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Efficient Molar-Scale Synthesis of 1-Methyl-5-acylimidazole Triflic Acid Salts

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Abstract:

A new process for the molar-scale preparation of 1-methyl-5-acylimidazole triflic acid salts was developed. The new process consists of: (i) regioselective ^3N-tritylation of 5-acylimidazole to give 3-trityl-5-acylimidazoles, (ii) ^1N-methylation of 3-trityl-5-acylimidazoles, and (iii) hydrolysis of the resulting quaternary ammonium salts to afford 1-methyl-5-acylimidazole triflic acid salts. This process is highly efficient, affording 1-methyl-5-acylimidazole triflic acid salts in 86−88% overall yield in three steps without chromatographic separation of products.

1-Methyl-5-formylimidazole is an important synthetic intermediate,[1−14] especially in the synthesis of natural products.[7−14] Three methods have been previously reported for the preparation of 1-methyl-5-formylimidazole. The first method is the transformation of the 5-formyl group from a corresponding 5-hydroxymethyl,[6−8,15] or 5-alkoxycarboxyl group.[6,8,15] The second method features the installation of the 5-formyl group via a 5-metalated 1-methylimidazole reactive species.[5,16−18] The third method entails a regioselective *N*-methylation of 5-formylimidazole.[4,14] In a program of our drug discovery, we required an easy access to a large amount of 1-methyl-5-formylimidazole triflic acid salt.[19]

While the first two methods can certainly be adapted to the preparation of 1-methyl-5-formylimidazole triflic acid salt, the low overall yields, chromatographic separation, or high vacuum sublimation of product make them impractical for large-scale preparation. We were most attracted to the third method, because exclusive regioselectivity and a good yield (75%) were obtained in the methylation of 5-formylimidazole with methyl triflate.[14] However, in this report, the product imidazole was isolated as the free base after column chromatography.[14] We anticipated that the methyl triflate used for methylation could be utilized as a direct source for the final triflic acid salt formation. Herein, we describe an efficient process for the large-scale synthesis of 1-methyl-5-formylimidazole triflic acid salt from commercially available 5-formylimidazole. The application of this newly developed process to the preparation of 1-methyl-5-methoxycarbonylimidazole triflic acid salt is also disclosed.[20]

The new process begins with the preparation of 1-trityl-4-formylimidazole **1a** (Scheme 1). This compound was previously prepared in 80% yield by tritylation of 5-formylimidazole with trityl chloride and triethylamine in chloroform.[21] To eliminate the environmentally unfriendly chloroform from the process, tritylation in other solvents was examined. Thus, treatment of **1a** with trityl chloride in acetonitrile in the presence of triethylamine gave smoothly **2a** which was isolated in 99% yield. ^{1}H NMR indicated that the tritylation reaction in acetonitrile was highly regioselective. The undesired regioisomer was not detected. Reaction of **2a** with methyl triflate in methylene chloride at room temperature overnight afforded the quaternary ammonium salt **3a**. Product **3a** was isolated as a somewhat unstable crystalline compound in 99% yield after solvent exchange from methylene chloride to hexane and filtration. It is important to remove any excess methyl triflate from **3a** to streamline and simplify the product isolation in the subsequent step. Treatment of **3a** with water in acetone gave 1-methyl-5-formylimidazole triflic acid salt **4a**. It was surprising that the deprotection reaction took place under such mild conditions. The ease with which the detritylation occurred is probably due to the resonance between **3a** and **3′a**, with **3′a** undergoing facile deprotection in aqueous acetone. The product **4a** from detritylation is highly soluble in water, whereas the byproduct, trityl alcohol **5**, is essentially insoluble in water after removal of acetone and thus can be completely removed by simple filtration. Upon concentration, the final product **4a** was obtained in 95% yield. 1-Methyl-5-methoxycarbonylimidazole **4b** can be prepared similarly in 90% overall yield following the procedures described above.

(1) Lee, J. J.; Huang, L.-F.; Zaw, K.; Bauer, L. *J. Heterocycl. Chem*. **1998**, *35*, 81.
(2) Jonas, R.; Prucher, H.; Wurziger, H. *Eur. J. Med. Chem*. **1993**, *28*, 141.
(3) Pfoertner, K.-H.; Montavon, F.; Bernauer, K. *Helv. Chim. Acta* **1985**, *68*, 600.
(4) Sakami, W. *J. Biol. Chem*. **1944**, *154*, 215.
(5) Walters, M. A.; Lee, M. D. *Tetrahedron Lett*. **1994**, *35*, 8307.
(6) Aulaskari, P.; Ahlgren, M.; Rouvinen, J.; Vainiotalo, P. *J. Heterocycl. Chem*. **1996**, *33*, 1345.
(7) Jones, R. G.; McLaughlin, K. C. *J. Am. Chem. Soc*. **1949**, *71*, 2444.
(8) Dener, J. M.; Zhang, L.-H.; Rapoport, H. *J. Org. Chem*. **1993**, *58*, 1159.
(9) Compagnone, R. S.; Rapoport, H. *J. Org. Chem*. **1986**, *51*, 1713.
(10) Tchissambou, L.; Benechie, M.; Khung-Huu, F. *Tetrahedron Lett*. **1978**, 1801.
(11) Tchissambou, L.; Benechie, M.; Khung-Huu, F. *Tetrahedron* **1982**, *38*, 2687.
(12) Shapiro, G.; Chengzhi, C. *Tetrahedron Lett*. **1992**, *33*, 2447.
(13) Link, H.; Bernauer, K. *Helv. Chim. Acta* **1972**, *55*, 1053.
(14) Daninos-Zeghal, S.; Mourabit, A. A.; Ahond, A.; Poupat, C.; Potier, P. *Tetrahedron* **1997**, *53*, 7605.
(15) Kirchlechner, R.; Casutt, M.; Heywang, U.; Schwarz, M. W. *Synthesis* **1994**, 247.
(16) Shapiro, G.; Marzi, M. *Tetrahedron Lett*. **1993**, *34*, 3401.
(17) El Borai, M.; Moustafa, A. H.; Anwar, M.; Ghattas, A. G. *Croat. Chem. Acta* **1981**, *54*, 211.
(18) Shapranova, N. I.; Somin, I. N.; Kuznetsov, S. G. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1973**, 1013.
(19) Compared to its free base, 1-methyl-5-formylimidazole triflic acid salt **4a** shows improved physical properties for better purification and handling.
(20) Methyl-5-methoxycarbonylimidazole is also an important synthetic intermediate, see, Wuonola, M. A.; Woodward, R. B. *J. Am. Chem. Soc*. **1973**, *95*, 284. Wuonola, M. A.; Woodward, R. B. *Tetrahedron* **1976**, *32*, 1085. See also refs 6, 8, and 15.
(21) Bernabe, M.; Burger, A. *J. Med. Chem*. **1971**, *14*, 883.

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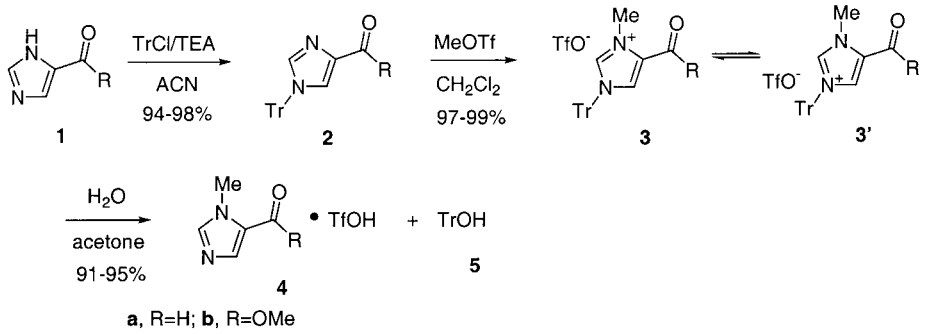
Scheme 1



In summary, a new process for the large-scale preparation of 1-methyl-5-acylimidazole triflic acid salts **4** has been developed. This process is highly efficient, giving **4** in 86−88% overall yield in three steps without chromatographic separation of products. It is expected that this process can be readily adapted to the preparation of other 1-alkyl-5-acylimidazoles.

Experimental Section

Melting points were taken on a Uni-Melt apparatus in open capillaries and are uncorrected. Proton and carbon-13 NMR spectra were recorded on a Bruker ARX-400 instrument using tetramethylsilane as internal standard. 5-Formylimidazole was purchased from Shikoku Chemical Corporation and used as is.

1-Trityl-4-formylimidazole 2a. To a 12 L three-necked round-bottomed flask equipped with a mechanical stirrer, a nitrogen bubbler, and an addition funnel was added **1a** (120.0 g, 1.25 mol), trityl chloride (383.0 g, 1.37 mol), and acetonitrile (4 L). The mixture was stirred at room temperature to give a slurry. Triethylamine (300 mL, 2.15 mol) was added dropwise over 2 h. After the addition was complete, the reaction mixture was stirred at room temperature for 20 h. Hexane (400 mL) and water (4 L) were added. The slurry was stirred for 30 min and filtered. The cake was washed with water (3 × 1 L) and dried in a house vacuum oven at 50 °C for 20 h to give 1-trityl-4-formylimidazole (**2a**), 398.0 g, 94%; mp 193−196 °C, lit.[21] mp 197−199 °C. The spectroscopic data were consistent with the structure of product.

1-Trityl-4-methoxycarbonylimidazole 2b. This compound was prepared in a way similar to that described above, 98% yield;[22] mp 144−146 °C, lit.[22] 145−146 °C. The spectroscopic data were consistent with the structure of product.

1-Methyl-3-trityl-5-formylimidazole Triflate 3a. To a 5 L three-necked round-bottomed flask equipped with a mechanical stirrer, a nitrogen bubbler, and an addition funnel was added **2a** (355.6 g, 1.05 mol) and methylene chloride (1.25 L). The mixture was stirred at room temperature to give a solution. A solution of methyl triflate (250.0 g, 1,52 mol) in methylene chloride (250 mL) was added dropwise over 5 h. After the addition was complete, the reaction mixture was stirred at room temperature for 20 h. The volume of the reaction mixture was reduced to about 750 mL. Hexane (1.0 L) was added. The slurry was stirred for 30 min and filtered. The cake was washed with hexane (3 × 500 mL) and suction-dried briefly to give 1-methyl-3-trityl-5-formylimidazole triflate, 520.0 g, 99%. This product is not stable on standing and was used as is without further purification.

1-Methyl-3-trityl-5-methoxycarbonylimidazole Triflate 3b. This compound was prepared in a way similar to that described above, 97% yield. This product is not stable on standing and was used as is without further purification.

1-Methyl-5-formylimidazole Triflic Acid Salt 4a. To a 3 L three-necked round-bottomed flask equipped with a mechanical stirrer and a nitrogen bubbler was added **3a** (520.0 g, 1.03 mol), water (400 mL), and acetone (800 mL). The mixture was stirred at room temperature for 4 h. The reaction mixture was filtered to remove trityl alcohol, and the cake was washed with water (2 × 100 mL). The filtrate was concentrated under reduced pressure to remove acetone. The resulting slurry was filtered again to remove trityl alcohol and the cake washed with water (2 × 50 mL). The filtrate was lyophilized to give 1-methyl-5-formylimidazole triflic acid salt **4a**, 255.7 g, 95%; mp 170−172 °C. ^{1}H NMR (DMSO-d_6) δ 4.03 (s, 3H), 8.53 (s, 1H), 9.21 (s, 1H), 9.88 (s, 1H). Calcd for $C_6H_7F_3N_2O_4S$: C 27.70, H, 2.71, N, 10.77; found: C 27.72, H, 2.68, N, 10.67.

1-Methyl-5-methoxycarbonylimidazole Triflic Acid Salt 4b. This compound was prepared in a way similar to that described above, 91% yield; mp 105−106 °C. ^{1}H NMR (DMSO-d_6) δ 3.88 (S, 3H), 3.99 (s, 3H), 6.7 (br s, 1H), 8.36 (s, 1H), 9.13 (s, 1H). Calcd for $C_7H_9F_3N_2O_5S$: C 28.97, H, 3.13, N, 9.65; found: C 28.82, H, 3.14, N, 9.47.

(22) Compound **2b** was previously prepared in 50% yield by reaction of **1b** with trityl bromide in methylene chloride, see: Belgodere, E.; Bossio, R.; Parrini, V.; Pepino, R. *Arzneim. Forsch.* **1980**, *30*, 1051.

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