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A Suzuki Coupling Approach to Trifluoromethyl Derivative of Targretin (LGD 1069)

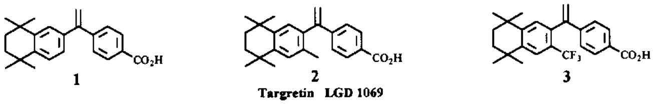
Feng-Ling Qing* and Junfa Fan

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032, P. R. China

Abstract The palladium-catalyzed Suzuki coupling reaction *o*-trifluoromethylated arylboronic acid 4 and vinyl triflate 5 provided the trifluoromethyl derivative of Targretin (LGD1069). © 1997 Elsevier Science Ltd.

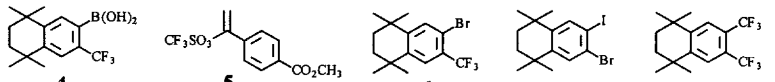
Retinoids, natural and synthetic analogs of vitamin A, play important roles in numerous biological functions including cell proliferation and cell differentiation.[1,2] Recent evidence has shown that retinoids exert their functions through at least two classes of nuclear receptors: RAR(α,β,γ) and RXR(α,β,γ). [3] Current research efforts in this field have focused on searching for receptor-specific ligands in order to elucidate the biological functions of each receptors.[4] Among them, introduction of a 3-methyl substituent to a weakly active RXRs compound **1**(Figure1) resulted in Targretin (LGD 1069 **2**) which selectively bind with high affinity to the RXRs and was currently in clinical trials for the treatment of cancer.[5] From this it may be safely concluded that the RXR selectivity and potency of retinoids were closely related to the nature of the C-3 substituent attached to the tetrahydronaphthyl moiety. Because of its high lipophilicity, powerful electron-withdrawing and small size, the trifluoromethyl group is an increasingly popular aromatic substituent in compounds synthesized for improving their biological activity.[6] From this perspective, we became interested in the incorporation of 3-trifluoromethyl substituent to retinoid **1**. The synthesis of compound **3** is described hereafter.

Figure 1



Since the Palladium catalyzed cross-coupling of boronic acid with an organic electrophile (Suzuki reaction)[7] was one of the best ways of constructing a C-C bond under mild conditions with high functional group tolerance in both coupling partners, it was of interest to apply the Suzuki reaction to the synthesis of **3**. Disconnection of aryl-double bond divides the target molecular **3** into two precursors *o*-trifluoromethylated arylboronic acid **4** and vinyl triflate **5** (Figure 2). The vinyl trifate **5** was easily prepared by treatment of methyl 4-acetyl benzoate with trifluoromethanesulfonic anhydride in the presence of anhydrous sodium carbonate.[8] Although many arylboronic acids have been commercially available or are easily prepared by standard procedures, the trifluoromethylated arylboronic acids are infrequently seen. Thus, we turned our attention to prepare the key precursor *o*-trifluoromethylated arylboronic acid **4**. Several years ago, Morgon et al described that *p*-trifluoromethyl-phenylboronic acid was obtained from 4-bromo-α,α,α-trifluorotoluene by treatment of the corresponding lithium compound with triethyl borate at low temperature.[9] Referring to this procedure, compound **6** (Figure 2) was chosen as a precursor for the preparation of arylboronic acid **4**. Attempted reaction of 2-bromo-α,α,α-trifluorotoluene with 2,5-dichloro-2,5-dimethylhexane under Friedel-Crafts conditions ($AlCl_3/CH_2Cl_2$) for the synthesis of **6** failed because of the powerful electron-withdrawing of trifluoromethyl group. Selective trifluoromethylation of **7** was also attempted in the hope of producing **6** , but none of the product **6** was obtained under various trifluoromethylation conditions ($FSO_2CF_2CO_2Me/CuI$, [10] CF_3SiMe_3/CuI,[11] $ClCF_2CO_2CH_3/KF/CuI$[12]). Because of the presence of trifluoromethyl group adjacent to bromo substituent in compound **6**, the carbon-bromine bond was activated and the further trifluoromathylation of **6** was easily occurred to produce **8**. In these circumstances **6** and **8** could not be separated by column chromatography or by recrystalization.

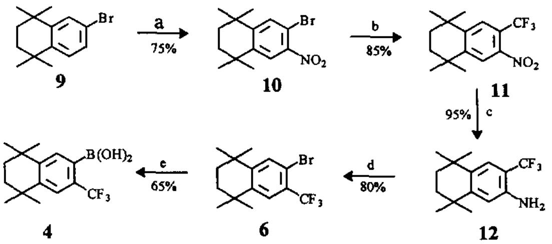
Figure 2



4 **5** **6** **7** **8**

Given the difficulties stated above, an alternative route was investigated (Scheme 1). Bromide **9**, prepared by reaction of bromobenzene with 2,5-dichloro-2,5-dimethylhexane in the presence of aluminum chloride , was used as the starting material for the synthesis of **6**. Nitration of **9** at 60°C gave a single nitro product **10** in 75% yield. Reaction of **10** with $FSO_2CF_2CO_2Me$ and CuI in DMF/HMPA (modified Chen's procedure [10]) afforded the trifluoromethylation product **11** in 85% yield. Reduction of **11** with Fe/HCl to the amine **12** , followed by reaction with $NaNO_2/H_2SO_4$ and KBr/CuBr produced the desired compound **6**. Treatment of **6** with *tert*-butyl lithium, and then $B(O\text{-}i\text{Pr})_3$ at -78°C gave the trifluoromethylated arylboronic acid **4** in 65% yield.

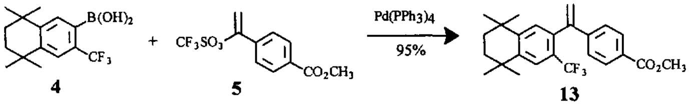
Scheme 1



Reagents and conditions: a. conc. HNO_3,conc H_2SO_4, 60°C; b. $FSO_2CF_2CO_2Me$, CuI, DMF, HMPA, 70°C; c. Fe/HCl, CH_3OH, reflux; d. $NaNO_2$, H_2SO_4,, KBr, CuBr, 60°C; e. *t*-BuLi, THF, -78°C, then B(O*i*Pr)$_3$, -78°C, aqueous NH_4Cl, 0°C.

With *o*-trifluoromethylated arylboronic acid **4** and vinyl triflate **5** available, palladium-catalyzed Suzuki coupling reaction was then performed (Scheme 2). To the best of our knowledge, no example exists in the literature of the use of sterically hindered, trifluoromethylated aryl boronic acid or vinyl triflate **5** in a palladium catalyzed coupling. We were delighted to observe the cross-coupling of vinyl triflate **5** with boronic acid **4** did occurr to give **13**. Thus a mixture of vinyl triflate **5** , 1.3 equiv of boronic acid **4**, 10 mol% of $Pd(PPh_3)_4$ and 3 equiv of potassium triphosphate trihydrate in dioxane [13] was refluxed for 6 h under nitrogen. The desired coupled product **13** [14] was isolated by column chromatography in 95% yield. The structure of **13** was confirmed by spectral of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and MS. Treatment of **13** with aqueous KOH in refluxing MeOH, followed by acidification, yielded the target molecular **3**. [15]

Scheme 2



In conclusion, we have developed an efficient method for the preparation of trifluoromethylated aryl boronic acid **4**. The palladium-catalyzed Suzuki coupling reaction of **4** with vinyl triflate **5** provided **13**, precursor for the trifluoromethyl derivative of Targretin (LGD 1069).

Acknowledgements

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14. Selected date for Compound **13**: m. p. 124-126°C. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26 (s, 6H), 1.33 (s, 6H), 1.72 (s, 4H), 3.90 (s, 3H), 5.34 (s, 1H), 5.94 (s, 1H), 7.17 (s, 1H), 7.61 (s, 1H), 7.31 (A_2B_2 J=8.4Hz, 2H), 7.95 (A_2B_2 J=8.4Hz, 2H)ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.8, 30.4, 31.6, 31.7, 34.5, 34.9, 52.0, 117.9, 124.7, 126.2, 126.6, 127.7, 129.2, 129.6, 129.9, 130.2, 136.5, 144.8, 144.9, 146.3, 148.8, 166.9. ^{19}F NMR ($CDCl_3$, CF_3CO_2H as internal standard): δ -20.3 (s) ppm. MS *m/z* 416 (M^+, 31), 401 (100), 359 (18), 345 (19), 327 (18), 161 (81), 43 (23). Anal. Calcd for $C_{25}H_{27}F_3O_2$: C, 72.09; H, 6.54, Found: C, 71.69; H, 6.95.

15. Selected date for Compound **3**: m. p. 225-227°C. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.20 (s, 6H), 1.27 (s, 6H), 1.67(s, 4H), 5.30 (s, 1H), 5.89 (s, 1H), 7.10 (s, 1H), 7.54 (s, 1H), 7.28 (A_2B_2 J=8.3Hz, 2H), 7.96 (A_2B_2 J=8.3Hz, 2H)ppm. ^{19}F NMR ($CDCl_3$, CF_3CO_2H as internal standard): δ -21.0 (s) ppm. MS *m/z* 402 (M^+, 26), 388 (23), 387 (91), 325 (23), 147 (100), 57 (39), 55 (22), 43(37).

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