Synthesis of Formylchromone Derivatives; Inactivators of Protein Tyrosine Phosphatase 1B

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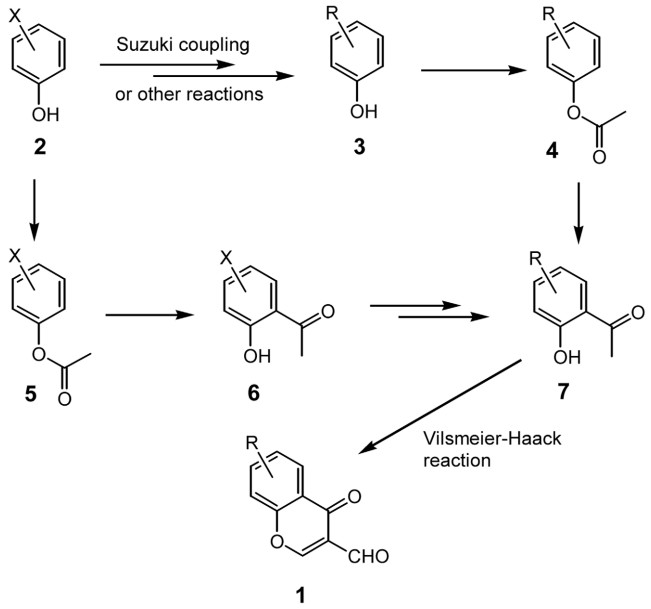
Received December 30, 2004

Key Words : Formylchromone, Protein tyrosine phosphatase, PTP1B, Inactivator

Protein tyrosine phosphatases (PTPases) represent a family of enzymes that hydrolyze phosphate moiety from phosphotyrosine residues of cellular proteins[1] and they constitute essential components for the dynamic and precise control of the phosphorylation level of signaling proteins.[2,3] Because of the importance of tyrosine phosphorylation in signal transduction, PTPases have emerged as potential targets for the treatment of a diverse of human diseases.[4-6] For example, inhibition of protein tyrosine phosphatase 1B (PTP1B) might be a strategy to compensate the defective insulin sensitivity commonly observed in the patients of type II diabetes.[7,8] In an effort to find potent and specific inhibitors of PTPases, we found that 3-formylchromone (4-oxo-4*H*-[1]-benzopyran-3-carboxaldehyde, 3-formyl-4-benzopyrone) derivatives **1** inactivate PTPases. Some of them were potent and selective against PTP1B and this result was reported recently.[9,10] Hereby, we report the synthesis of the formylchromone derivatives.

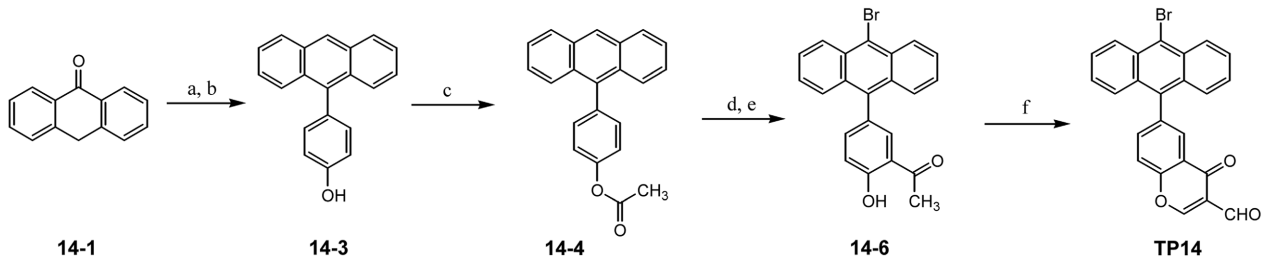
One of the synthetic strategy involves the preparation of appropriately substituted phenol derivatives **3** followed by Friedel-Crafts acylation to obtain 2-acetylphenol derivatives **7** (top line of Scheme 1). Alternatively, **7** could be obtained by acetylation prior to the introduction of the substituent R (second line of Scheme 1). The core structure was then formed by Vilsmeier-Haack reaction in which 2-acetylphenol moiety in **7** was converted to 3-formylchromone structure in the presence of $POCl_3$ and DMF (Scheme 1).[11-13] Other routes have been precedented for the construction of 3-formylchromone, but the most convenient was the method via Vilsmeier-Haack reaction.[14]

Synthesis of the PTPase inactivators are summarized in Schemes 2-7. For the synthesis of **TP14**, the anthracene

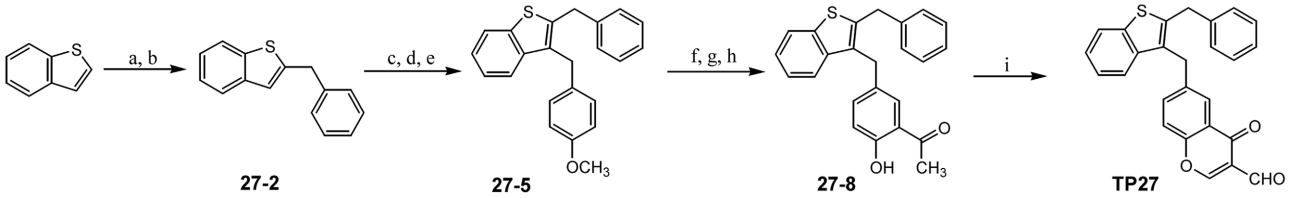


Scheme 1. Synthetic strategy.

structure was constructed by reaction of anthrone with anisyl magnesium bromide followed by concomitant aromatization of the ring.[15] Acetylation at the *ortho*-position of the hydroxy group was accomplished by converting the phenolic compound **14-3** into acetate **14-4** followed by heating with $AlCl_3$. Friedel-Crafts acylation of phenol derivatives under usual reaction condition (Ac_2O or AcCl, $AlCl_3$) complicated the reaction by acetylation at unwanted position. Vilsmeier-Haack reaction of the 2-acetylphenol derivative **14-6** completed the synthesis.



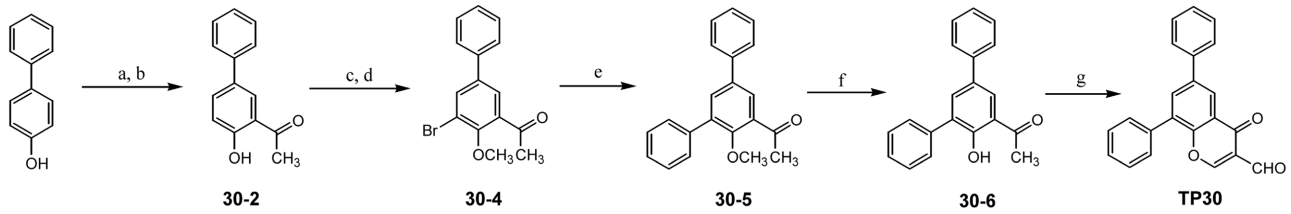
Scheme 2. Reagents and conditions: (a) $CH_3OC_6H_5MgBr$, benzene, 10 °C → 70 °C, 69%; (b) BBr_3, CH_2Cl_2, 96%; (c) $(CH_3CO)_2O$, pyridine, CH_2Cl_2, 75%; (d) $AlCl_3$, 1,2-Dichlorobenzene, 100 °C; 33%; (e) Br_2, Et_2O, 98%; (f) $POCl_3$, DMF, –20°C → 50 °C, 3 h, 50%.



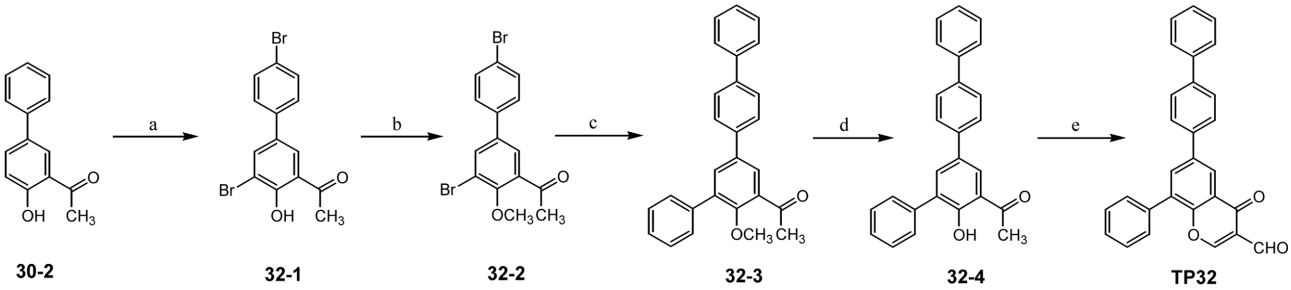
Scheme 3. Reagents and conditions: (a) i) n-BuLi, THF, −78 °C; ii) benzaldehyde, −78 °C → r.t., 91%; (b) $NaBH_4$, Et_2O, then 18 equiv. CF_3COOH, 98%; (c) *p*-Anisoylchloride, CS_2, 89%; (d) $LiAlH_4$, Et_2O, 99%; (e) $NaBH_4$, Et_2O, then 3.7 equiv. CF_3COOH, 99%; (f) BBr_3, CH_2Cl_2, 99%; (g) $(CH_3CO)_2O$, pyridine, CH_2Cl_2, 81%; (h) $AlCl_3$, 1,2-Dichlorobenzene, 95 °C; 33%; (i) $POCl_3$, DMF, −20 °C → 50 °C, 2 h, 67%.

Skeletal construction for **TP27** was accomplished by two consecutive acylation/reduction of benzothiophene (Scheme 3). Regiospecific benzoylation at C-2 of benzothiophene followed by reduction of the carbonyl group afforded **27-2**, which in turn acylated under Friedel-Crafts condition and then reduced to obtain **27-5**.[16-18] The rest of the steps for the synthesis of **TP27** are the same as those for **TP14**; removal of the methyl protecting group, O-acetylation, rearrangement under Friedel-Crafts condition and Vilsmeier-Haack reaction as the last step.

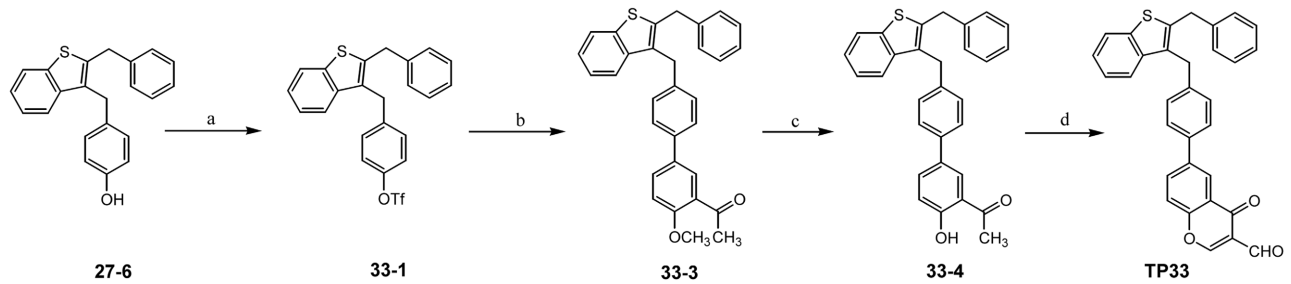
Synthesis of **TP30** and **TP32** involves bromination and Suzuki coupling steps to introduce phenyl substituents (Scheme 4 and 5).[19,20] Pinacol ester of phenylboronic ester was an effective reagent for the coupling reaction resulting in better yields compared to phenylboronic acid. Controlled bromination of **30-2** afforded monobrominated product **30-4** or dibrominated compound **32-1** selectively and they were subjected to Suzuki reaction. For the synthesis of **TP32**,



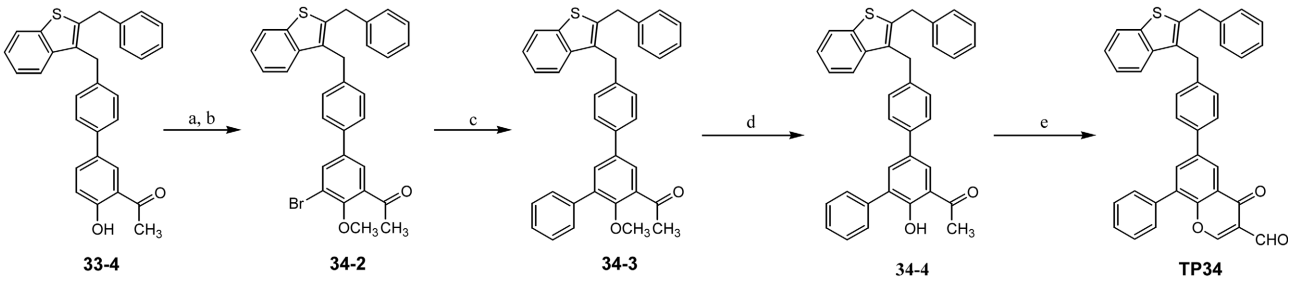
Scheme 4. Reagents and conditions: (a) $(CH_3CO)_2O$, pyridine, CH_2Cl_2, 86%; (b) $AlCl_3$, neat, 180 °C, 30 min; 40%; (c) Br_2, CH_2Cl_2, 77%; (d) CH_3I, K_2CO_3, acetone, 50 °C, 90%; (e) 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-ylbenzene, K_3PO_4, $Pd(PPh_3)_4$, DMF, 80 °C, 86%; (f) BBr_3, CH_2Cl_2, 90%; (g) $POCl_3$, DMF, −20 °C → 50 °C, 4 h, 57%.



Scheme 5. Reagents and conditions: (a) Br_2, CH_2Cl_2, 60%; (b) CH_3I, K_2CO_3, acetone, 40 °C, 73%; (c) 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-ylbenzene, K_3PO_4, $Pd(PPh_3)_4$, DMF, 80 °C, 70%; (d) BBr_3, CH_2Cl_2, 84%; (e) $POCl_3$, DMF, -20 °C → 50 °C, 4 h, 77%.



Scheme 6. Reagents and conditions: (a) $(CF_3SO_2)_2O$, 2,6-lutidine, CH_2Cl_2, 75%; (b) 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acetophenone, K_3PO_4, $PdCl_2(dppf)$, DMF, 80 °C, 90%; (c) BBr_3, CH_2Cl_2, 93%; (d) $POCl_3$, DMF, r.t. → 50 °C, 2 h, 41%.



Scheme 7. Reagents and conditions: (a) Br_2, acetate buffer, pH 3.7, 93%; (b) CH_3I, K_2CO_3, acetone, 40 °C, 94%; (c) 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-ylbenzene, K_3PO_4, $Pd(PPh_3)_4$, DMF, 80 °C, 84%; (d) BBr_3, CH_2Cl_2, 87%; (e) $POCl_3$, DMF, r.t. → 50 °C, 4 h, 71%.

double coupling reaction was performed to obtain **32-3**.

Synthesis of **TP33** (Scheme 6) was branched from the intermediate **27-6** in the synthesis of **TP27**. Triflate ester **33-1** was treated with boronate ester of protected 2-acetylphenol to obtain the coupling product **33-3**. After demethylation, **33-4** was subjected to Vilsmeier-Haack reaction. The boronate ester was prepared by reaction of 2-methoxy-5-bromoacetophenone with bis(pinacolato)diboron.[19] Compound **TP34** is an extended version of **TP33** with an additional phenyl substituent and, therefore, its synthesis involves another Suzuki coupling reaction step (Scheme 7).

The compounds synthesized in this study inactivated 50% of the *p*-nitrophenol phosphatase activity of PTP1B at low micromolar concentrations (IC_{50} values: **TP14**, 2.5 μM; **TP27**, 3.2 μM; **TP30**, 3.3 μM; **TP32**, 2.0 μM; **TP33**, 1.1 μM; **TP34**, 1.0 μM respectively). Biochemical data of those together with dozens of less potent formylchromone derivatives were reported in separate publications.[9,10]

Formylchromones have been of synthetic and biological interest because of their synthetic utility based on the three electrophilic carbon atoms and the biological activities associated with the formylchromone derivatives or structurally modified compounds.[21-23] In this study, we have described the synthesis of a variety of 3-formylchromone derivatives which behaved as potent and selective inactivators of PTP1B. This preparation extends the synthetic utility of 3-formylchromones and provides easy access to the compounds for medicinal or biological application.

Supplementary Materials. Detailed experimental procedures and the spectral data of the compounds are available from the author upon request.

Acknowledgements. This work was supported by the grant from Inha University (2005). S. Shrestha is a recipient of BK21 fellowship.

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