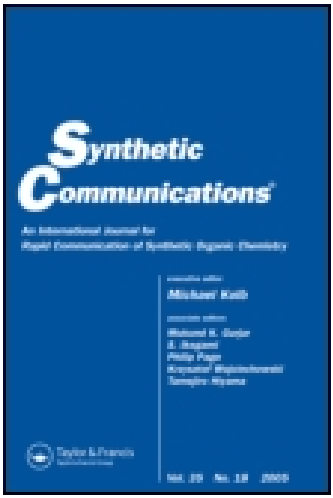

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Efficient Synthesis of 2-(N-Substituted)-2-imidazolines and 2-(N-Substituted)-1,4,5,6-tetrahyd

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Efficient Synthesis of 2-(*N*-Substituted)-2-imidazolines and 2-(*N*-Substituted)-1,4,5,6-tetrahydropyrimidines

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Abstract: A general method for the preparation of 2-(*N*-Substituted)-2-imidazolines and 2-(*N*-Substituted)-1,4,5,6-tetrahydropyrimidines is described. These heterocycles can be synthesized from their respective anilines with 2-chloro-2-imidazoline or 2-chloro-1,4,5,6-tetrahydropyrimidine, generated *in situ* from imidazolidin-2-one and tetrahydropyrimidin-2(*1H*)-one activated by dimethyl chlorophosphate, in good to excellent yields.

Keywords: 2-(*N*-Substituted)-2-imidazolines, 2-(*N*-substituted)-1,4,5,6-tetrahydropyrimidines

INTRODUCTION

2-(*N*-Substituted)-2-imidazolines and 2-(*N*-substituted)-1,4,5,6-tetrahydropyrimidines are unique classes of chemicals that contain an endocyclic C═N double bond. Many drug molecules contain these structures. One of the examples is clonidine, 2-[*N*-(2,6-dichlorophenyl)]-imidazolidine, which is a commonly used antihypertensive.[1] Literature review showed that

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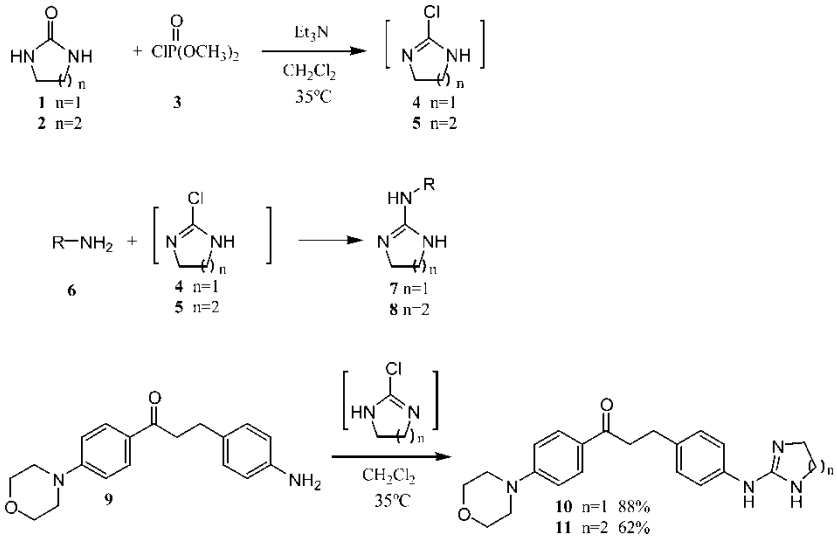
these heterocycles can be synthesized by several methods. One of them employed nucleophilic substitution of 2-chloro-4,5-dihydro-1*H*-imidazole[2] or 2-nitroamino-4,5-dihydro-1*H*-imidazole[3] by their respective anilines to form *N*-substituted imidazolines. However, the preparation of these reagents requires the use of hazardous chemicals such as chlorine gas, which is dangerous for large-scale preparation. Another approach uses 2-methylthio-2-imidazoline[4,5] as reagent, which allows a milder reaction but requires longer reaction times. Moreover, the preparation of 2-methylthio-4,5-dihydro-1*H*-imidazole has an unpleasant stench reagent. Conversely, little information is available for the preparation of *N*-substituted-1,4,5,6-tetrahydropyrimidines although the methods previously discussed may be applicable. In this article, we report an efficient method for the synthesis of these two classes of chemicals.

RESULTS AND DISCUSSION

We planned to generate 2-chloro-4,5-dihydro-1*H*-imidazole **4** and 2-chloro-1,4,5,6-tetrahydropyrimidine **5** in situ, which prevents the isolation of these hazardous chemicals. Previously, Etemad-Moghadam et al.[6] described the synthesis of phospho-biotin models. He suggested that imidazolidin-2-one **1** may form 2-chloro-4,5-dihydro-1*H*-imidazole **4** when it reacts with alkyl or aryl chlorophosphates. Using their experimental method[6] for the in situ generation of 2-chloro-4,5-dihydro-1*H*-imidazole **4** or 2-chloro-1,4,5,6-tetrahydropyrimidine **5** resulted in poor yields. After extensive study, we found that the optimal condition for the generation of these chloro-reagents is by using one equivalent of imidazolidin-2-one or tetrahydropyrimidin-2(*1H*)-one and three equivalents of dimethyl chlorophosphate and triethylamine in refluxing dichloromethane for 5 h. Afterwards, one equivalent of the respective amine was added. Most reactions were completed within another 5 h. The results are summarized in Scheme 1 and Table 1. With the exception of very electro-withdrawing anilines, such as nitro-aniline, *N*-substituted-imidazolines were synthesized in excellent yields and tetrahydropyrimidines were prepared in good yields. 4-Nitro-aniline failed to provide any product even after 4 days of reaction. It is probably due to the lack of basicity of the nitroaniline. For a similar reason, aminopyridine gave inferior results for the preparation of *N*-(2-pyridyl)-1,4,5,6-tetrahydropyrimidine. Nevertheless, this method is applicable to most anilines. Moreover, aliphatic amine **6a** also reacts accordingly. Apparently, the method is applicable for the preparation of both *N*-alkyl and *N*-aryl derivatives. To verify that the method is of practical value, we used it for the preparation of a recently reported prostacyclin antagonist **10**[7] and its derivative **11**. Using this method, both compounds **10** and **11** were prepared in excellent and good yields respectively. The use of chlorine gas for the generation of chloro-imidazoline is avoided. In conclusion, an efficient method for the



Scheme 1.

synthesis of *N*-substituted imidazolines and tetrahydropyrimidines is described that should be applicable for wide varieties of amines.

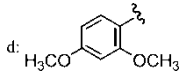
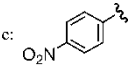
EXPERIMENTAL

Proton NMR spectra were recorded on a 300-MHz Varian Mercury-300 NMR spectrometer. Carbon NMR spectra were recorded on a 75-MHz Varian Mercury-300 NMR spectrometer. Proton and carbon chemical shifts are reported on the delta scale as parts per million (ppm) downfield from tetramethylsilane (TMS) as internal reference. Mass spectra were measured with a VG Analytical Model 70-250s mass spectrometer. All reagents were used as obtained commercially.

General Procedure for the Synthesis of Compounds 7, 8, 10, and 11

Dimethyl chlorophosphate **3** (3 equiv) and Et_3N (3 equiv) was added into a solution of the imidazolidin-2-one **1** (or tetrahydro-pyrimidin-2-one **2**) in CH_2Cl_2 at room temperature under nitrogen. The reaction mixture was stirred at 35°C for 5 h. The appropriate amine **6** (1 equiv) was dissolved in CH_2Cl_2 and added dropwise into the reaction mixture. The progress of the reaction was monitored by TLC. After an aqueous workup the solvent was evaporated under reduced pressure and the residue was purified on silica gel (50% ethyl acetate/hexane).

Table 1.

Entry	R	**7**, $n = 1$	**8**, $n = 2$ (yield %)
1	a: 	97	39
2	b: 	95	67
3	c: 	95	47
4	d: 	94	63
5	c: 	—	—
6	f: 	5	30

(4,5-Dihydro-1*H*-imidazol-2-yl)-isopropyl-amine (**7a**) was prepared as previously described (97%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.82 (1H, bs, –NH), 6.19 (1H, bs, –NH), 3.90 (1H, sept, $J = 6.6$ Hz), 3.87 (2H, t, $J = 8.7$ Hz), 3.40 (2H, t, $J = 8.7$ Hz), 1.12 (6H, d, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 159.1, 41.9, 41.6, 36.6, 22.7; HRMS calcd. for $C_6H_{13}N_3$: 127.1109, found: 127.1104.

Benzyl-(4,5-dihydro-1*H*-imidazol-2-yl)-amine (7b)[3] was prepared similar to the general procedure (95%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.41 (1H, bs, –NH), 7.32–7.22 (5H, m), 5.67 (1H, bs, –NH), 4.47 (2H, d, $J = 5.7$ Hz), 3.97 (2H, t, $J = 7.8$ Hz), 3.44 (2H, td, $J = 7.8$, 2.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.9, 153.5, 128.5, 127.4, 127.2, 43.6, 42.1, 36.8; EI-MS m/z (rel. int.%): 175 (M^+, 1), 106 (100), 91 (18), 85 (9), 77 (4); HRMS calcd. for $C_{10}H_{13}N_3$: 175.1109; found: 175.1105.

(4,5-Dihydro-1*H*-imidazol-2-yl)-phenylamine (7c) was prepared similar to the general procedure (95%): mp 139–140°C (water) (lit.[5] 138–139°C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.50 (2H, dd, $J = 7.5$, 1.2 Hz), 7.30 (2H, td, $J = 7.5$, 1.8 Hz), 7.06 (1H, td, $J = 7.5$, 1.2 Hz), 5.93 (1H, bs, –NH), 4.03 (2H, t, $J = 7.8$ Hz), 3.50 (2H, t, $J = 7.8$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.8, 137.7, 128.9, 123.5, 119.7, 42.0, 36.6; HRMS calcd. for $C_9H_{11}N_3$: 161.0953; found: 161.0958.

(4,5-Dihydro-1*H*-imidazol-2-yl)-(2,4-dimethoxy-phenyl)-ammonium Chloride (**7d**) was prepared as described in the general procedure (94%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.04 (1H, dd, $J = 2.1$, 8.4 Hz), 6.48–6.44

(2H, m), 4.05 (2H, t, $J = 7.8$ Hz), 3.82 (3H, s), 3.77 (3H, s), 3.51 (2H, t, $J = 7.8$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.6, 156.1, 150.7, 150.0, 120.5, 103.7, 98.7, 55.8, 55.5, 42.1, 36.7; HRMS calcd. for $C_{11}H_{16}ClN_3O_2$: 257.0931; found: 257.0928.

(4,5-Dihydro-1*H*-imidazol-2-yl)-pyridin-2-yl-amine (7f) was prepared by following the general procedure (5%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.29 (1H, ddd, $J = 0.9$, 1.8, 5.1 Hz), 8.06 (1H, dt, $J = 0.9$, 8.4 Hz), 7.67 (1H, td, $J = 1.8$, 7.2 Hz), 6.99 (1H, ddd, $J = 0.9$, 5.1, 7.2 Hz), 5.77 (1H, bs, –NH), 4.05 (2H, t, $J = 7.6$ Hz), 3.56 (2H, t, $J = 7.6$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.2, 157.0, 148.0, 138.1, 119.1, 113.6, 42.0, 36.6; EI-HRMS calcd. for $C_8H_{10}N_4$: 162.0905; found: 162.0901.

Isopropyl-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-amine (8a) was prepared similarly (39%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.15(1H, bs, –NH), 5.43 (1H, bs, –NH), 3.94 (1H, sept, $J = 6.6$ Hz), 3.81 (2H, t, $J = 5.7$ Hz), 3.30 (2H, t, $J = 5.7$ Hz), 1.92 (2H, quin, $J = 5.7$ Hz), 1.16 (6H, d, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 157.8, 43.5, 42.8, 41.4, 23.1, 22.5; HRMS calcd. for $C_7H_{15}N_3$: 141.1266; found: 141.1270.

Benzyl-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-amine (8b)[3] was prepared similarly (67%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.32–7.22 (5H, m), 5.11 (1H, bs, –NH), 4.46 (2H, d, $J = 5.7$ Hz), 3.87 (2H, t, $J = 6.0$ Hz), 3.33 (2H, td, $J = 6.0$, 2.1 Hz), 1.95 (2H, quin, $J = 6.1$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 156.1, 155.3, 128.5, 127.5, 127.1, 44.4, 41.5, 40.9, 21.5; EI-MS m/z (rel. int.%): 189 (M^+, 1), 106 (100), 91 (19), 77 (4); HRMS calcd. for $C_{11}H_{15}N_3$: 189.1266; found: 189.1264.

Synthesis of Phenyl-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-amine (8c)[5] was prepared similarly (47%): ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.54 (2H, dd, $J = 7.8$, 1.8 Hz), 7.38 (2H, t, $J = 7.8$ Hz), 7.15 (1H, dd, $J = 7.8$, 1.8 Hz), 3.94 (2H, t, $J = 6.0$ Hz), 3.40 (2H, t, $J = 6.0$ Hz), 2.06 (2H, quin, $J = 6.0$ Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ: 155.9, 140.9, 129.1, 121.5, 118.1, 37.0, 36.9, 31.2; HRMS calcd. for $C_{10}H_{13}N_3$: 175.1109; found: 175.1112.

(2,4-Dimethoxy-phenyl)-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-ammonium Chloride (8d) was prepared similarly (63%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.06 (1H, dd, $J = 1.8$, 8.7 Hz), 6.47–6.43 (2H, m), 5.68 (1H, bs, –NH), 3.90 (2H, t, $J = 5.7$ Hz), 3.85 (3H, s), 3.77 (3H, s), 3.34 (2H, t, $J = 5.7$ Hz), 1.97 (2H, quin, $J = 5.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 156.2, 156.0, 152.4, 150.2, 120.7, 103.6, 98.6, 55.8, 55.4, 41.2, 40.8, 21.5; HRMS calcd. for $C_{12}H_{18}ClN_3O_2$: 271.1088l; found: 271.1080.

Pyridin-2-yl-(1,4,5,6-tetrahydro-pyrimidin-2-yl)amine (8f) was prepared by following the general procedure (30%): ^{1}H NMR ($CDCl_3$, 300 MHz)

δ: 12.16 (1H, bs, –NH), 8.30 (1H, d, $J = 3.9$ Hz), 8.10 (1H, d, $J = 8.4$ Hz), 7.70 (1H, t, $J = 7.2$ Hz), 7.01 (1H, ddd, $J = 0.9$, 5.1, 6.0 Hz), 5.53 (1H, bs, –NH), 3.92 (2H, t, $J = 6.0$ Hz), 3.40 (2H, td, $J = 2.7$, 6.0 Hz), 2.02 (2H, quin, $J = 6.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 155.8, 152.3, 130.9, 128.8, 119.0, 114.9, 41.7, 41.0, 21.4; EI-HRMS calcd. for $C_9H_{12}N_4$: 176.1062; found: 176.1066.

3-[4-(4,5-Dihydro-1*H*-imidazol-2-yl-amino)-phenyl]-1-(4-morpholin-4-yl-phenyl)-propan-1-one (10)[7] was prepared as described in the general procedure (88%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 10.14 (1H, s, –NH), 7.89 (2H, d, $J = 9.0$ Hz), 7.42 (2H, d, $J = 8.4$ Hz), 7.19 (2H, d, $J = 8.4$ Hz), 6.86 (2H, d, $J = 9.0$ Hz), 4.91 (1H, s, –NH), 4.06 (2H, t, $J = 7.2$ Hz), 3.86 (4H, t, $J = 4.8$ Hz), 3.52 (2H, t, $J = 8.1$ Hz), 3.30 (4H, t, $J = 4.8$ Hz), 3.19 (2H, t, $J = 7.2$ Hz), 3.00 (2H, t, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 197.7, 158.5, 154.0, 150.7, 136.9, 135.8, 130.1, 128.9, 120.0, 113.5, 66.5, 47.7, 42.1, 40.0, 36.7, 29.9; EI-MS m/z (rel. int.%): 337 ($M^+ - C_2H_3N$,11), 336 (47), 204 (22), 190 (100), 163 (16), 132 (40); HRMS calcd. for $C_{22}H_{26}N_4O_2 - C_2H_3N$: 337.1790; found: 337.1791.

1-(4-Morpholin-4-yl-phenyl)-3-[4-(1,4,5,6-tetrahydro-pyrimidin-2-yl-amino)-phenyl]-propan-1-one (11) was prepared similarly (62%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 11.57 (1H, s, –NH), 7.90 (2H, d, $J = 8.7$ Hz), 7.43 (2H, d, $J = 8.4$ Hz), 7.20 (2H, d, $J = 8.4$ Hz), 6.87 (2H, d, $J = 8.7$ Hz), 5.56 (1H, bs, –NH), 3.93 (2H, t, $J = 5.7$ Hz), 3.87 (4H, t, $J = 4.8$ Hz), 3.39 (2H, td, $J = 5.7$, 2.4 Hz), 3.32 (4H, t, $J = 4.8$ Hz), 3.22 (2H, t, $J = 7.2$ Hz), 3.02 (2H, t, $J = 7.8$ Hz), 2.02 (2H, quin, $J = 6.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 197.7, 156.3, 154.1, 152.6, 136.7, 136.2, 130.0, 128.7, 127.6, 120.4, 113.3, 66.5, 47.4, 41.2, 40.9, 39.9, 29.9, 21.4; EI-MS m/z (rel. int.%): 337 ($M^+ - C_3H_5N$,13), 336 (58), 190 (100), 163 (11), 132 (53); HRMS calcd. for $C_{23}H_{28}N_4O_2 - C_3H_5N$: 337.1790; found: 337.1792.

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