Pergamon

Tetrahedron Vol. 51, No. 7, pp. 1861-1866, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)01053-6

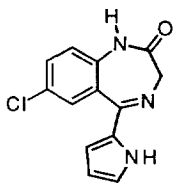
Improved Synthesis of 2-Amino-5-chlorophenyl-2'-pyrrylketone, a Key Intermediate in the Synthesis of HIV Tat-Antagonists

Masami Okabe* and Ruen-Chu Sun

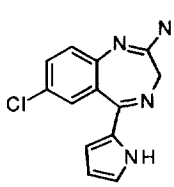
Roche Research Center, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Abstract: The reaction of a 2-phenylbenzoxazinone with pyrryl Grignard reagent is very efficient compared with that of a 2-methylbenzoxazinone. The title compound was prepared from 5-chloroanthranilic acid via the 2-phenylbenzoxazinone in 92% overall yield. This method was also successfully applied to the synthesis of 2-aminobenzophenones.

The human immunodeficiency virus-1 (HIV-1) trans-activator for transcription (Tat),[1] which regulates HIV gene expression, was chosen as one of the targets for the development of anti-HIV drugs even though the molecular mechanism of Tat-mediated transcriptional activation was not clearly understood.[2] The benzodiazepine **1** from the Roche compound repository was found to be an effective Tat antagonist which inhibited viral replication with an IC_{50} between 0.1-1 μM and 90% inhibitory concentration (IC_{90}) of 1-3 μM.[3] A systematic study of the structure-activity relationship of related benzodiazepines revealed that the corresponding amidines **2** were also quite active. Among these, based on favorable animal toxicity data, **2b** was selected for clinical development.[2] In an effort to develop economical and efficient routes to these Tat antagonists, we investigated the preparation of the key intermediate, 2-amino-5-chlorophenyl-2'-pyrrylketone (**3**). Here we describe the results of this study, which led to an improved method to prepare 2-aminobenzophenones.

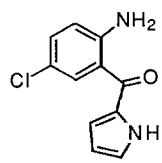


1



2

a: $R^1 = R^2 = H$
b: $R^1 = Me$, $R^2 = H$
c: $R^1 = R^2 = Me$
d: $R^1 + R^2 = -(CH_2)_4-$
e: $R^1 = NH_2$, $R^2 = H$

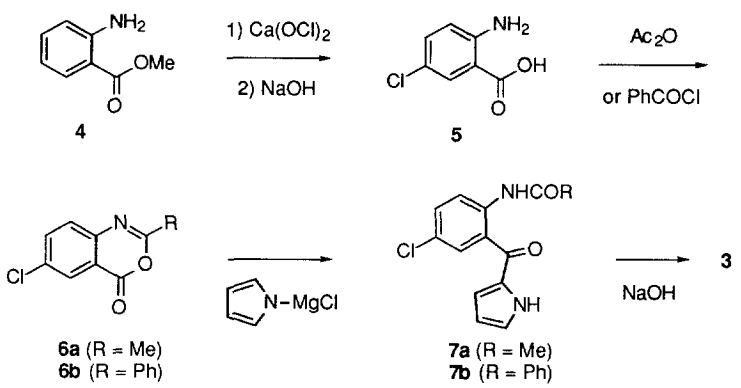


3

In the original preparation of **3**, 5-chloroanthranilic acid (**5**) was converted to the 2-methylbenzoxazinone **6a** in about 80% yield.[4] The reaction of a Grignard reagent with a 2-methylbenzoxazinone is commonly employed to prepare 2-aminobenzophenones[4] even though the yields are often not satisfactory (typically, 25-50%).[4,5] After extensive development the overall yield of **3** from **5** was improved to *ca.* 65%.[6] However, some drawbacks still remained, among these being: harsh conditions required for the preparation of **6a** (refluxing acetic anhydride), susceptibility of **6a** to moisture, moderate yield of **3**, and relatively high cost of **5**.

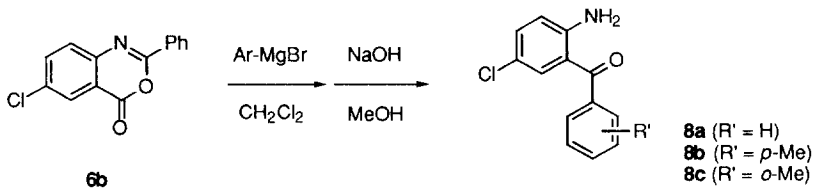
First, the high cost of **5** prompted us to develop an economical synthesis of this compound. Compound **5** was originally prepared in 49% yield by treating anthranilic acid with sulfuryl chloride.[7] However, this procedure was not desirable for scale-up because the reaction produces large quantities of HCl and SO_2. We chose methyl anthranilate (**4**), a cheap abundant raw material, as the starting material and studied its chlorination. Nickson and Roche-Dolson have published the chlorination of deactivated anilines with *N*-chlorosuccinimide,[8] in which methyl *p*-aminobenzoate and anthranilonitrile, both structurally closely related to **4**, were chlorinated in refluxing acetonitrile in 89 and 71% yields, respectively. However, under these conditions **4** failed to give any usable product. The authors[8] speculated that the *ortho*-methoxycarbonyl group could participate as a neighboring group thus facilitating by-product formation. We thought that by lowering the reaction temperature the side reactions could be minimized. When **4** was treated with calcium hypochlorite in aqueous acetone at 0°C,[9] the desired chlorinated product was detected by TLC and NMR analyses in a complex mixture of products but could not be isolated. Finally, using a dichloromethane-water two-phase system the reaction with calcium hypochlorite proceeded satisfactorily and, after hydrolysis, **5** was obtained in 58% yield from **4**.

Next, we examined the formation and reactivity of the 2-phenylbenzoxazinone **6b** instead of **6a**, since 2-phenylbenzoxazinones can be prepared under very mild conditions[10] and are reported to be much more stable toward moisture than the corresponding 2-methylbenzoxazinones (such as **6a**).[11] Surprisingly, the reaction of a 2-phenylbenzoxazinone with a Grignard reagent, to the best of our knowledge, has not been reported.[12] Treatment of **5** with benzoyl chloride (2 equiv) and sodium carbonate *at room temperature* gave **6b** in quantitative yield. Indeed, **6b** is quite resistant to hydrolysis and was isolated *after being washed with water and methanol*. Pyrrylmagnesium chloride (2 equiv) reacted smoothly with **6b** at room temperature to afford initially the corresponding pyrroleamide by C-N bond formation, which was converted to **7b** (C-C bond formation) upon reflux.[13] Hydrolysis of **7b** gave the title compound **3** in 92% overall yield from **5**.



As an extension of this very efficient method, we investigated the reaction of **6b** with other aryl Grignard reagents. The reactions were carried out in CH_2Cl_2 at -70°C to -35°C using 2.5 equiv of Grignard reagents. Hydrolysis of the products[14] with sodium hydroxide proceeded well to give 2-aminobenzophenones **8a-c** in *ca.* 85% overall yields from the anthranilic acid **5**.[15,16] It should be noted that the overall yields of 2-aminobenzophenones from anthranilic acids via 2-methylbenzoxazinones, such as **6a**, are typically 20-

40%.[4,5] When only 1.2 equiv of phenylmagnesium bromide was used, only partial reaction (*ca.* 50%) occurred at -70°C and the complete reaction was achieved only after being warmed to 0°C, but with concomitant formation of the corresponding tertiary alcohol. The reaction of **6b** with phenyllithium instead of the Grignard reagent led to increased amounts of the tertiary alcohol via bis-arylation. With 1.2 equiv of phenyllithium at <-65°C, the mono-arylation product, bis-arylation product, and **6b** were obtained in the ratio of 2:2:1, respectively. Recently, Zhang et al. also reported that treatment of a related 2-phenylnaphthoxazinone (2-phenyl-4*H*-naphtho[2,3-*d*]-1,3-oxazin-4-one) with 1.2 equiv of (*o*-fluorophenyl)-lithium at -78°C furnished the desired mono-arylation product in only 51% yield, accompanied by 18% of the bis-arylation product and 27% of the unchanged starting material.[12] These results strongly suggest that *aggregation of the magnesium salts is of importance to achieve selective mono-arylation,* while the nature of aggregation remains open to investigation.



6b

8a (R' = H)
8b (R' = *p*-Me)
8c (R' = *o*-Me)

Conclusion

Overall yields of the title compound **3** and 2-aminobenzophenones from anthranilic acids were increased by more than 25% yield by simply replacing the 2-methyl group of the benzoxazinones with the phenyl group.[17] 2-Phenylbenzoxazinones have additional advantages over the commonly used 2-methylbenzoxazinones in terms of the ease of preparation and increased stability toward moisture as Zhang et al. also indicated.[12] Selective mono-arylation of the 2-phenylbenzoxazinone was achieved when treated with excess Grignard reagent at low temperature. Aryllithiums, on the other hand, tend to give a larger amount of tertiary alcohols via bis-arylation even when only one equivalent of the reagent is used at -78°C. Although the development of the Tat antagonist **2b** was discontinued due to the lack of efficacy in a Phase II clinical study, benzodiazepines in general are becoming increasingly important as key components of peptidomimetics.[18] Because of the renewed interests on benzodiazepines, the efficient method to prepare 2-aminobenzophenones reported here is of importance with the promise of broad utility. Although this study focused exclusively on **6b**, the procedures should also be useful for the preparation of other 2-aminobenzophenones.

Experimental Section

Melting points are determined using a capillary melting point apparatus and are uncorrected. NMR spectra were recorded on Varian XL-200 and 400 instruments and are reported in ppm relative to Me_4Si. Electron-impact mass spectra were determined on a VG ZAB-1F instrument at 70 eV. All moisture-sensitive reactions were carried out under a positive pressure of argon.

5-Chloroanthranilic Acid (5). A mixture of methyl anthranilate (**4**) (200 g, 1.32 mol), CH_2Cl_2 (2 L), and AcOH (100 mL) was cooled to 5°C, followed by the addition of ice-water mixture (1 L). To this mixture with vigorous stirring was added calcium hypochlorite (150 g, 1.36 mol as active chlorine) at once. The temperature reached 17°C within 5 min. After 30 min, the CH_2Cl_2 layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 10% Na_2SO_3 solution, dried over Na_2SO_4, and concentrated to dryness. The residue was suspended in hexane (1 L) and then stored in a refrigerator overnight. The precipitate was collected by filtration and washed with hexane. Drying under high vacuum gave 149 g (61% yield) of crude methyl 5-chloroanthranilate as a dark amber solid. This material was used in the following step without any purification.

A mixture of the crude methyl ester (126 g, 681 mmol) and 1N NaOH solution (885 mL) was refluxed for 1 h. While it was hot, the insoluble material was removed by filtration and washed with hot water. After adding AcOH (88.5 mL) and cooling to 5°C, the precipitate was collected by filtration and washed with water. Drying at 100 °C under 70 mm Hg afforded 111 g (96% yield) of **5** as an off-white solid: mp 212-216°C (lit.[7] 204-205°C).

6-Chloro-2-phenyl-4H-3,1-benzoxazin-4-one (6b) After a mixture of **5** (55.6 g, 324 mmol) and THF (648 mL) was cooled to 5°C, Na_2CO_3 (powder, 68.7 g, 648 mmol) was added followed by benzoyl chloride (94.0 mL, 810 mmol). After 10 min, the cold-bath was removed, and the mixture was stirred at room temperature overnight. Water (648 mL) was added, and the mixture was stirred for 10 min prior to filtration. The solid was washed with water and then with 50% aqueous MeOH. The additional precipitate from the filtrate was collected by filtration and washed. The combined crops were dried at 50°C under high vacuum to give 84.1 g (100 % yield) of **6b** as a white solid: mp 192-196°C.(lit.[19] 195-197°C); ^{1}H NMR ($CDCl_3$) δ 7.53 (t, J = 7.3 Hz, 2 H), 7.58 (t, J = 7.3 Hz, 1 H), 7.66 (d, J = 8.6 Hz, 1 H), 7.77 (dd, J = 8.6 and 2.4 Hz, 1 H), 8.22 (d, J = 2.4 Hz, 1 H), 8.31 (d, J = 7.3 Hz, 1 H); IR (KBr) 1756 cm^{-1}; MS *m/z* 257 (M^+). Anal. Calcd for $C_{14}H_8ClNO_2$: C, 65.26; H, 3.13; N, 5.44; Cl, 13.76. Found: C, 64.78; H, 2.91; N, 5.40; Cl, 13.48. This material was used in the following steps without any purification.

N-[4-Chloro-2-(1H-pyrrol-2-ylcarbonyl)phenyl]benzamide (7b). After a mixture of 2M EtMgCl in THF (52.5 mL, 105 mmol) and THF (20 mL) was cooled to 2°C, a solution of pyrrole (7.98 mL, 115 mmol) in toluene (7.98 mL) was added dropwise over 20 min, keeping the temperature below 15°C. After the mixture was stirred at room temperature for 20 min, **6b** (12.9 g, 50 mmol) was added with the aid of THF (35 mL). After 45 min of stirring, the mixture was refluxed for 3 h. Saturated NH_4Cl solution (11.5 mL) was then added to the hot mixture over 5 min. After 20 min of stirring, Na_2SO_4 (powder, 11.5 g) was added. The suspension was stirred for 20 min prior to the filtration. The collected solid was washed with THF, and the combined filtrate and washes were concentrated to dryness. The residue was suspended in toluene (50 mL), and the suspension was cooled with an ice-water bath for 20 min. The solid was collected by filtration and washed with hexane. Drying at room temperature overnight under high vacuum gave 15.7 g (97%) of **7b** as a greenish light brown solid: mp 171-173°C; ^{1}H NMR ($CDCl_3$) δ 6.41 (m, 1 H), 6.93 (m, 1 H), 7.20 (m, 1 H), 7.51 (t, J = 7.1 Hz, 2 H), 7.54 (m, 1 H), 7.57 (dd, J = 9.0 and 2.5 Hz, 1 H), 7.95 (d, J = 2.5 Hz, 1 H), 7.99 (d, J = 7.1 Hz, 1 H), 8.76 (d, J = 9.0 Hz, 1 H), 9.54 (bs, 1 H), 11.35 (bs, 1 H); IR (KBr) 1674 cm^{-1}; MS *m/z* 324

(M^+). Anal. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63; Cl, 10.92. Found: C, 66.25; H, 3.95; N, 8.52; Cl, 10.81.

2-Amino-5-chlorophenyl-2'-pyrrylketone (3). A mixture of **7b** (15.7 g, 48.2 mmol), 10N NaOH (14.4 mL), and MeOH (48.2 mL) was heated at reflux overnight. Water (70 mL) was added, and the mixture was slowly cooled to room temperature and stirred for 3 h. The solid was filtered and washed with water. Drying at 50°C under high vacuum overnight gave 10.1 g (95%) of **3** as a yellow solid: mp 147-148°C; ^{1}H NMR ($CDCl_3$) δ 5.52 (bs, 2 H), 6.36 (m, 1 H), 6.67 (d, J = 8.7 Hz, 1 H), 6.87 (bs, 1 H), 7.12 (bs, 1 H), 7.23 (dd, J = 8.7 and 2.5 Hz, 1 H), 7.82 (d, J = 2.5 Hz, 1 H), 9.50 (bs, 1 H); UV (EtOH) λ_{max} 236 (ε 23920), 306 (ε 10990), 374 (ε 6600) nm; MS m/z 220 (M^+). Anal. Calcd for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.70; Cl, 16.07. Found: C, 59.57; H, 3.91; N, 12.52; Cl, 15.77.

General Procedure for 2-Aminobenzophenones 8a-c. To a suspension of **6b** (2.57 g, 10 mmol) in 100 mL of CH_2Cl_2 at -70°C was added 1-3 M arylmagnesium bromide in ether (25 mmol) over 20 min. After completion of the reaction, the excess reagent was quenched with aqueous NH_4Cl. The crude product obtained after extractive workup was purified by chromatography on silica gel using 0-30% hexane in CH_2Cl_2. The product was then suspended in MeOH (10 mL) and 10 N NaOH (3 mL). After 4 h at reflux, the mixture was cooled with an ice-water bath to solidify the product. The mixture was then diluted with water (20 mL) and stored in a refrigerator prior to filtration. The collected yellow solid was washed with MeOH-H_2O (1:3) and dried to give pure **8a-c**.

8a: 3.1 M Phenyl-MgBr in ether at -70°C for 4 h; 1.96 g (85% yield): mp 98°C (lit.[4] mp 99°C). Anal. Calcd for $C_{13}H_{10}ClNO$: C, 67.40; H, 4.35; N, 6.05; Cl, 15.30. Found: C, 67.16; H, 4.10; N, 5.94; Cl, 15.16.

8b: 1.0 M *p*-Tolyl-MgBr in ether at -70°C for 1.5 h and then to -55°C over 1.5 h; 2.10 g (86% yield): mp 107-110°C (lit.[4] mp 105-108°C). Anal. Calcd for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70; Cl, 14.43. Found: C, 68.25; H, 4.97; N, 5.59; Cl, 14.30.

8c: 2.0 M *o*-Tolyl-MgBr in ether at -70°C for 1 h and then to -35°C over 3 h; 2.10 g (86% yield): mp 45-47°C[20] (lit.[4] mp 50-55°C). Anal. Calcd for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70; Cl, 14.43. Found: C, 68.24; H, 4.70; N, 5.59; Cl, 14.16.

References and Notes

1. a) Arya, S. K.; Guo, C.; Josephs, S. F.; Wong-Staal, F. *Science* **1985**, *229*, 69. b) Sodroski, J. G.; Rosen, C. A.; Wong-Staal, F.; Salahuddin, S. Z.; Popovic, M.; Arya, S.; Gallo, R. C. *Science* **1985**, *227*, 171.
2. Hsu, M.-C.; Tam, S. In *The Search for Antiviral Drugs;* Adams, J.; Merluzzi, V. J., Eds.; Birkhäuser: Boston, 1993; p 153 and references therein.
3. Hsu, M.-C.; Schutt, A. D.; Holly, M.; Slice, L. W.; Sherman, M. I.; Richman, D. D.; Potash, M. J.; Volsky, D. J. *Science* **1991**, *254*, 1799.
4. For a review, see: Walsh, D. A. *Synthesis* **1980**, 677.

5. a) Hsu, M.-C.; Huryn, D. M.; Tam, S. Y.-K. Eur. Pat. Appl. EP 491,218, 1992; *Chem. Abstr.* **1992**, *117*, 151025. b) Frye, S. V.; Johnson, M. C.; Valvano, N. L. *J. Org. Chem.* **1991**, *56*, 3750. c) Suzuki, K.; Obase, H.; Karasawa, A.; Shirakura, S.; Kubo, K.; Miki, I.; Ishii, A. Eur. Pat. Appl. EP 347,831, 1989; *Chem. Abstr.* **1990**, *113*, 23890. d) Hino, K.; Kawashima, K.; Oka, M.; Nagai, Y.; Uno, H.; Matsumoto, J.-I. *Chem. Pharm. Bull.* **1989**, *37*, 110. e) Egorov, V. S.; Krasheninnikov, V. B.; Mamaev, V. V.; Babin, E. A.; Ryzhov, M. G.; Kazika, A. I.; Vauchskii, Yu. P.; Sagiyan, A. S. U.S.S.R. SU 1,456,406, 1989; *Chem. Abstr.* **1989**, *111*, 96828. f) Zieger, H. E.; Bright, D. A.; Haubenstock, H. *J. Org. Chem.* **1986**, *51*, 1180. g) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790. h) Adams, J. H.; Brown, P. M.; Gupta, P.; Khan, M. S. *Tetrahedron* **1981**, *37*, 209. i) Sternbach, L. H.; Fryer, R. I.; Metlesics, W.; Sach, G.; Stempel, A. *J. Org. Chem.* **1962**, *27*, 3781.
6. Regenye, R. W.; Exon, C. M., private communication.
7. Endicott, M. M.; Alden, B. W.; Sherrill, M. L. *J. Am. Chem. Soc.* **1946**, *68*, 1303.
8. Nickson, T. E.; Roche-Dolson, C. A. *Synthesis* **1985**, 669.
9. Nwaukwa, S. O.; Keehn, P. M. *Synth. Commun.* **1989**, *19*, 799.
10. Bain, D. I.; Smalley, R. K. *J. Chem. Soc. (C)* **1968**, 1593.
11. Errede, L. A.; Oien, H. T.; Yarian, D. R. *J. Org. Chem.* **1977**, *42*, 12.
12. Recently, the reaction of 2-phenylnaphthoxazinone with aryllithium was reported. See: a) Zhang, W.; Koehler, K. F.; Harris, B.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1994**, *37*, 745. b) Zhang, W.; Liu, R.; Cook, J. M. *Heterocycles* **1993**, *36*, 2229.
13. Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P. *Tetrahedron Lett.* **1981**, *22*, 4647.
14. Hydrolysis of the benzanilide under acidic conditions has been reported. See, reference 12.
15. One-step synthesis of 2-aminophenyl heterocyclic ketones from anthranilic acids was reported in 31-63% yield. See: Fryer, R. I.; Zhang, P.; Rios, R. *Synth. Commun.* **1993**, *23*, 985.
16. Synthesis of 2-aminobenzophenones via in situ trapping of aryllithiums by anthranilic acid *N*-methoxy-*N*-methylamide was reported (35-70% yield). See reference 5b.
17. The increase in yield is presumably due to the removal of the somewhat acidic 2-methyl hydrogens and the relative increase in the stability of the benzoxazinone when going from the 2-methyl to the 2-phenylbenzoxazinone.
18. a) James, G. L.; Goldstein, J. L.; Brown, M. S.; Rawson, T. E.; Somers, T. C.; McDowell, R. S.; Crowley, C. W.; Lucas, B. K.; Levinson, A. D.; Marsters, Jr., J. C. *Science* **1993**, *260*, 1937. b) Ripka, W. C.; DeLucca, G. V.; Bach II, A. C.; Pottorf, R. S.; Blaney, J. M. *Tetrahedron* **1993**, *49*, 3593 and 3609. c) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997. d) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Whitter, W. L.; Garsky, V. M.; Gilbert, K. F.; Leighton, J. L.; Carson, K. L.; Mellin, E. C.; Veber, D. F.; Chang, R. S. L.; Lotti, V. J.; Freedman, S. B.; Smith, A. J.; Patel, S.; Anderson, P. S.; Freidinger, R. M. *J. Med. Chem.* **1993**, *36*, 4276.
19. Desai, D. R.; Patel, V. S.; Patel, S. R. *J. Indian Chem. Soc.* **1966**, *43*, 351; *Chem. Abstr.* **1966**, *65*, 08906e.
20. Crystallization was induced by the addition of seed crystals.

(*Received in USA* 30 *October* 1994; *accepted* 28 *November* 1994)