THE REGIOSELECTIVE ACYLATION REACTIONS OF IMIDAZOPYRIDINES[1]

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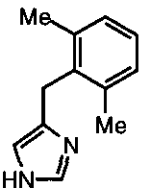
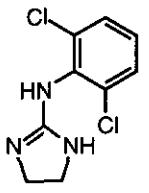
Abstract - The regioselectivity of acylation in imidazopyridines can be controlled by two mechanism-specific reactions. As expected acylation reactions under Friedel-Crafts conditions result in reaction at the most electron-rich site in imidazopyridines. However, depending on the structure of the imidazopyridine, ylid intermediates are proposed to direct reaction to the electron-deficient site in the parent heterocycles. These observations led to the selective synthesis of acylimidazopyridines and this methodology was used in the preparation of analogs of the α_2-adrenergic agonists MPV-207 and clonidine.

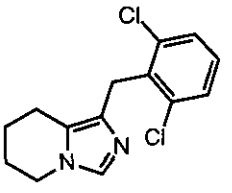
The α_2-adrenergic agonist MPV-207[3] (**1**) possesses antihypertensive properties by activating central α_2-receptors presumably at the same binding site as the α_2-agonist clonidine (**2**).[4] Clonidine stimulates α_2-adrenergic receptors in the central nervous system which results in a hypotensive and bradycardic response in humans. Clonidine is used clinically for the treatment of hypertension. MPV-207 was an unusual departure in structure from the typical α_2-adrenergic agonists such as clonidine since the imidazole portion of the molecule is a weak base. We sought to discover novel α_2-agonists with improved pharmacological properties by preparing analogs with modifications to the imidazole portion of MPV-207. During the course of developing the needed synthetic methods, we discovered that seemingly related reaction conditions afforded exclusive acylation at the 1- or 3-ring position of imidazo[1,5-*a*]pyridine.[5] In our preliminary report, imidazo[1,5-*a*]pyridine was shown to exhibit similar reactivity as imidazole to afford acylation at the 3-position through a formal 1,2-acyl transfer via a postulated nitrogen ylid intermediate.[5] This paper describes a more complete study of these regioselective acylation reactions and the use of this chemistry to prepare an analog (**3**) of MPV-207 and clonidine.



MPV-207 (**1**)



clonidine (**2**)



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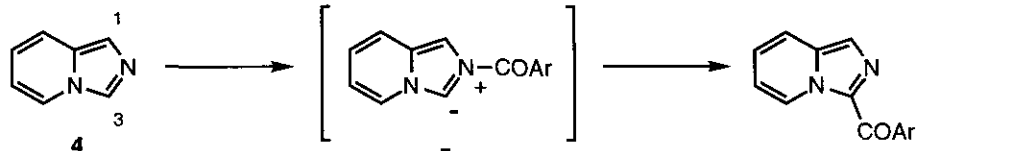
Imidazo[1,5-*a*]pyridine[6] (**4**) is known to undergo electrophilic substitution reactions at the 1-position, however, when the 1-position is substituted, then reaction can occur at the 3-position.[7] Thus, Friedel-Crafts acylation of imidazo[1,5-*a*]pyridine (**4**) with acetyl chloride/aluminum chloride affords 1-acetylimidazo[1,5-*a*]pyridine, and acylation of 1-methylimidazo[1,5-*a*]pyridine under the same conditions gave 1-methyl-3-acetylimidazo[1,5-*a*]pyridine.[6]

RESULTS AND DISCUSSION

Selective substitution reactions of **4** at the 3-position were not previously described until our preliminary report.[5] We demonstrated that acylation of **4** with benzoyl chloride under thermal conditions or in the presence of base led to acylation exclusively at the 3-position to give **6a**, presumably through the ylid (**5**) (Scheme 1). Analogous ylid species derived from imidazoles have been proposed as intermediates in the acylation reactions of imidazole.[8] These imidazole ylids may also be viewed as carbenes, since in these systems the carbene and ylid are isoelectronic. The probability that the ylid/carbene species were intermediates in these reactions was strengthened by the recent structural elucidation by X-Ray crystallography of the first stable and crystalline imidazol-2-ylidene carbene.[9] In contrast to the results obtained under thermal or triethylamine-mediated conditions, the Friedel-Crafts acylation reaction occurs exclusively at the 1-position of **4** to give **7a** (Scheme 2). Also, when either **6a** or **7a** were subjected to reaction conditions under which the other regioisomer was formed, no interconversion occurred. This fact and the fact that the acylation reactions were completely regioselective suggest that entirely different reaction pathways and intermediates led to either **6a** or **7a**.

Scheme 1. Acylation at the C3-Position *via* the Proposed Ylid Intermediate (5).

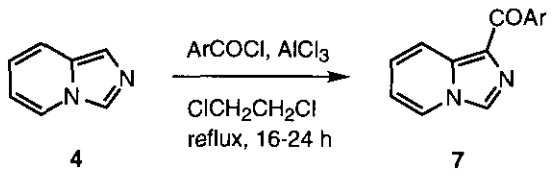


6a Ar = phenyl
6b Ar = 2,4,6-trimethylphenyl

Method	Conditions	Isolated Yield (%)
Thermal Acylation:	PhCOCl, xylenes, reflux, 20 h	**6a**, 62
	2,4,6-$(Me)_3$-PhCOCl, xylenes, reflux, 21 h	**6b**, not detected
Triethylamine-Mediated Acylation:	PhCOCl, Et_3N, MeCN, rt, 12 h	**6a**, 87
	2,4,6-$(Me)_3$-PhCOCl, Et_3N, MeCN, rt, 20 h	**6b**, not detected

We attempted to extend these acylation reactions using *ortho*-substituted benzoyl chlorides to prepare compounds that would be close analogs of MPV-207 and clonidine. The Friedel-Crafts acylation reaction with 2,4,6-trimethylbenzoyl chloride and 2,6-dichlorobenzoyl chloride gave the desired compounds (**7b**) and (**7c**) in 70% and 92% yield, respectively. However, acylation with 2,4,6-trimethylbenzoyl chloride under the thermal or triethylamine-mediated acylation conditions even under forcing conditions (reflux/21 h) did not afford the desired product (**6b**), only recovered starting material was obtained. The initial acylimidazolium species was formed since a precipitate forms on addition of the acid chloride to **4** and the ylid (**5b**) may form as well when triethylamine is added. However, we propose that due to steric hindrance of the 2,4,6-trimethylbenzoyl group the acylation of the ylid does not occur and starting material (**4**) is recovered after aqueous work up by hydrolysis of **5b**. The use of **7c** in the preparation of analogs of MV-207 and clonidine is described later in this paper.

Scheme 2. Friedel-Crafts Acylation at the C1-Position of Imidazo[1,5-*a*]pyridine.

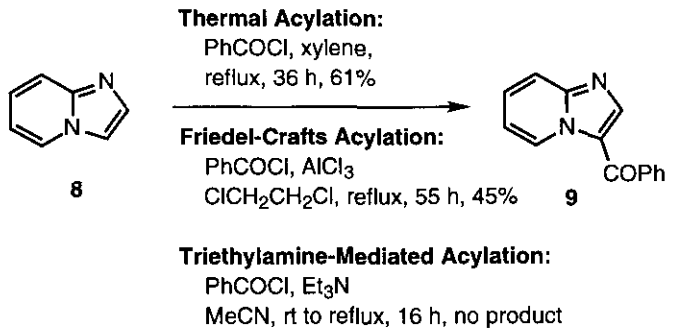


4 **7**

Compd	Ar =	Isolated Yield (%)
7a	phenyl	76
7b	2,4,6-trimethylphenyl	70
7c	2,6-dichlorophenyl	92

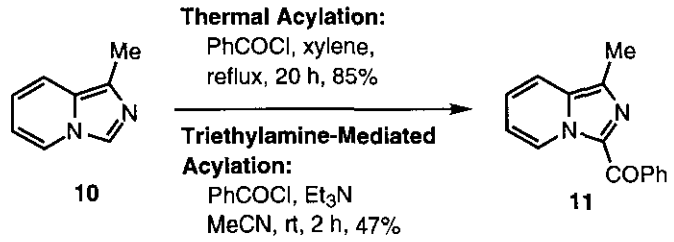
We then examined the isomeric heterocycle imidazo[1,2-*a*]pyridine (**8**) to determine if the analogous chemistry would work in this example (Scheme 3). In contrast to the reactivity of **4**, both the thermal acylation and Friedel-Crafts acylation conditions with **8** gave reaction at the 3-position to give **9** in 61% and 45% yields, respectively. The reaction of **8** under the triethylamine-mediated acylation conditions under forcing conditions (room temperature up to 16 h at reflux) gave no **9**. In this example, acylation of **8** occurs at the most nucleophilic/electron-rich site, the 3-position, through a direct acylation mechanism presumably involving a σ-complex. Due to structural differences **8** is unable to form a stabilized ylid analogous to **5**. In the case of **5**, the formal anion at the 3-position is stabilized by the electron withdrawing 2-acyl group, but also is stabilized by the two adjacent electron-deficient nitrogen atoms. Apparently in the 1-acylimidazolium species formed from **8** the proton at the 2-position is not acidic enough for anion formation, since a formal anion at the 2-position is stabilized by the 1-acyl group and only one adjacent nitrogen atom.

Scheme 3. Acylation of Imidazo[1,2-*a*]pyridine (8).



When the 1-position of **4** is substituted, as *in* 1-methylimidazo[1,5-*a*]pyridine[6] (**10**), acylation under both thermal conditions and triethylamine-mediated conditions afforded the 3-acyl derivative (**11**), in 85% and 47% yields, respectively. Friedel-Crafts acylation of **10** is known to also afford the 3-acyl derivative.[6]

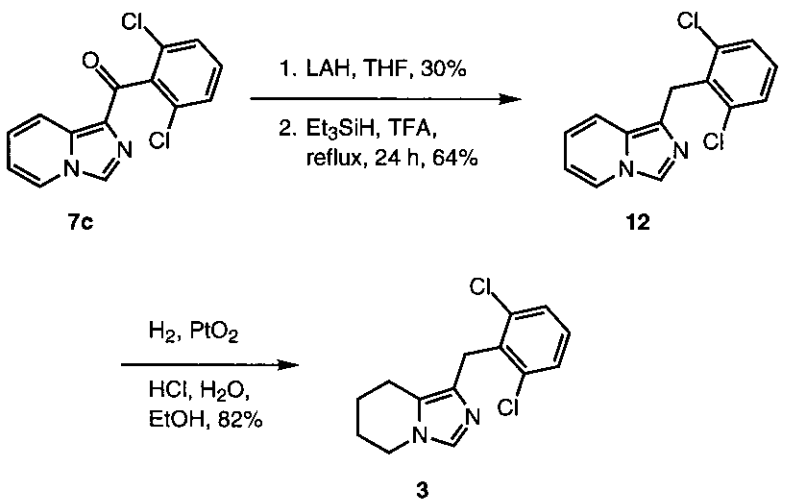
Scheme 4. Acylation of 1-Methylimidazo[1,5-*a*]pyridine (10).



The acylation methodology was applied to the synthesis of an analog of MPV-207 and clonidine. Treatment of 2,6-dichlorobenzoylimidazo[1,5-*a*]pyridine (**7c**) with lithium aluminum hydride gave the intermediate alcohol which was further reduced to the methylene derivative (**12**) with triethylsilane/trifluoroacetic acid. The desired analog for biological testing was obtained by hydrogenation of **12** over platinum oxide to give the tetrahydroimidazo[1,5-*a*]pyridine (**3**). In an α_2-adrenergic receptor binding assay, both derivatives (**12**) and (**3**) were tested for the ability to displace tritiated clonidine from its receptors in homogenized rat cerebral cortex.[10] At 1 μM the analog (**12**) was inactive, however, the analog (**3**) inhibited tritiated clonidine binding at 50%. These derivatives were significantly less potent than clonidine and were of no further interest as leads for analog synthesis.

In summary, we have shown that the regioselectivity of acylation in imidazo[1,5-*a*]pyridines can be controlled based on mechanism-specific reaction conditions. The details of these acylation reactions are described and their use in the related heterocycles imidazo[1,2-*a*]pyridine (**8**) and 1-methylimidazo[1,5-*a*]pyridine (**10**) show that structural requirements dictate the ability to form ylid intermediates (e.g. **5**) or a σ-complex leading to the selective formation of acylimidazopyridines.

Scheme 5. Synthesis of Target Analogs (12) and (3).



EXPERIMENTAL

Method A. Thermal Acylation. Imidazo[1,5-*a*]pyridin-3-ylphenylmethanone (6a). A mixture of imidazo[1,5-*a*]pyridine[6] (10.0 g, 85 mmol) and benzoyl chloride (10.3 g, 89 mmol) in 300 mL of xylenes was refluxed for 20 h. After cooling, the mixture was diluted with ethyl acetate and washed successively with 1N HCl, water, 5% NaOH, water, and then brine. The organic extract was dried over $MgSO_4$, filtered, and concentrated to give 19.1 g of a brown oil. Preparative HPLC of the crude product on silica gel eluted with 15% ethyl acetate in hexanes gave 11.8 g (62%) of **6a** as yellow crystals: mp 75-77 °C (cyclohexane); IR (KBr) ; ^{1}H NMR (DMSO-d_6) δ 7.24 (t, J = 6.8 Hz) and 7.38 (t, J = 6.8 Hz) (2H), 7.63 (m, 3H), 7.88 (s) and 7.98 (d, J = 8.9 Hz) (2H), 8.38 (d, J = 7.4 Hz, 2H), 9.74 (d, J = 7.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 180.9, 137.8, 134.4, 134.1, 131.8, 130.3, 127.8, 126.1, 125.0, 123.9, 118.2, 116.8; MS 223 (MH^+). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.79; H, 4.63; N, 12.61.

Method B. Triethylamine-Mediated Acylation. Imidazo[1,5-*a*]pyridin-3-ylphenylmethanone (6a). To a solution of imidazo[1,5-*a*]pyridine (1.181 g, 10 mmol) and triethylamine (2.9 mL, 21 mmol) in 40 mL of acetonitrile at 0 °C and under nitrogen was added dropwise benzoyl chloride (2.5 mL, 22 mmol). The reaction mixture was stirred at rt for 12 h, concentrated, diluted with water and extracted with ethyl acetate (2X). The organic extracts were washed with water, 5% aqueous 3-(dimethylamino)propylamine, water, 1N HCl, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 2.20 g of a brown oil. Flash chromatography on silica gel eluted with 10% ethyl acetate in hexanes gave 1.94 g (87%) of **6a** as yellow crystals: mp 70-77 °C.

Method C. Friedel-Crafts Acylation. Imidazo[1,5-*a*]pyridin-1-ylphenylmethanone (7a). To aluminum chloride (2.67 g, 20 mmol) in 20 mL of 1,2-dichloroethane at rt was added dropwise benzoyl chloride (2.3 mL, 20 mmol). After stirring for 20 min, the reaction was cooled in an ice bath and

imidazo[1,5-*a*]pyridine (1.188 g, 10 mmol) in 10 mL of 1,2-dichloroethane was added dropwise. The dark green mixture was refluxed for 22 h, cooled to rt, poured onto ice-water, basified with 35% NaOH, and immediately extracted with methylene chloride (2X). The organic extracts were washed with water, 5% aqueous 3-(dimethylamino)propylamine, water, 1N HCl, and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 2.61 g of a greenish oil. Crystallization from ethyl acetate-hexanes gave 1.684 g (76%) of **7a** as yellow crystals: mp 92.5-94.5 °C ; ^{1}H NMR (DMSO-d_6) δ 7.07 (t, J = 6.7 Hz, 1H), 7.42 (dd, J = 6.9 Hz, 8.8 Hz, 1H), 7.60 (m, 3H), 8.40 (d, J = 6.8 Hz, 3H), 8.62 (s, 1H), 8.67 (d, J = 6.9 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 185.9, 138.6, 135.0, 131.4, 130.0, 129.3, 128.7, 127.7, 127.0, 124.8, 119.2, 114.9; MS 223 (MH^+). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.66; H, 4.62; N, 12.59.

Method C. Friedel-Crafts Acylation. Imidazo[1,5-*a*]pyridin-1-yl-2,4,6-trimethylphenylmethanone (7b). Method C gave 11.6 g (70%) of **7b** as a yellow solid: mp 144.5-147 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 6H), 2.25 (s, 3H), 6.73 (m, 3H), 7.14 (m, 1H), 8.00 (m, 3H). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.40; H, 6.20; N, 10.49.

2,6-Dichlorophenylimidazo[1,5-*a*]pyridin-1-ylmethanone (7c). Method C gave 40 g (92%) of **7c** as a light yellow crystals: mp 253-254 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 6.83 (m, 1H), 7.23 (m, 4H), 8.01 (m, 2H), 8.38 (m, 1H). Anal. Calcd for $C_{14}H_8N_2OCl_2$: C, 57.76; H, 2.77; N, 9.62. Found: C, 57.80; H, 2.89; N, 9.63.

Method A. Imidazo[1,2-*a*]pyridin-3-ylphenylmethanone (9). The reaction of imidazo[1,2-*a*]pyridine (1.183 g, 10 mmol) and benzoyl chloride (1.74 mL, 15 mmol) in 40 mL of xylenes following Method A gave a yellow oil. Flash chromatography on silica gel eluted with 60% ethyl acetate in hexanes gave 1.35 g (61%) of **9** as a white solid: mp 101-104 °C ($EtOH/H_2O$); ^{1}H NMR ($CDCl_3$) δ 7.16 (t, J = 6.8 Hz, 1H), 7.56 (m, 4H), 7.82 (d, J = 8.9 Hz, 1H), 7.90 (d, J = 7.3 Hz, 2H), 8.22 (s, 1H), 9.76 (d, J = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 184.8, 148.1, 145.7, 139.2, 132.0, 129.3, 128.9, 128.8, 128.5, 123.5, 117.7, 115.1; MS 223 (MH^+). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.55; H, 4.67; N, 12.28.

Method C. Imidazo[1,2-*a*]pyridin-3-ylphenylmethanone (9). Method C gave 2.56 g of crude product that was purified by flash chromatography on silica gel eluted with 70% ethyl acetate in hexanes to give 1.00 g (45%) of **9** as a yellowish solid: mp 96-100 °C.

Method A. Thermal Acylation. 1-Methylimidazo[1,5-*a*]pyridin-3-ylphenylmethanone (11). Method A after refluxing the reaction for 20 h, work up, and flash chromatography on silica gel eluted with 15% ethyl acetate in hexanes gave 2.00 g (85%) of **11** as yellow crystals: mp 68-71 °C; ^{1}H NMR (DMSO-d_6) δ 2.56 (s, 3H), 7.22 (t, J = 7.0 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.57 (m, 3H), 7.95 (d, J = 8.9 Hz, 1H), 8.32 (d, J = 6.6 Hz, 2H), 9.71 (d, J = 7.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 180.1, 138.1, 132.4, 132.3, 131.8, 131.6, 130.2, 127.8, 126.0, 124.1, 117.8, 117.0, 12.57; MS 237 (MH^+). Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.08; H, 5.02; N, 11.99.

Method B. Triethylamine-Mediated Acylation. 1-Methylimidazo[1,5-*a*]pyridin-3-yl-phenylmethanone (11). Method B after stirring the reaction at rt for 2 h, work up, and flash chromatography on silica gel eluted with 15% ethyl acetate in hexanes gave 1.12 g (47%) of **11** as yellow crystals: mp 68-70 °C.

1-(2,6-Dichlorophenylmethyl)imidazo[1,5-*a*]pyridine (12). To 200 mL of THF at 0 °C under nitrogen was added lithium aluminum hydride (6.1 g, 70 mmol), then a solution of **7c** (36 g, 120 mmol) in 300 mL of THF was added dropwise. The reaction mixture was stirred at 0 °C for 20 min, and then at rt for 16 h. After cooling in an ice bath, the reaction was quenched by the successive dropwise addition of 6.1 mL water, 6.1 mL 1N NaOH, and then 18.5 mL water. The mixture was stirred for 15 min, filtered through $MgSO_4$ and concentrated to give 20.4 g of crude product. The residue was passed through a column of florisil with 50% ethyl acetate in hexanes to give 10.4 g (30%) of the intermediate alcohol as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 4.10 (m, 1H), 6.48 (m, 1H), 7.22 (m, 5H), 7.75 (m, 1H), 7.96 (s, 1H).

To a stirred solution of the alcohol (10.4 g, 36 mmol) in 45 mL of trifluoroacetic acid was added triethylsilane (13.5 mL, 85 mmol) and the reaction mixture was refluxed for 24 h. On cooling, the reaction was poured onto ice-35% NaOH and extracted with ether (3X). The combined extracts were extracted with 6N HCl, and the acid layer was made basic with 35% NaOH, and then extracted with ethyl acetate (3X). The organic extracts were dried over $MgSO_4$, filtered, and concentrated to give 7.8 g of a yellow solid. Trituration with hexanes gave 6.4 g (64%) of **12** as a pale yellow solid: mp 157-161 °C; ^{1}H NMR ($CDCl_3$) δ 4.50 (s, 2H), 6.38 (m, 2H), 7.15 (cm, 4H), 7.69 (m, 1H), 7.90 (s, 1H). Anal. Calcd for $C_{14}H_{10}N_2Cl_2$: C, 60.67; H, 3.64; N, 10.11. Found: C, 60.44, H, 3.75; N, 9.81.

1-(2,6-Dichlorophenylmethyl)-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine hydrochloride (3). A mixture of **12** (6.0 g, 22 mmol), platinum oxide (100 mg), and 20 mL of conc. HCl in 250 mL of ethanol was hydrogenated on a Parr apparatus at 50 psi for 3 days. The mixture was filtered, the catalyst was washed with ethanol, the filtrate was concentrated, and the residue was taken up in hot ethanol and diluted with ether. Crystals formed and were collected to give 5.7 g (82%) of **3** as a pale yellow solid: mp 220.5-223 °C (decomp); ^{1}H NMR ($CDCl_3$) δ 1.85 (m) and 2.12 (m)(6H), 4.31 (m) and 4.44 (s)(4H), 7.23 (m, 3H), 9.25 (s, 1H). Anal. Calcd for $C_{14}H_{14}N_2Cl_2 \cdot HCl$: C, 52.94; H, 4.76; N, 8.82. Found: C, 52.77, H, 4.66; N, 8.67.

REFERENCES AND NOTES

1. This research was conducted at Sterling Winthrop Pharmaceuticals Research Division prior to its acquisition by Sanofi, Inc.
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