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Efficient Synthesis of 2-(Trifluoromethyl)nicotinic Acid Derivatives from Simple Fluorinated Precursors

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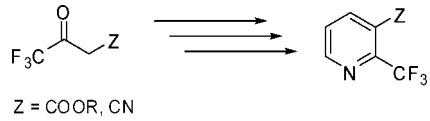
ABSTRACT



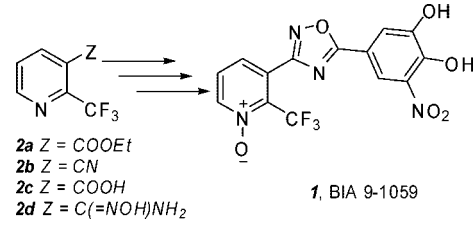
Novel routes to 2-trifluoromethyl-nicotinic acid derivatives have been developed involving synthesis of the pyridine ring. These pyridyl compounds serve as key intermediates in the manufacture of the recently discovered COMT inhibitor, 3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-2-(trifluoromethyl)pyridine 1-oxide.

Inhibitors of the enzyme catechol-*O*-methyltransferase (COMT) are used in the treatment of central and peripheral nervous system disorders such as Parkinson′s Disease (PD). COMT is responsible for the inactivation of endogenous catechol neurotransmitters and xenobiotic catechols used in PD therapy such as L-DOPA.[1]

Recently, our group has discovered a series of novel heterocycle-based nitrocatechols as long-acting, orally active COMT inhibitors. It was found that certain oxadiazoles substituted with a (trifluoromethyl)pyridine residue display greatly increased activity and selectivity against the COMT enzyme.[2] For example, BIA 9-1059 [3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-2-(trifluoromethyl)-pyridine 1-oxide] **1** was identified as a very potent and peripherally selective COMT inhibitor that may possess therapeutic advantages over established COMT inhibitors such as entacapone and tolcapone.

To support preclinical pharmacology and toxicology studies, we were faced with an urgent requirement for kilogram quantities of **1**. 1,2,4- Oxadiazoles are usually prepared by condensation of amidoximes with activated carboxylic acids.[3] In the case of **1**, the required amidoxime is represented by structure **2d** (Scheme 1). Amidoxime **2d** can be easily obtained from the nitrile **2b** by reaction with hydroxylamine, and **2b** in turn can be obtained from **2a** or **2c** by conversion to the corresponding carboxamide followed by dehydration.

Scheme 1



(1) (a) Axelrod, J.; Senoh, S.; Witkop, B. *J. Biol. Chem.* **1958**, *233*, 697. (b) Guldberg, H.; Marsden, C. *Pharmacol. Rev.* **1975**, *27*, 135.

(2) Learmonth, D.; Kiss, L.; Leal Palma, P.; Dos Santos Ferreira, H.; Araújo Soares Da Silva, P. WO 2007013830A1, 2007. *Chem. Abstr.* **2007**, *146*, 206312.

(3) (a) Meyer, E.; Joussef, A.; Gallardo, H. *Synthesis* **2003**, *6*, 899. (b) Pipik, B.; Ho, G.; Williams, M.; Conlon, D. *Synth. Commun.* **2004**, *34*, 1863.

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Although trifluoromethylated nicotinic acids or their derivatives have been prepared by various methods,[4] very few approaches to the preparation of **2a**−**c** have been described in the literature.[5] The existing syntheses of compounds **2a**−**c** are based on very expensive starting materials that are neither readily available from commercial sources or easily prepared. Furthermore, the previously described methods would not be appropriate for larger-scale operations, due to the employment of very low temperatures, long reaction times, dispensing of air-sensitive alkyllithium reagents, and quenching with solid carbon dioxide. Thus, we directed our efforts to designing more convenient and practical synthetic methods to prepare 2-(trifluoromethyl)nicotinic acid derivatives **2a**−**c**.

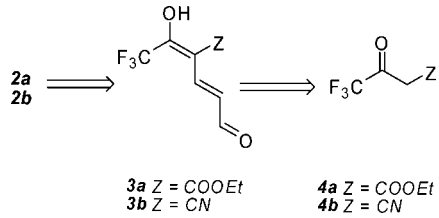


Figure 1. Retrosynthetic analysis of compounds **2a** and **2b**.

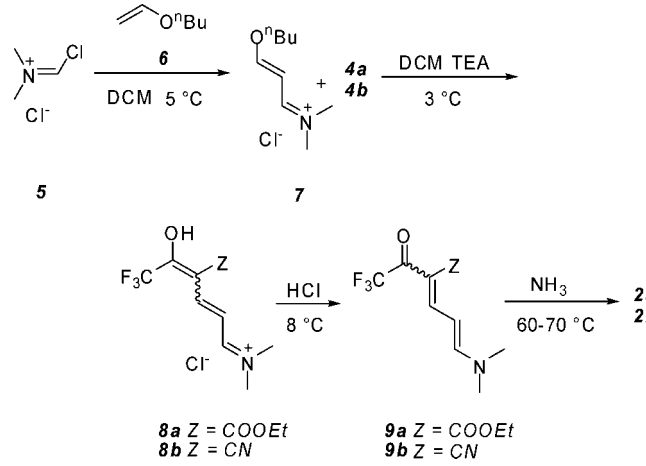
Our retrosynthetic analysis is presented in Figure 1. Ethyl 4,4,4-trifluoro-acetoacetate **4a** seemed to us to represent a particularly convenient raw material, as it is relatively cheap and abundantly available in bulk. We envisioned that the pyridyl ester **2a** could be easily accessed via a short, two-step process involving a Vilsmeier-type reaction of **4a** with an alkyl vinyl ether followed by cyclization of the resulting dienyl aldehyde **3a** with a source of ammonia.

Vilsmeier reactions of ketones[6] and β-ketoesters[7] have been well-known in the literature for decades. However, formylation reactions using vinylogous iminium salts are usually limited to more reactive substrates,[8] and a powerful activating group is normally required to achieve a successful vinylogous Vilsmeier reaction.

The Vilsmeier reagent **5** (freshly prepared by the reaction of DMF with oxalyl chloride) was treated with 1.3 equiv of *n*-butyl-vinylether **6** in dichloromethane to give the vinylogous butoxyiminium chloride **7**, which was then reacted directly without isolation with the β-ketoester **4a** in the presence of triethylamine, with the temperature maintained below 3 °C. The resulting adduct **8a** was then quenched with 1 N aqueous HCl solution. Somewhat surprisingly, hydrolysis of iminium salt **8a** did not lead to the formation of the expected terminal aldehyde **3a**. Instead, the yellowish-orange dimethylamino compound **9a** was obtained as a mixture of (2*E*,4*E*) and (2*Z*,4*E*) geometric isomers in a fairly good yield of 56%. The stereochemistry of both isomers was proven by NOESY NMR experiments.[9]

The versatile intermediate **9a** was smoothly converted to the pyridyl ester **2a** in excellent yield of 90% upon heating at 70 °C in the presence of excess aqueous ammonium hydroxide in ethanol (Scheme 2).

Scheme 2. Vinylogous Vilsmeier reaction of Ethyl 4,4,4-Trifluoro-acetoacetate and 2-(Trifluoroacetyl)-acetonitrile



Subsequently, we modified this procedure to directly obtain the nitrile **2b**. Analogous Vilsmeier-type vinylogous formylation of 2-(trifluoroacetyl)-acetonitrile[10] **4b** gave the corresponding vinyl nitrile **9b**, which was isolated as bright-yellow crystals in 51% yield. Only one stereoisomer was observed by NMR[9] when the cyano staring material **4b** was used. The subsequent cyclization reaction was effected in a mixture of methanol and aqueous ammonium hydroxide at 60 °C, leading to formation of the required nitrile **2b** in 65% yield.

Although the obtained yields are slightly lower, nitrile **2b** can thereafter be directly converted to the amidoxime **2d** in one step by reaction with hydroxylamine.

Finally, an alternative route to the key intermediates **9a** and **9b** was investigated as outlined in Scheme 3. These

(4) (a) Mïller, P. European Patent EP 1340747, 2003. *Chem. Abstr.* **2003**, *139*, 214341. (b) Cooke, J. WB.; Coleman, M. J.; Caine, D. M.; Jenkins, K. P. *Tetrahedron Lett.* **1998**, *39*, 7965. (c) Cocco, M. T.; Congiu, C.; Onnis, V. *J. Het. Chem.* **1995**, 543. (d) Katsuyama, I.; Ogawa, S.; Nakamura, H.; Yamaguchi, Y.; Funabiki, K.; Matsui, M.; Muramatsu, H.; Shibata, K. *Heterocycles* **1998**, *48*, 779. (e) Katsuyama, I.; Ogawa, S.; Yamaguchi, Y.; Funabiki, K.; Matsui, M.; Muramatsu, H.; Shibata, K. *Synthesis* **1997**, *11*, 1321. (f) Goble, S. D.; Pasternak, A.; Mills, S. G.; Zhou, C.; Yang, L. WO 2004082616A2, 2004. *Chem. Abstr.* **2004**, *141*, 314341.

(5) (a) Schlosser, M.; Marull, M. *Eur. J. Org. Chem.* **2003**, *8*, 1569. (b) Cottet, F.; Marull, M.; Lefebvre, O.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, *8*, 1559. (c) Loska, R.; Majcher, M.; Makosza, M. *J. Org. Chem.* **2007**, *72*, 5574. (d) Shigehara, I.; Makajima, T.; Nishide, H.; Tanimura, T. Japanese Patent 03081263, 1989. *Chem. Abstr.* **1989**, *115*, 183112. (e) Caroll, W.; Perez-Medrano, A.; Florjancic, A.; Nelson, D.; Peddi, S.; Li, T.; Bunnelle, E.; Hirst, G.; Li, B. US Patent 0052374, 2006. *Chem. Abstr.* **2006**, *144*, 292764. (f) Roy, P. J.; Dufresne, C.; Lachance, N.; Leclere, J. P.; Boisvert, M.; Wang, Z.; Leblanc, Y. *Synthesis* **2005**, *16*, 2751.

(6) (a) Žemlička, J.; Arnold, Z. *Collect. Czech. Chem. Commun.* **1961**, *26*, 2852. (b) Marson, C. *Tetrahedron* **1992**, *48*, 3659.

(7) Gagan, J.; Lane, A.; Lloyd, D. *J. Chem. Soc.* **1970**, *C*, 2484.

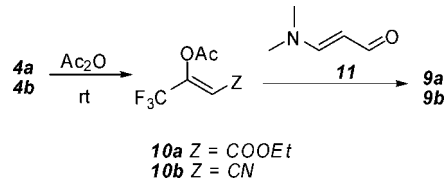
(8) Jutz, C. *Chem. Ber.* **1958**, *91*, 850.

(9) See Supporting Information.

(10) Sumimoto Shinzaburo, A.; Ichiro Ishizuka, T.; Hiroyuki Kai, K.; Shiro Ueda, O.; Akira Takase, K. European Patent EP 220947, 1987. *Chem. Abstr.* **1987**, *107*, 134298.

(11) (a) Schröder, L. US Patent 4987232, 1991. *Chem. Abstr.* **1990**, *113*, 191170. (b) Schröder, L. European Patent EP 462639, 1991. *Chem. Abstr.* **1992**, *116*, 128679.

Scheme 3. Aldol Condensation of Trifluoromethylenolacetates Derivatives with 3-Dimethylaminoacrolein



compounds **9a** and **9b** can be considered to be formally aldol type condensed products of the trifluoromethyl-β-ketoester **4a** and -β-ketonitrile **4b** with 3-dimethylaminoacrolein **11**. Thus, we next focused on the aldol reaction to develop an operationally simpler, more easily scalable procedure for preparation of **9a** and **9b**. Initial attempts were performed reacting the β-ketoester **4a** and β-ketonitrile **4b** directly with aldehyde **11** under base-catalyzed conditions in various organic solvents. Although this malonate-type condensation has been reported to prepare similar pentadienoic acid derivatives,[11] unfortunately only trace amounts of the desired products **9a** and **9b** were observed.

Gratifyingly however, the in situ prepared enolacetates **10a** and **10b** of the fluorinated reactants **4a** and **4b** rapidly underwent condensation with aldehyde **11** in acetic anhydride at room temperature in the absence of any base to furnish the required pentadienoic acid derivatives **9a** and **9b** in fair to good yield (**9a**: 83%, **9b**: 47%) Both compounds **9a** and **9b** gave the same ratio of isomers as was found in the case of the vinylogous Vilsmeier reaction. Indeed this second approach would be even more suitable for scale up due to operational simplicity and avoidance of strongly acidic conditions.

In conclusion, we have developed novel and convenient two-step synthetic routes to 2-(trifluoromethyl)nicotinic acid and nitrile derivatives **2a** and **2b**, respectively, that involve preparation of versatile pentadienoic acid intermediates **9a** and **9b** in moderate to good yields using vinylogous Vilsmeier reaction followed by aromatization with ammonia. In addition, a simplified approach to **9a** and **9b** has been developed that involves an aldol condensation of the enolacetates of β-ketoester **4a** and β-ketonitrile **4b** with aldehyde **11**. Both of these methods have proven to be superior to literature methods for preparation of 2-(trifluoromethyl)nicotinic acid derivatives in terms of milder conditions, ease of production, commercial availability, and cost of the starting materials.

Further work is currently in progress to scale the reactions up and extend the scope of the method to include other substituted pyridines.

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Supporting Information Available: Detailed experimental procedures, characterization data, copies of ^{1}H, ^{13}C, NOESY NMR, IR, HRMS spectra, and elemental analysis for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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