A One-Pot Synthesis of 1-(2,2,6,6-tetramethyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(2-amino-4-pyrimidinyl)-imidazole: A Potent Inhibitor of P38 MAP Kinase

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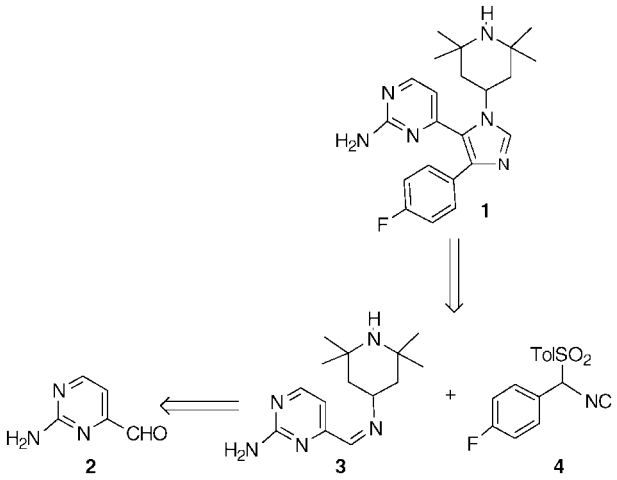
The 1,4,5-trisubstituted imidazole **1** is representative of a general class of compounds which exhibit potent binding affinities for p38 MAP kinase, a recently discovered protein kinase which appears to be involved in an inflammation regulatory pathway.[1] As part of the development of compounds of this class for the treatment of arthritis, a flexible route capable of preparing kilogram quantities of imidazole **1**, as well as analogues, was required.

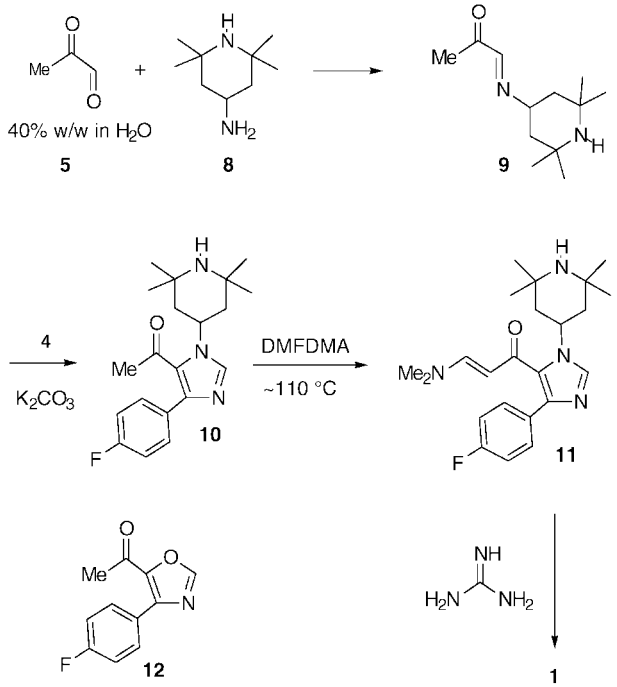
Of the methods considered for the synthesis of **1**,[2] the van Leusen method[3] for preparing imidazoles by annulation of TosMIC derivatives with imines seemed best suited for our purposes. In fact, a similar strategy has already been reported for the synthesis of the analogous 5-*pyridinyl*-substituted imidazoles.[4] The commercial availability of the various pyridine aldehydes required for that series of compounds, however, had streamlined and simplified their preparation.

Adapting the van Leusen strategy for the synthesis for **1** involved base-promoted annulation of imine **3** with tosyl isonitrile **4**[5] to provide the 1,4,5-trisubstituted imidazole (Scheme 1).[6] While the yield for this transformation on a small scale routinely exceeded 65%, the overall strategy was plagued with several problems which would likely be compounded on scale-up. Most notable was that pyrimidine aldehyde **2**,[7] which served as the precursor to the requisite imine **3**, was prone to polymerization and difficult to isolate due to its appreciable water solubility.

Scheme 1



Scheme 2



An alternative approach to **1** that avoids aldehyde **2** was devised which targeted the 5-acetylimidazole **10** as a key intermediate (Scheme 2). Although no general procedure for the preparation of this class of compounds could be found in the literature,[8] the van Leusen TosMIC chemistry[3] again appeared to be the most promising approach. The unprecedented reaction of an α-ketoaldimine (**9**) with isonitrile **4** would be the pivotal reaction, providing a novel and concise route to the imidazole **10**. Elaboration of the methyl ketone of **10** using the Brederick procedure[7] would complete the synthesis of **1**.

(1) Lee, J. C.; Laydon, J. L.; McDonnel, P. C.; Gallagher, T. F.; Kumar, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Heyes, J. R.; Landvatter, S. W.; Strickler, J. F.; McLaughlin, M. M.; Siemens, I. R.; Fisher, S. M.; Livi, G. P.; White, J. R.; Adams, J. L.; Young, P. R. *Nature (London)* **1994**, *372*, 739.

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(3) van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem*. **1977**, *42*, 1153.

(4) Boehm, J. C.; Smientana, J. M.; Sorenson, M. E.; Garigipati, R. S.; Gallagher, T. F.; Sheldrake, P. L.; Bradbeer, J.; Badger, A. M.; Laydon, J. T.; Lee, J. C.; Hillegass, L. M.; Griswold, D. E.; Breton, J. J.; Chabot-Fletcher, M. C.; Adams, J. L. *J. Med. Chem*. **1996**, *39*, 3929.

(5) Sisko, J.; Mellinger, M.; Sheldrake, P. W.; Baine, N. H. *Tetrahedron Lett*. **1996**, *37*, 8113.

(6) The details of this general approach to **1** will be published separately.

(7) Bredereck, H.; Sell, R.; Effenberger, F. *Chem. Ber*. **1964**, *97*, 3407.

(8) Acetylimidazole syntheses have been reported. However, these methods would not be suitable for the synthesis of **10**. See: Reiter, L. A. *J. Org. Chem*. **1987**, *52*, 2714 and references therein. Rahman, A.; Ila, H.; Junjappa, H. *J. Chem. Soc., Chem. Commun*. **1984**, 430. Veronese, A. C.; Cavicchioni, G.; Servadio, G.; Vecchiati, G. *J. Heterocycl. Chem*. **1980**, *17*, 1723. Bierer, D. E.; O'Connell, J. F.; Parquette, J. R.; Thompson, C. M.; Rapoport, H. *J. Org. Chem*. **1992**, *57*, 1390.

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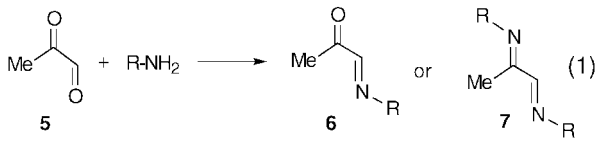
Results and Discussion

Since their first reported preparation in 1978,[9] α-ketoaldimines (**6**) have found little use in synthesis.[10] In that seminal report, van Koten showed that condensation of *tert*-butylamine with pyruvaldehyde (**5**) produced the imine **6** (R = *t*-Bu) in 70% isolated yield (eq 1).[9] This



result contrasted earlier reports[11] in which less sterically demanding amines, such as methylamine, reacted with pyruvaldehyde to produce the α-diimines **7** (R = Me) exclusively. The success of this approach relied on the ability to selectively prepare the monoimine when the aminopiperidine required for **1** was used. It was gratifying, therefore, to find that addition of 2,2,6,6-tetramethyl-4-aminopiperidine (**8**) with pyruvaldehyde (**5**) in TBME led to a 71% isolated yield of the monoimine **9** with none of the corresponding α-diimine detected in the reaction mixture. More importantly, reaction of imine **9** with tosyl isonitrile **4** and K_2CO_3 produced a 78% isolated yield of the ketone **10** on the first attempt.

Concerns about the stability of imine **9** led us to pursue the construction of imidazole **10** in a single pot, without isolation of the imine **9**. This strategy had several potential pitfalls. First, generation of the anion of isonitrile **4** would have to be conducted in the presence of a considerable amount of water since pyruvaldehyde is only available as a 40% aqueous solution. In addition, complete conversion of pyruvaldehyde to the imine **9** would be imperative since any residual aldehyde would also react with **4** to produce the oxazole **12**.[12] These concerns proved to be unwarranted. Combining equal portions of amine **8** and pyruvaldehyde in DMF for 10−20 min followed by the addition of the isonitrile **4** and K_2CO_3 produced an 80% isolated yield of the imidazole **10**, and <5% of the oxazole **12**. Attempts to remove water from the reaction medium by adding $MgSO_4$ or molecular sieves had little effect on the yield or purity of the product.

Completion of the synthesis of **1** required conversion of the methyl ketone of **10** to a 2-aminopyrimidine ring.[7] Heating **10** with an excess of *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) produced the vinylogous amide **11** which was reacted directly with guanidine hydrochloride and NaOMe at 80 °C. In this manner, the pyrimidine **1** could be prepared in 72% isolated yield from **10**.

The synthesis of **1** was ultimately demonstrated in one pot starting from pyruvaldehyde. Mixing pyruvaldehyde and the amine **8** in DMSO prior to adding the isonitrile **4** and K_2CO_3 produced a solution of the imidazole **10**, still containing water from the 40% aqueous pyruvaldehyde solution. This solution was easily dried by adding toluene and distilling the water/toluene azeotrope under vacuum prior to adding the DMFDMA to avoid its hydrolysis. The resulting solution was heated with DMFDMA to produce the vinylogous amide **11** which was treated directly with guanidine·HCl and K_2CO_3. After 7 h of heating at 100 °C the imidazole **1** was produced in 36% yield on the basis of isonitrile **4** *in a single pot*.

In conclusion, a novel and concise route to the antiinflammatory agent **1** was developed which employs the annulation of the isonitrile **4** with an α-ketoaldimine as the key reaction. This reaction is remarkably tolerant of water and reactive functional groups, such as the unprotected piperidine of **8**. These considerations highlight the potential of this method to prepare a wide array of analogous imidazoles. Further examination of substituted TosMIC reagents, such as **4**, reacting with functionalized imines under partially aqueous conditions is underway and these results will be reported in due course.

Experimental Section

General. Unless otherwise noted, solvents and reagents were obtained from commercial suppliers and used without further purification. Unless otherwise noted, reagents were added by syringe. Filtrations through silica were done using Merck 60 (230−400 mesh) silica gel. Unless otherwise noted, NMR spectra were measured as solutions in $CDCl_3$ and chemical shifts are expressed in ppm relative to internal $CHCl_3$ (7.26 ppm). ^1H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz.

α-(*p*-Toluenesulfonyl)-4-fluorobenzylisonitrile (4). To a stirred suspension of α-(*p*-toluenesulfonyl)-4-fluorobenzylformamide[5] (20 g, 65 mmol) in THF (150 mL) was added $POCl_3$ (12.2 mL, 130 mmol). The solution was stirred for 10−15 min and then cooled to between −5 and 0 °C. Triethylamine (55 mL, 390 mmol) was added dropwise to the slurry over 45 min at such a rate as to keep the reaction temperature below 0 °C but above −5 °C. After complete Et_3N addition, the yellow slurry was stirred for 30 min at 0 °C. The reaction was diluted with EtOAc (100 mL) and water (50 mL), stirred for 10 min at ∼10 °C, and transferred to a separatory funnel. The aqueous layer was removed, and the organic phase was washed with water (2 × 100 mL), a saturated $NaHCO_3$ solution (100 mL), and water (100 mL) again. The organic phase was concentrated under vacuum until about 10−15% of the initial volume remained. 1-Propanol (100 mL) was added, and the solution was concentrated again under vacuum at 35 °C until about 10% of the initial volume remained. The solution was allowed to stand for 30−45 min at 0 °C, and the fine, yellow precipitate which formed was collected by suction filtration and rinsed with 1-propanol (20 mL). The off-white solid was dried to a constant weight at 30−40 °C/<1 mm to give 15.1 g (80%) of the title compound. **WARNING**: The isonitrile **4** is thermally unstable at temperatures above 80 °C. To obtain a margin of safety, isonitrile **4** should not be dried or used at temperatures >40 °C: IR (KBr) 3077, 2998, 2137, 1335 cm^{-1}; ^1H NMR δ 7.62 (2H, d, J = 6.7 Hz), 7.46 (4H, m), 7.08 (2H, t, J = 8.6 Hz), 5.62 (1H, s), 2.46 (3H, s); ^{13}C NMR δ 166.7, 164.1 (d, J = 250 Hz), 146.8, 130.5 (d, J = 6.6 Hz), 130.4, 130.1, 129.9, 122.6, 116.0 (d, J = 22.1 Hz), 75.7, 21.8. Anal. Calcd for $C_{15}H_{12}NO_2FS$: C, 62.3; H, 4.2; N, 4.8. Found: C, 62.5; H, 4.1; N, 4.6.

2,2,6,6-Tetramethyl-4-(2-oxopropylidene)aminopiperidine (9). To a solution of pyruvaldehyde (40% w/w solution in water, 2.68 mL, 17.5 mmol) in 30 mL of TBME at room temperature was added 2,2,6,6-tetramethyl-4-aminopiperidine (2.0 mL, 14.0 mmol). After 30 min, the solution was diluted with 50 mL of TBME and washed with 3 × 25 mL of water and 25 mL of brine. The solution was concentrated in vacuo to yield 2.1 g (71%) of the imine product as an oil which was used as

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(11) tom Kieck, H.; Renk, I. W. *Chem. Ber.* **1971**, *104*, 110. Krumholz, P.; Serra, O. A.; Paoli, M. A. *Inorg. Chim. Acta* **1975**, *15*, 25.

(12) van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, 2369.

such in the subsequent step: IR (neat) 3310, 1685, 1630, 1360 cm^{-1}; ^1H NMR δ 7.60 (1H, s), 3.67 (1H, tt, J = 4.0, 11.5 Hz), 2.30 (3H, s), 1.57 (2H, dd, J = 4.0, 13.0 Hz), 1.28 (2H, dd, J = 11.5, 13.0 Hz), 1.17 (6H, s), 1.10 (6H, s); ^{13}C NMR δ 200.1, 158.4, 62.3, 50.2, 45.2, 34.9, 28.8, 24.5.

1-(2,2,6,6-Tetramethyl-4-piperidinyl)-4-(4-fluorophenyl)-5-acetylimidazole (10) from Imine 9. To a solution of imine **9** (2.50 g, 11.9 mmol) in 30 mL of DMF at room temperature were added isonitrile **4** (3.12 g, 10.8 mmol) and K_2CO_3 (1.64 g, 11.9 mmol). After 16 h, the solution was diluted with 100 mL of EtOAc and washed with 2 × 75 mL of 3 N HCl. The aqueous layers were combined and made basic with excess solid K_2CO_3 to pH 10−11. The aqueous layer was transferred to a separatory funnel and extracted with 2 × 100 mL of EtOAc. The combined organics were washed with 3 × 100 mL of water, concentrated in vacuo, and recrystallized from $CHCl_3$/hexanes to give the title compound **10** (2.90 g, 78%): mp = 134−136 °C; IR (KBr) 3430, 3144, 1659, 1653, 1219 cm^{-1}; ^1H NMR δ 7.76 (1H, s), 7.43 (2H, m), 7.12 (2H, t, J = 8.7 Hz), 5.39 (1H, tt, J = 3.1, 12.5 Hz), 2.11 (3H, s), 2.10 (2H, dd, J = 3.1, 11.9), 1.50 (2H, dd, J = 11.9, 12.5 Hz), 1.37 (6H, s), 1.22 (6H, s); ^{13}C NMR δ 190.8, 163.0 (d, J = 246.5 Hz), 149.8, 137.4, 131.4 (d, J = 8.1 Hz), 131.4, 127.0, 115.4 (d, J = 21.6 Hz), 52.0, 50.6, 46.2, 34.6, 30.5, 28.1. Anal. Calcd for $C_{20}H_{26}N_3OF$: C, 69.9; H, 7.6; N, 12.2. Found: C, 69.6; H, 7.6; N, 12.1.

1-(2,2,6,6-Tetramethyl-4-piperidinyl)-4-(4-fluorophenyl)-5-acetylimidazole (10) from Pyruvaldehyde (5). To a solution of pyruvaldehyde (40% w/w solution in water, 1.34 mL, 8.74 mmol) in 12 mL of DMSO at room temperature was added 2,2,6,6-tetramethyl-4-aminopiperidine (1.50 mL, 8.74 mmol). After 10 min, isonitrile **4** (1.69 g, 5.83 mmol) and K_2CO_3 (0.81 g, 5.85 mmol) were added. After 16 h, the solution was diluted with 100 mL of EtOAc and washed with 2 × 75 mL of 3 N HCl. The aqueous layers were combined and made basic with excess solid K_2CO_3 to pH 10−11. The aqueous layer was transferred to a separatory funnel and extracted with 2 × 100 mL of EtOAc. The combined organics were washed with 3 × 50 mL of water and concentrated in vacuo to give **10** as a brown oil. This material was recrystallized from $CHCl_3$/hexanes to give **10** (1.61 g, 80%) whose spectra were identical to those listed for **10** above.

1-(2,2,6,6-Tetramethyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(3-*N*,*N*-dimethylamino-*trans*-2-propen-1-one)imidazole (11). The ketone **10** (0.75 g, 2.18 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (0.43 mL, 3.28 mmol) were dissolved in 10 mL of toluene and heated at 110 °C for 20 h. The solution was cooled to room temperature, and the solvents were removed under vacuum. The residue was eluted through a short plug of silica gel with EtOAc/MeOH (1:1) and concentrated to give the title compound (0.65 g 76%) as a waxy solid: IR (neat) 3300, 1630, 1550, 1530 cm^{-1}; ^1H NMR δ 7.65 (1H, s), 7.56 (2H, m), 7.46 (1H, d, J = 12.4 Hz), 7.01 (2H, t, J = 8.8 Hz), 5.32 (1H, tt, J = 3.1, 12.4 Hz), 5.01 (1H, d, J = 12.4 Hz), 2.96 (3H, br s), 2.48 (3H, br s), 2.09 (2H, dd, J = 3.1, 12.2 Hz), 1.44 (2H, dd, J = 12.2, 12.4 Hz), 1.31 (6H, s), 1.17 (6H, s); ^{13}C NMR δ 182.3, 162.4 (d, J = 244.8 Hz), 153.2, 143.0, 135.4, 131.7, 131.0 (d, J = 7.9 Hz), 128.0, 114.7 (d, J = 21.2 Hz), 98.5, 51.7, 49.6, 46.4, 44.7, 36.8, 34.7, 28.2; HRMS calcd for $C_{23}H_{31}N_4OF$ 398.2481, found 398.2481.

1-(2,2,6,6-Tetramethyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(2-amino)-4-pyrimidinyl)imidazole (1) from Ketone 10. A solution of ketone **10** (8.5 g, 24.8 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (6.6 mL, 49.5 mmol) was heated at 100 °C for 6 h. The solution was cooled to 80 °C, and 1-PrOH (25 mL), guanidine·HCl (3.55 g, 37.1 mmol), and NaOMe (25% w/w in MeOH, 8.5 mL, 37.1 mmol) were added. After 17 h, the solution was cooled to room temperature, diluted with 200 mL of EtOAc, and washed with a 10% NaOH solution (2 × 100 mL). The organics were washed with 150 mL of 3 N HCl, and the separated aqueous layer was made basic with 50% NaOH to pH 11−12. The aqueous layer was extracted with TBME (200 mL) and concentrated to 100 mL in vacuo. The solution was diluted with 50 mL of hexane, and after 30 min the crystals that formed were filtered to give 7.0 g (72%) of the title compound: mp = 221−222 °C; IR (KBr) 3345, 3319, 3155, 1645, 1562 cm^{-1}; ^1H NMR δ 8.17 (1H, d, J = 5.2 Hz), 7.72 (1H, s), 7.45 (2H, m), 7.00 (2H, t, J = 8.7 Hz), 6.49 (1H, d, J = 5.2 Hz), 5.30 (1H, tt, J = 3.2, 12.6 Hz), 5.12 (2H, br s), 2.04 (2H, dd, J = 3.2, 12.4 Hz), 1.48 (2H, dd, J = 12.4, 12.6 Hz), 1.24 (6H, s), 1.17 (6H, s); ^{13}C NMR (DMSO-d_6) δ 163.7, 161.1 (d, J = 242.4 Hz), 158.8, 158.5, 138.7, 135.4, 130.9, 128.9 (d, J = 8.0 Hz), 125.1, 115.0 (d, J = 21.1 Hz), 111.0, 50.8, 48.7, 44.7, 34.1, 28.1. Anal. Calcd for $C_{22}H_{27}N_6F$: C, 67.0; H, 6.9; N, 21.3. Found: C, 67.4; H, 6.9; N, 21.4.

1-(2,2,6,6-Tetramethyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(2-amino)-4-pyrimidinyl)imidazole (1) from Pyruvaldehyde (5). To a solution of pyruvaldehyde (40% w/w solution in water, 5.82 mL, 38.04 mmol) in 70 mL of DMSO at room temperature was added 2,2,6,6-tetramethyl-4-aminopiperidine (6.52 mL, 38.04 mmol). After 15−20 min, isonitrile **4** (10 g, 34.6 mmol) and K_2CO_3 (5.02 g, 36.3 mmol) were added. After 19 h, 30 mL of toluene was added and the solution was heated at 65 °C while the toluene/water azeotrope was removed under vacuum. The toluene addition/distillation was repeated two times more. *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) (9.2 mL, 69.2 mmol) was added, and the solution was heated at 100 °C for 8−10 h. Guanidine·HCl (6.61 g, 69.2 mmol) and K_2CO_3 (9.56 g, 69.2 mmol) were added, and the resulting solution was heated at 100 °C for 6−7 h. After being cooled to room temperature, the solution was filtered through a pad of Celite, diluted with 250 mL of EtOAc, and washed with 4 × 200 mL of 3 N HCl. The aqueous layers were combined and made basic with solid KOH to pH = 12. The aqueous layer was transferred to a separatory funnel and extracted with EtOAc (3 × 200 mL). The combined organics were washed with 3 × 100 mL of a 3 N KOH solution and 50 mL of brine, dried over Na_2SO_4 and activated charcoal, filtered through Celite, and concentrated in vacuo. The residue was dissolved in 50 mL of MeOH, and the crystals that formed were filtered and washed with 100 mL of EtOAc to yield the title compound (4.89 g, 36%) as a tan solid whose spectra matched those listed above.

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