RMN ^{1}H ($CDCl_3$, 400 MHz): δ 2.21 (s, 3H), 2.35 (s, 3H), 3.90 (s, 2H), 6.56 (m, 1H), 7.02 (m, 1H), 7.28 (m, 2H), 7.38 (s, 1H), 7.91 (m, 1H), 8.21 (m, 1H), 9.89 (s, 1H, NH). RMN ^{13}C ($CDCl_3$, 100.6 MHz): δ 21.30, 21.18, 37.4, 109.9, 113.3, 115.0, 115.2, 121.9, 124.8, 128.4, 132.5, 133.8, 134.7, 136.0, 139.6, 145.8, 167.9. SM (IS): *m/z* = 359 [M + 1].

***N*-(2-Bromophenyl)-7-methylimidazo[1,2-*a*]pyridin-2-yl-acetamide 10.** RMN ^{1}H ($CDCl_3$, 400 MHz): δ 2.28 (s, 3H), 3.90 (s, 2H), 6.47 (d, *J* = 4.2Hz, 1H), 6.83 (t, *J* = 4.7 Hz, 1H), 7.19(t, *J* = 5 Hz, 1H), 7.35 (s, 1H), 7.41 (d, *J* = 5 Hz, 1H), 7.86 (d, *J* = 4.2 Hz, 1H), 8.37 (d, *J* = 5.3 Hz, 1H), 10.08 (s, 1H, NH). RMN ^{13}C ($CDCl_3$, 100.6 MHz): δ 21.0, 37.3, 109.9, 113.4, 114.8, 114.9, 122.0, 124.7, 124.8, 127.7, 132.2, 136.0, 136.3, 139.2, 145.6, 168.0. SM (IS): *m/z* = 345 [M + 1].

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