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Michael addition of 3-bromoinden-1-one: an expedient synthesis of 5-bromo-3-trifluoroacetamidoindan-1-one

Yong-Jin Wu*

Department of Neuroscience Chemistry, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA

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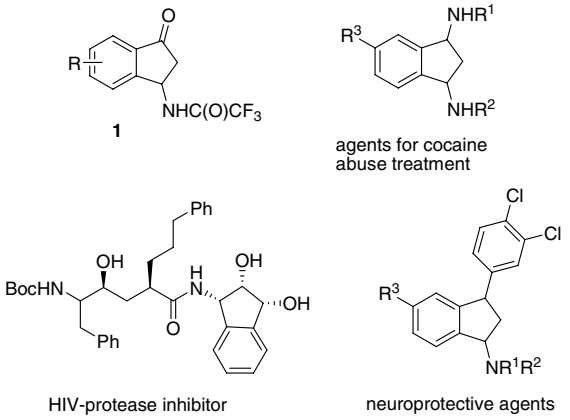
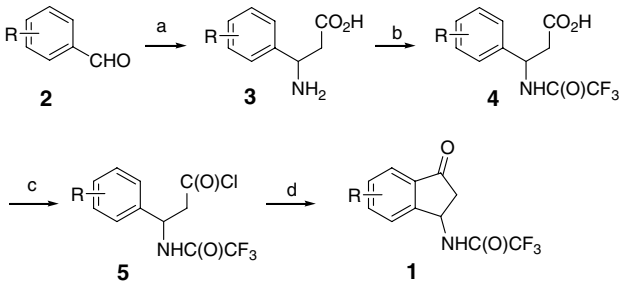
Abstract—The Michael addition of 5-bromo-inden-1-one with ammonia followed by acylation with trifluoroacetic anhydride provides 5-bromo-3-trifluoroacetamidoindan-1-one in 51% yield in one-pot.

During the course of a medicinal chemistry program, I desired to have easy access to 3-aminoindan-1-one derivatives **1** (Scheme 1). These derivatives are versatile synthetic intermediates toward the 1-aminoindane moiety embedded in many biologically important compounds, including HIV protease inhibitors,[1] neuroprotective agents,[2] and the drugs used for cocaine abuse treatment (Scheme 1).[3] A classic approach to these compounds involves Rodionow–Johnson reaction of arylaldehydes with malonic acid and ammonium acetate followed by intramolecular Friedel–Crafts cyclization of acid chlorides (Scheme 2).[4] It is well known that this



Scheme 1.



Scheme 2. Reagents and conditions: (a) NH_4Ac, $CH_2(CO_2H)_2$; (b) $(CF_3CO)_2O$; (c) $SOCl_2$ and (d) $AlCl_3$.

type of cyclizations suffers from poor regioselectivity with unsymmetrically substituted acid chlorides and lack of reactivity with substrates bearing electron-withdrawing groups. Recently, Hallberg and co-workers described the synthesis of masked 3-aminoindan-1-ones by means of the palladium-catalyzed three-component annulation reaction involving salicyclic aldehyde triflates, ethylene glycol vinyl ether, and various secondary amines.[5] For example, compound **8** was prepared in a 48% yield from diphenylmethylamine. The diphenylmethyl group was then removed selectively via hydrogenolysis to give primary amine **9** (Scheme 3). Conceivably, this amine can be converted to **1a** by acylation followed by deprotection of the ketal. As this approach uses diphenylmethylamine as the ammonia synthon and requires hydrogenolysis to provide the primary amine, it may not be suitable for the synthesis of **1** bearing halogen substituents. Therefore, there is still a need to develop alternative methods for the preparation of 3-aminoindanone derivatives.

* Tel.: +1 203 677 7485; fax: +1 203 677 7702; e-mail: yong-jin.wu@bms.com

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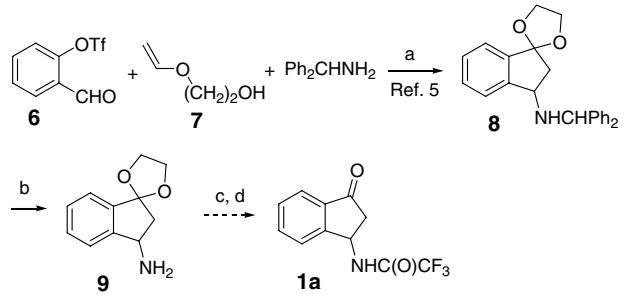
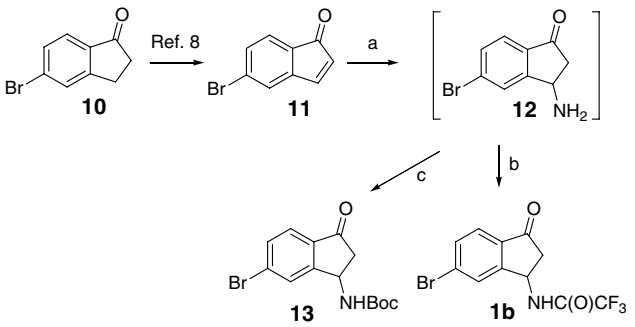


Scheme 3. Reagents and conditions: (a) $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane (DPPP), 1,2,2,6,6-pentamethylpiperidine (PMP), 48%; (b) Pd/C, HCO_2NH_4, 64% and (c) $(CF_3CO)_2O$; (d) acid.



Scheme 4. Reagents and conditions: (a) NH_3 in dioxane; (b) $(CF_3CO)_2O$, 51% and (c) Boc_2O, 25%.

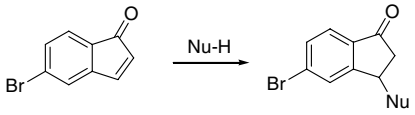
A majority of previous methodologies employ the five-membered ring closure as the key step. On the other hand, there are a number of commercially available indanones, which can be converted to **1** via indenones using Michael addition with ammonia or its synthon. Surprisingly, this strategy has not been widely used in natural product synthesis,[6,7] and to my knowledge, there has been no report on the 1,4-addition of ammonia to indenones. This report describes a facile synthesis of 5-bromo-3-acetamido-indan-1-one (**1b**) and my preliminary studies on the Michael addition of 5-bromo-inden-one (**11**) with a variety of nucleophiles.

Indenone **11** was prepared following the procedures of Hauser et al. (Scheme 4).[8] Thus, 5-bromoindanone (**10**) was treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylamine to give the trimethylsilyl enol ether, which without purification underwent Saegusa oxidation with palladium acetate. The crude product was filtered through a pad of silica gel and concentrated to give a brownish solid, which again without purification was stored in a refrigerator and used for my studies. In the outset of my investigation, I was concerned about the instability of indenone **11** as indenones in general are known to be unstable compounds and they are usually used immediately after preparation.[8] After several experiments, I found that the stability of **11** is manageable. For example, a NMR sample of **11** in $CDCl_3$ at room temperature even without light protection for four days or a sample of **11** stored in a refrigerator (−20 °C) for three months showed no appreciable decomposition. However, significant decomposition was observed under thermal conditions. For this reason, reactions of **11** were carried out at room temperature.

Treatment of **11** with 3 equiv ammonia in dioxane (0.50 M), followed by trapping with excess trifluoroacetic anhydride in one-pot, afforded **1b** in 51% yield.[9] A much poorer yield was obtained when 2 M ammonia in methanol was employed. Consistent with a previous report,[4a] intermediate amine **12** is unstable and decomposes upon silica gel flash chromatography. Therefore, no efforts were made to purify **12**. Crude amine **12** was also trapped with Boc_2O to give the *N*-Boc derivative **13** in a 25% yield. Not surprisingly, attempted addition of trifluoroacetylamide to **11** did not yield any desired product.

Next, I explored other nucleophiles in the Michael addition of **11** as this would provide a facile approach to 3-functionalized indanones. All the reactions were performed in THF at room temperature for 12 h using 3 equiv of the nucleophile, and the results are summarized in Table 1.[10] The additions worked well for primary amines including aniline (entries 1–6 and 9). Of note is that 3-aminopyridine, a poor nucleophile, resulted in the desired adduct in a 29% yield (entry 11). Good yields were also obtained with secondary amines: pyrrolidine (entry 7), morpholine (entry 8) and even *N*-methylaniline (entry 10). Among several nitrogen-containing heterocycles, pyrazole, imidazole, and triazole gave satisfactory results, benzotriazole afforded a moderate yield, and no addition was detected with pyrrole. Like their nitrogen counterparts, *t*-butylthiol and benzenethiol underwent smooth addition to furnish the 1,4-adducts in good yields. However, this procedure failed to give any desired adduct in the case of sodium azide (entry 19).

Table 1. Michael addition of **11** with various nucleophiles[10]



Entry	Nucleophile	Yield (%)[a]
1	Allylamine	57
2	Cyclopropylamine	62
3	*t*-Butylamine	64
4	Benzylamine	52
5	2,4-Dimethoxybenzylamine	69
6	Dimethylamine	62
7	Pyrrolidine	53
8	Morpholine	68
9	Aniline	72
10	*N*-Methylaniline	73
11	3-Aminopyridine	29
12	Pyrrole	0
13	Pyrazole	74
14	Imidazole	60
15	1,2,4-Triazole	60
16	Benzotriazole	33
17	*t*-Butylthiol	70
18	Benzenethiol	62
19	Sodium azide[b]	0

[a] Isolated yield.
[b] DMF was used as the solvent.

In summary, Michael addition of 5-bromo-inden-1-one provides an operationally simple and efficient approach to 5-bromo-3-trifluoroacetamido-indan-1-one and 3-functionalized indanones. Future efforts will be directed toward delineating the full scope of this approach, installing an enantioselective version and applying this methodology to the synthesis of biologically important compounds.

Acknowledgments

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9. Procedure for compound **1b**: ammonia (0.50 M) in dioxane (1.74 mL, 0.87 mmol) was added to indenone **11** (60 mg, 0.29 mmol, crude product from Saegusa oxidation), and the resulting bluish solution was stirred at room temperature for 3 h. A stream of nitrogen gas was bubbled through the reaction mixture for 5 min to remove excess ammonia, trifluoroacetic anhydride (0.30 mL) was added dropwise, and the bluish color faded immediately upon addition. The reaction mixture was stirred at room temperature for 2 h, and the solvents were removed in vacuo. The residue was purified by preparative TLC eluting with 30% ethyl acetate/70% hexanes to give 5-bromo-3-acetamido-indan-1-one as a white solid (47 mg, 51%). ^{1}H NMR (400 MHz, CD_3CN) δ 2.62 (1H, dd, $J = 3.6$, 18.8 Hz, AB quartet), 3.11 (1H, dd, $J = 8.0$, 18.8 Hz), 5.56 (1H, dt, $J = 3.2$, 8.0 Hz), 7.59 (1H, d, $J = 8.4$ Hz), 7.69 (1H, d, $J = 8.4$ Hz), 7.83 (1H, s), and 8.04 (1 H, br s). ^{13}C NMR (100 MHz, CD_3CN) δ (attached protons) 43.30 (2), 48.09 (1), 116.30 (0, d, $J = 285$ Hz), 124.72 (1), 129.91 (1), 130.01 (0), 133.29 (1), 136.40 (0), 154.58 (0), 157.60 (0, q, $J = 37$ Hz), 201.50 (0). HRMS m/z calcd for $C_{11}H_6F_3NO_2Br$ $(M-H)^+$ 319.9534, found 319.9531. The spectroscopic data is identical with that of **1b** prepared following Ref. 4a.
10. Representative procedure: To a solution of indenone **11** (60 mg, 0.29 mmol, crude product from Saegusa oxidation) in THF (0.20 mL) was added morpholine (50 μL, 0.58 mmol), and the resulting reaction mixture was stirred at room temperature for 12 h. THF was removed in vacuo, and the residue was purified by preparative TLC eluting with 50% ethyl acetate/50% hexanes to give 5-bromo-3-morpholino-2,3-dihydro-1*H*-inden-1-one as a white solid (58 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (2H, m), 2.51 (2H, m), 2.59 (1H, dd, $J = 7.2$, 18.8 Hz, AB quartet), 2.75 (1H, d, $J = 3.6$ Hz, AB quartet), 3.69 (4H, m), 4.49 (1H, dd, $J = 3.6$, 7.2 Hz), 7.54 (1H, d, $J = 8.0$ Hz), 7.57 (1H, d, $J = 8.0$ Hz), and 7.85 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ (attached protons) 35.84 (2), 48.79 (2), 62.47 (1), 67.06 (2), 124.56 (1), 129.97 (1), 130.36 (0), 132.53 (1), 136.41 (0), 155.49 (0), and 202.75 (0). HRMS m/z calcd for $C_{13}H_{15}NO_2Br$ $(M+H)^+$ 296.0286, found 296.0287.