

A Highly Regioselective Preparation of 4-Chloromethyl-5-methyl-2-aryl-1,3-oxazoles

George T. Lee,^a Xinglong Jiang,^a T. R. Vedananda,^b Kapa Prasad,^{a,*} Oljan Repič^a

^a Process R&D, Chemical and Analytical Development, Novartis Institute for Biomedical Research, One Health Plaza, East Hanover, NJ 07936, USA

Fax: (+1)-973-781-2188, Prasad.kapa@pharma.novartis.com

^b Novartis Institutes for Biomedical Research, Inc., 400 Technology Square, Cambridge, MA 02139, USA

Received: May 12, 2004 · Accepted: August 23, 2004

Abstract: A facile highly regioselective process is described for the formation of 4-chloromethyl-1,3-oxazoles from 1,3-oxazole *N*-oxide/HCl salts. An explanation is presented for the high regioselectivity in deoxygenation-chlorination using POCl₃ with HCl salts compared to the corresponding free *N*-oxides. The

method is quite general and the products are isolated by direct precipitation in all cases studied.

Keywords: 4-chloromethyl-1,3-oxazoles; deoxygenation-chlorination; *N*-oxide/HCl salts; POCl₃

Introduction

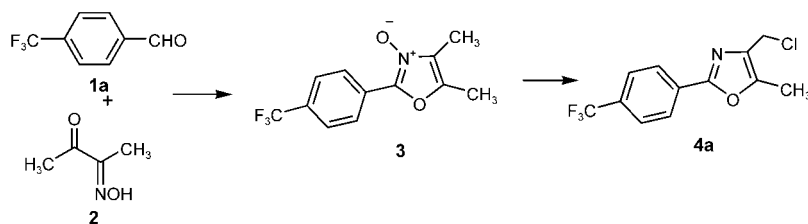
Peroxisome proliferator activated receptors (PPAR) are a highly conserved set of ligand activated transcription factors in the nuclear hormone receptor superfamily. Three distinct PPAR subtypes, PPAR α , PPAR γ and PPAR δ , have been identified in most mammalian species. These receptors function as sensors of metabolic state, responding to metabolites and dietary components, and triggering the required metabolic adaptation at the level of the cell, the organ and the organism. We embarked on a program^[1] to develop agonists of PPARs that necessitated the development of a short, versatile and regioselective synthesis of suitably substituted 4-chloromethyloxazoles as alkylating agent. In the literature^[2] they are typically made from condensation of aldehyde **1a** with 2,3-butanedione monoxime **2** with the intermediacy of compound **3**. The second step in this process is a deoxygenation-chlorination step as shown in Scheme 1.

The reported yields^[3] of 65% for **3** and 30% (after chromatographic purification) for **4a** are rather low,

and we needed multi-kilo quantities of **4a** for making different active pharmaceutical ingredients. In spite of the low yield, we embarked on optimizing this approach as we believed that this is the most direct way to the targeted compounds. These investigations led to a highly regioselective and practical preparation of the title compounds, and these results are reported in this publication.

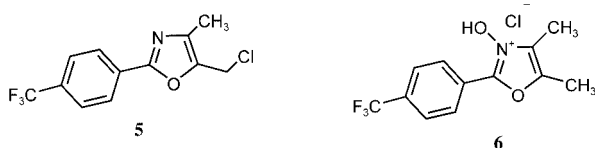
Results and Discussion

At the outset, compound **3** was prepared by the condensation of **1** with **2** in acetic acid/HCl as reported in the literature.^[4] The free *N*-oxide **3** was isolated after quenching with ammonia and extractive work-up with dichloromethane. Compound **3** on deoxygenation-chlorination with POCl₃ in refluxing chloroform yielded a mixture of **4a** and its regioisomer **5** in the ratio of 65:35 (Table, entry 1).^[5] The desired **4** was isolated by chromatographic purification in 43% yield. The structures of **4** and **5** were confirmed by NMR and by a single-crystal X-ray



Scheme 1. Preparation of 4-chloromethyloxazole.

of the drug substance produced from **4a**. As the selectivity obtained is not practical, we investigated the effect of solvent and other additives in the deoxygenation-chlorination step. By switching to acetonitrile as the solvent, the selectivity remained unchanged (Table 1, entry 2). Interestingly by adding tetrabutylammonium chloride to the reaction medium, the selectivity dramatically shifted to >99% (Table 1, entry 3). Assuming the shift in selectivity was attributable to the presence of excess chloride ion, we studied the use of the *N*-oxide HCl salt **6a**, which is the initial intermediate in the condensation of **1a** and **2** under these deoxygenation-chlorination conditions.



Subjecting salt **6a** to the deoxygenation-chlorination step with POCl₃ in acetonitrile, we obtained **4a** in higher than 99% regioselectivity. With this high selectivity in hand the desired **4a** was isolated by precipitation with water, followed by filtration, in 85% yield. This simplified the isolation and in turn avoided chromatography.

Application of this method to other substituted benzaldehydes gave the 4-chloromethyloxazoles **4b–d** in a highly regioselective manner, and these results are summarized in the Table 1.

The dramatic change in the regioselectivity in the presence of excess chloride ion was a pleasant surprise, but understandable, if one considers the mechanism for the deoxygenation-chlorination process as shown in the Scheme 2. In principle, there are two possible pathways. The desired compound **4** can be formed either by an intramolecular pathway (a) or an intermolecular pathway (b, not shown in Scheme 2), while the undesired **5** can form only via pathway (b). In the presence of excess chloride ion (entries 3 and 4) the pathway (a) incorporating an intramolecular step predominates thus explaining the increase in regioselectivity.

Conclusion

A facile process for a highly regioselective formation of 4-chloromethyl-1,3-oxazoles is described starting from readily available raw materials. An explanation for observed high regioselectivity in the presence of excess chloride ion is proposed. The method is quite general and the products are isolated by direct precipitation in all cases studied.

Experimental Section

General Methods

All chemical were obtained from commercial suppliers and used without further purification. ¹H and

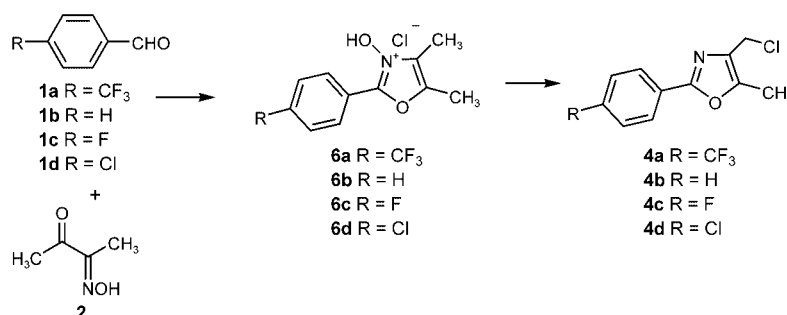
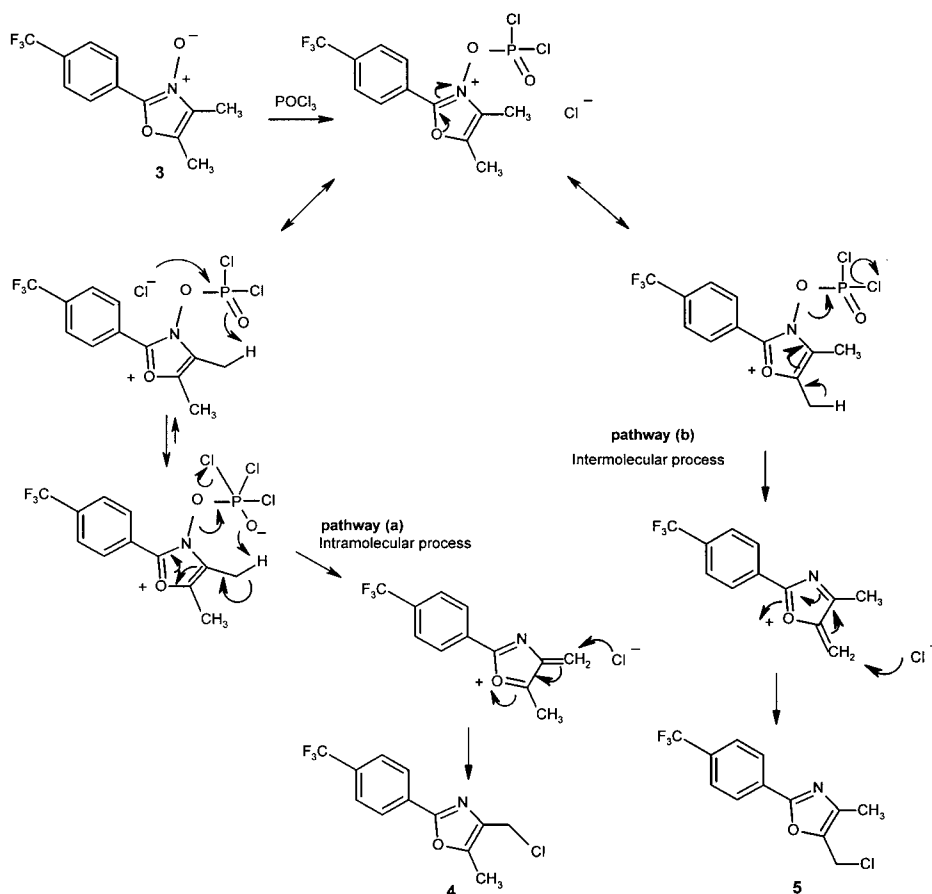


Table 1. Preparation of 4-chloromethyloxazoles.

Entry	Compound used	Deoxygenation-chlorinating agent/solvent/additive	Ratio ^[a] of 4 : 5	Product isolated (yield)
1	3	POCl ₃ (1.1 equivs.)/CHCl ₃	65:35	4a (43% after chromatography)
2	3	POCl ₃ (1.86 equivs.)/CH ₃ CN	65:35	Not isolated
3	3	POCl ₃ (1.86 equivs.), CH ₃ CN/Bu ₄ N ⁺ Cl [−] (2 equivs.)	>99/1	Not isolated
4	6a	POCl ₃ (1.86 equivs.)/CH ₃ CN	>99/1	4a (85%)
5	6b	POCl ₃ (1.86 equivs.)/CH ₃ CN	>99/1	4b (86%)
6	6c	POCl ₃ (1.86 equivs.)/CH ₃ CN	>99/1	4c (83%)
7	6d	POCl ₃ (1.86 equivs.)/CH ₃ CN	>99/1	4d (90%)

^[a] Ratio of **4**:**5** is based on ¹H NMR of crude product mixture.



Scheme 2. Mechanism for the deoxygenation-chlorination process.

^{13}C NMR spectra were recorded at 500 or 300 and at 125 and 75 MHz respectively, in CDCl_3 unless otherwise mentioned. Proton and carbon chemical shifts are expressed in ppm relative to internal tetramethylsilane; coupling constants (J) are expressed in Hertz. Melting points were measured on a Büchi 535 melting point apparatus.

4,5-Dimethyl-2-(4-trifluoromethylphenyl)-oxazole 3-Oxide Hydrochloride (**6a**)

Into a solution of 4-trifluoromethylbenzaldehyde (**1**, 400 g, 2.273 mol) and 2,3-butanedione monoxime (**2**, 212 g, 2.055 mol) in 1 L of acetic acid at $2-5^\circ\text{C}$, hydrogen chloride gas (250 g, 6.781 mol) was slowly bubbled at $2-5^\circ\text{C}$ over 1 h. The pale-yellow homogeneous mixture was stirred at $2-5^\circ\text{C}$ for 1 h. Methyl *t*-butyl ether (3.75 L) was slowly added into the mixture at $5 \rightarrow 25^\circ\text{C}$ over 30 min. The resulting white suspension was stirred at 22°C for 30 min. The contents were cooled to 10°C and filtered. The filter cake was washed with 2×250 mL methyl *t*-butyl ether. The filter cake was dried under vacuum at 55°C overnight to give **3d** as a white solid; yield: 550 g (91%); mp $182-184^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3): $\delta = 8.48-8.51$ (2H, d, $J = 0.03$ Hz), $7.85-7.88$ (2H, d, $J = 0.03$ Hz), 2.53 (3H, s), 2.48 (3H, s); ^{13}C NMR (300 MHz, CDCl_3): $\delta =$

145.59, 143.30, 132.25, 131.82, 131.38, 130.95, 130.22, 129.54, 126.60, 126.13, 126.08, 125.98, 125.93, 125.21, 124.96, 122.32, 118.71, 11.47, 6.61; MS (ESI): $m/z = 258$ (M^+); anal. calcd. for $\text{C}_{12}\text{H}_{11}\text{ClF}_3\text{NO}_2$: C 49.08, H 3.78, N 4.77, Cl 12.07; found: C 49.04, H 3.72, N 4.66, Cl 12.17.

Compounds **6b**, **6c** and **6d** were prepared as above starting from the corresponding benzaldehydes, and their physical properties and spectral data are as follows.

4,5-Dimethyl-2-phenyloxazole 3-oxide hydrochloride (6b): Yield: 94%; white solid; mp $179-181^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3): $\delta = 8.32-8.35$ (2H, d, $J = 0.03$ Hz), $7.67-7.70$ (1H, t, $J = 0.03$ Hz), $7.58-7.63$ (2H, t, $J = 0.03$ Hz), 2.49 (3H, s), 2.47 (3H, s); ^{13}C NMR (300 MHz, CDCl_3): $\delta = 154.32$, 145.13 , 135.02 , 129.98 , 128.71 , 128.50 , 119.77 , 11.39 , 7.56 ; MS (ESI): $m/z = 190$ (M^+); anal. calcd. for $\text{C}_{11}\text{H}_{12}\text{ClNO}_2$: C 58.54, H 5.36, N 6.21; found: C 58.46, H 5.54, N 6.26, Cl 15.95.

4,5-Dimethyl-2-(4-fluorophenyl)-oxazole 3-oxide hydrochloride (6c): Yield: 91%; white solid; mp $181-182^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3): $\delta = 8.37-8.42$ (2H, q, $J = 0.01$ Hz), $7.72-7.33$ (2H, t, $J = 0.03$ Hz), 2.49 (3H, s), 2.46 (3H, s); ^{13}C NMR (300 MHz, CDCl_3): $\delta = 168.25$, 164.81 , 153.47 , 145.12 , 131.61 , 131.48 , 128.45 , 117.79 , 117.49 , 116.22 , 116.18 , 11.38 , 7.51 ; MS (ESI): $m/z = 208$ (M^+); anal. calcd. for $\text{C}_{11}\text{H}_{11}\text{ClFNO}_2$: C 54.22, H 4.55, N 5.75, Cl 14.55; found: C 54.08, H 4.22, N 5.67, Cl 15.16.

4,5-Dimethyl-2-(4-chlorophenyl)-oxazole 3-oxide hydrochloride (6d): Yield: 84%; white solid; mp $188-190^\circ\text{C}$;

^1H NMR (300 MHz, CDCl_3): δ = 8.28–8.31 (2H, d, J = 0.03 Hz), 7.57–7.60 (2H, d, J = 0.03 Hz), 2.50 (3H, s), 2.45 (3H, s); ^{13}C NMR (300 MHz, CDCl_3): δ = 153.40, 145.51, 141.62, 130.42, 129.88, 128.63, 118.19, 11.42, 7.48; MS (ESI): m/z = 224 (M^+); anal. calcd. for $\text{C}_{11}\text{H}_{11}\text{Cl}_2\text{NO}_2$: C 50.79, H 4.26, N 5.38, Cl 27.26; found: C 51.06, H 3.75, N 5.32, Cl 27.59.

4,5-Dimethyl-2-(4-trifluoromethylphenyl)-oxazole 3-Oxide (3)

Into a suspension of **6a** (30 g, 0.102 mol) in 270 mL of water and 300 mL of methylene chloride, concentrated ammonium hydroxide (30 mL) was slowly added and the mixture stirred at 22 °C for 30 min. The bottom organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give **4d** as a white solid; yield: 25.5 g (97%); mp 147–147.5 °C; ^1H NMR (300 MHz, CDCl_3): δ = 8.56–8.59 (2H, d, J = 0.03 Hz), 7.72–7.75 (2H, d, J = 0.03 Hz), 2.39 (3H, s), 2.22 (3H, s).

4-Chloromethyl-5-methyl-2-(4-trifluoromethylphenyl)-oxazole (4a)

A suspension of 4,5-dimethyl-2-(4-trifluoromethylphenyl)-oxazole 3-oxide hydrochloride (**3d**, 500 g, 1.702 mol) in 4.06 L of acetonitrile was stirred at 22 °C for 30 min and cooled to 10 °C. Phosphorus oxychloride (491 g, 3.17 mol) was added at 15–18 °C over 15 min. The reaction mixture was warmed up slowly to 28 °C by its own exotherm over 1 h and stirred at 28 → 22 °C for 16 h. TLC analysis (5% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$) of the reaction mixture showed no starting material. Water (6.0 L) was slowly added into the mixture at 10 → 25 °C over 1 h. The resulting white suspension was stirred at 22–28 °C for 16 h. The contents were filtered at 22 °C, and the filter cake was washed with 4 × 500 mL water. The solid was dried under vacuum at 60 °C overnight to give **4a** as a white solid; yield: 400 g (85%); mp 97–98 °C; ^1H NMR (300 MHz, CDCl_3): δ = 8.09–8.12 (2H, d, J = 0.03 Hz), 7.68–7.71 (2H, d, J = 0.03 Hz), 4.56 (2H, s), 2.45 (3H, s); ^{13}C NMR (300 MHz, CDCl_3): δ = 159.01, 147.88, 133.88, 132.44, 130.68, 126.77, 126.17, 126.12, 126.07, 37.37, 10.80; MS (ESI): m/z = 276 (MH^+); anal. calcd. for $\text{C}_{12}\text{H}_9\text{ClF}_3\text{NO}$: C 52.29, H 3.29, N 5.08, Cl 12.86; found: C 52.13, H 3.29, N 4.97, Cl 12.85.

Compounds **4b**, **4c**, and **4d** were prepared following the procedure described for **4a**, and their physical and spectroscopic data are as follows.

4-Chloromethyl-5-methyl-2-phenyloxazole (4b): Yield: 86%; white solid; mp 84–85 °C; ^1H NMR (300 MHz, CDCl_3): δ = 7.99–8.02 (2H, m), 7.42–7.45 (3H, m), 4.55 (2H, s), 2.42

(3H, s); ^{13}C NMR (300 MHz, CDCl_3): δ = 160.45, 146.97, 132.28, 130.67, 129.10, 127.59, 126.57, 37.69, 10.78; MS (ESI): m/z = 208 (MH^+); anal. calcd. for $\text{C}_{11}\text{H}_{10}\text{ClNO}$: C 63.62, H 4.85, N 6.75, Cl 17.07; found: C 63.39, H 4.63, N 6.39, Cl 17.17.

4-Chloromethyl-5-methyl-2-(4-fluorophenyl)-oxazole

(4c): Yield: 83%; white solid; mp 77–78 °C; ^1H NMR (300 MHz, CDCl_3): δ = 7.96–8.01 (2H, m), 7.09–7.15 (2H, m), 4.54 (2H, s), 2.41 (3H, s); ^{13}C NMR (300 MHz, CDCl_3): δ = 166.02, 162.69, 159.61, 146.98, 133.30, 128.72, 128.61, 123.98, 123.93, 116.42, 116.13, 37.60, 10.71; MS (ESI): m/z = 226 (MH^+); anal. calcd. for $\text{C}_{11}\text{H}_9\text{ClFNO}$: C 58.55, H 4.02, N 6.21, Cl 15.71; found: C 58.66, H 3.94, N 6.24, Cl 15.66.

4-Chloromethyl-5-methyl-2-(4-chlorophenyl)-oxazole

(5c): Yield: 90%; white solid; mp 97.5–98.5 °C; ^1H NMR (300 MHz, CDCl_3): δ = 7.90–7.95 (2H, m), 7.27–7.42 (2H, m), 4.54 (2H, s), 2.41 (3H, s); ^{13}C NMR (300 MHz, CDCl_3): δ = 159.50, 147.22, 136.72, 133.49, 129.81, 129.42, 129.10, 128.72, 128.10, 127.83, 126.06, 37.54, 10.77; MS (ESI): m/z = 242 (MH^+); anal. calcd. for $\text{C}_{11}\text{H}_9\text{Cl}_2\text{NO}$: C 54.57, H 3.75, N 5.79, Cl 29.29; found: C 54.43, H 3.60, N 5.56, Cl 29.28.

References and Notes

- [1] a) A. T. Bach, P. K. Kapa, G. T. Lee, E. M. Loeser, M. L. Sabio, J. L. Stanton, T. R. Vedananda, *Patent WO 03/043985 A1*, **2003**; *Chem. Abstr.* **2003**, 139, 6767; b) M. Boehringer, D. Hunziker, H. Kuehne, B. M. Loeffler, R. Sarabu, H. P. Wessel, *Patent WO 03/037327 A1*, **2003**; *Chem. Abstr.* **2003**, 138, 368754; c) Y. Momose, T. Maekawa, T. Yamano, M. Kawada, H. Odaka, H. Ikeda, T. Sohma, *J. Med. Chem.* **2002**, 45, 1518–1534 and references cited therein.
- [2] M. S. Malamas, J. Sredy, I. Gunawan, B. Mihan, D. R. Sawicki, L. Seestaller, D. Sullivan, B. R. Flam, *J. Med. Chem.* **2000**, 43, 995–1010 and references cited therein.
- [3] Our work was started with the study of 4-trifluoromethylbenzaldehyde as the starting material mentioned in the above reference. The importance of the effect of substituents on the aromatic ring on the regioselectivity of deoxygenation-chlorination of free *N*-oxides was not addressed by us. However, the corresponding HCl salts are highly selective.
- [4] P. M. Weintraub, *J. Med. Chem.* **1972**, 15, 419–420 and references cited therein.
- [5] To our knowledge, no one has addressed the regioselectivity issue in this type of deoxygenation-chlorinations using oxazole *N*-oxides.