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ACETYLATED DIMETHOXYANILINE AS A KEY INTERMEDIATE FOR THE SYNTHESIS OF AMINOFLAVONES AND QUINOLONES

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Abstract-3,5-Dimethoxyaniline was acetylated and found to be a key intermediate for the synthesis of a variety of biologically active aminoflavones and quinolones.

INTRODUCTION

Aminoflavones have been reported by several authors as tyrosine kinases inhibitors[1,2] and as antimitotic agents.[3] 2-Phenyl-4-quinolones which are the aza analogues of flavones have been also extensively studied as cytotoxic, antimitotic and antibacterial agents.[4-7] The synthetic strategies adopted for the synthesis of aminoflavones, generally consist of nitration of already elaborated flavones and reduction of the nitro groups to amines.[1,2] However, such strategies do not warrant any selectivity, especially when precise position are targeted.

In an ongoing research program aimed at the synthesis of biologically actives flavones (**I**) and quinolones (**II**) (Figure 1), we found out that the presence of hydroxyl groups at positions 5 and 7, is frequently required for higher biological activities (Figure 1).[8-10] These structural criteria have been reported by many authors in studying different biological activities.[11,12] Since, hydroxyl and amino groups are isosters, we can presume that replacing of one of the hydroxyls (at positions 5 and 7) in flavones with an amino group can be beneficial for the biological activity. For example, 5-aminoflavone has been synthesized by Akama *et al*. which possess a promising antitumor activities.[3]

Hence, we report a simple and general methodology to access 5-amino-7-methoxyflavones, 7-amino-5-methoxyflavones and 2-phenyl-4-quinolones using the same starting material.

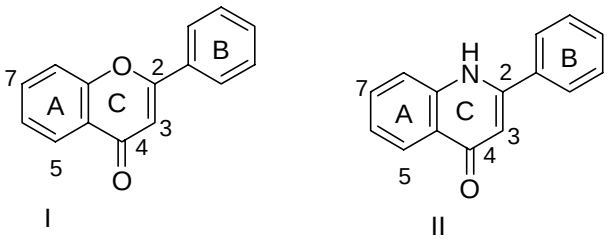
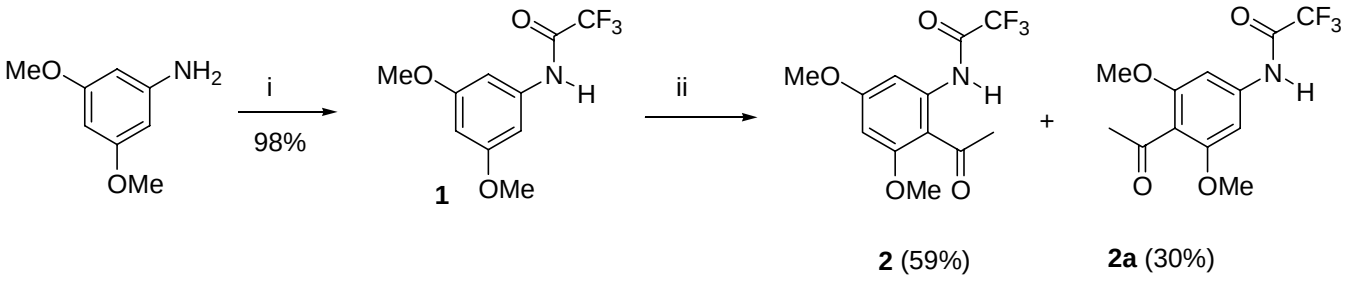


Figure 1.

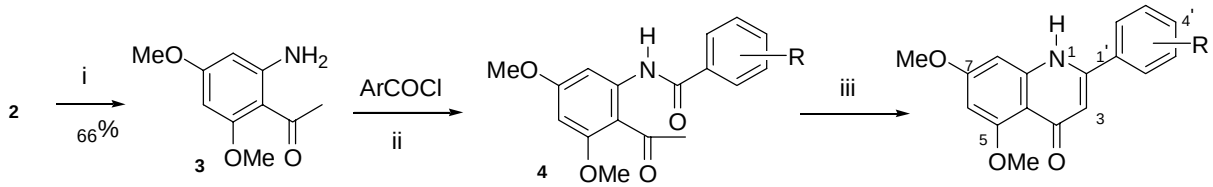
RESULTS AND DISCUSSION

We found that acetyl-3,5-dimethoxyaniline can be a useful starting block for the synthesis of such molecules. Protection of 3,5-dimethoxyaniline as its trifluoroacetamide was accomplished in quantitative yield by treatment with trifluoroacetic anhydrie (TFAA) in the presence of triethylamine. Freidel-Craft acetylation of **1** with acetyl chloride in the presence of $SnCl_4$ afforded *N*-(2-acetyl-3,5-dimethoxyphenyl)trifluoroacetamide (**2**) in 59% together with its regioisomer (**2a**) (obtained in 30% yield).[13] The trifluoroacetyl protecting group was chosen because it provides good overall yield, can be easily removed and provides the regioisomer (**2a**) with high yield.



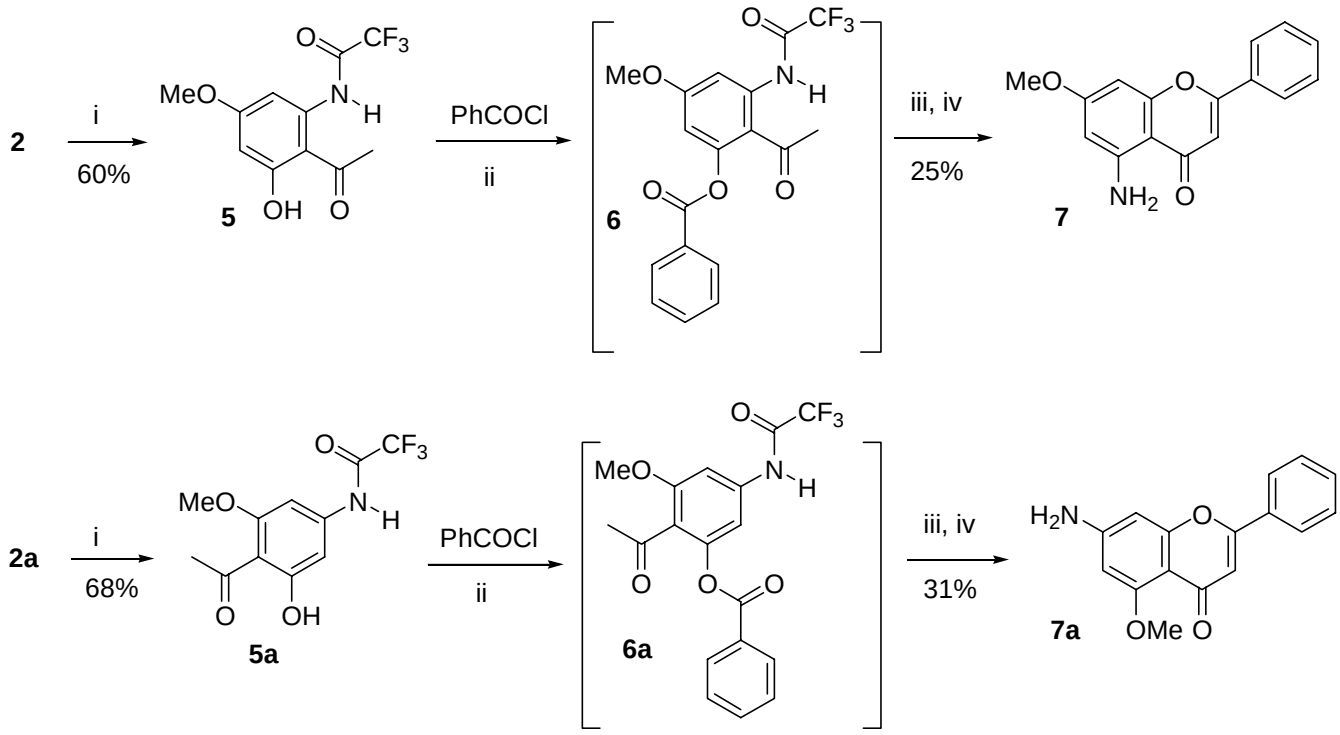
Scheme 1. (**i**). TFAA, Et_3N, CH_2Cl_2. (**ii**). MeCOCl, $SnCl_4$, 1,2-dichloroethane.

(2-Acetyl-3,5-dimethoxyphenyl)trifluoroacetamide (**2**) can be used in the synthesis of 2-phenyl-4-quinolones as shown in Scheme 2. Deprotection of **2** with K_2CO_3 in MeOH affords 2-acetyl-3,5-dimethoxyaniline (**3**) in 66% yield. The latter was prepared in multi-grams scale and can be stored for several months without any special cautions. Condensation of **3** with a benzoyl chloride or a benzoic acid gives the corresponding amide (**4**) which can be cyclized in the presence of *t*-BuOK to yield 2-phenyl-4-quinolones as it was reported before.[13] To the best of our knowledge, compound (**3**) has not been reported before and we believe that **3** is a useful starting material for the synthesis of quinolones. For example, if appropriately substituted benzoyl chlorides or benzoic acids are selected, intermediate (**3**) can allow the synthesis of divers quinolones.



Scheme 2. (**i**). K_2CO_3, MeOH, reflux. (**ii**). Et_3N, CH_2Cl_2. (**iii**). *t*-BuOK, THF, reflux

Regioisomers (**2**) and (**2a**) can be easily converted to 5-amino-7-methoxyflavone and 7-amino-5-methoxyflavone respectively (Scheme 3). Thus, treatment of **2** or **2a** with BBr_3 in CH_2Cl_2 yields the monodemethylated derivatives (**5**) and (**5a**). In the case of **2**, the demethylation took place on the methoxy adjacent to the carbonyl group (the methoxy group in *para* position to the acetyl group remains intact). This selectivity is due to the chelating effect induced by the ketone group.[14] The phenols (**5**) and (**5a**) were reacted with benzoyl chloride to give the corresponding esters (**6**) and (**6a**) which were immediately subjected to cyclization by treatment with *t*-BuOK in THF. The final step is the trifluoroacetamide group removal which was accomplished with K_2CO_3 in MeOH treatment to yield 5-amino-7-methoxyflavone (**7**) and 7-amino-5-methoxyflavone (**7a**). Here again, regioisomers (**2**) and (**2a**) can allow the synthesis of divers flavones doted of the required substituents on the 5 and 7 positions.



Scheme 3. i. BBr_3, CH_2Cl_2. **ii**. NaH, THF. **iii**. *t*-BuOK, THF, reflux. **iv**. K_2CO_3, MeOH, reflux.

In conclusion, acetylation of (3,5-dimethoxyphenyl)trifluoroacetamide yield two useful intermediates: 2-acetyl-3,5-dimethoxyaniline and 4-acetyl-3,5-dimethoxyaniline which can be conveniently used for the synthesis of divers and biologically active aminoflavones and 2-phenyl-4-quinolones.

EXPERIMENTAL

General: Melting points were determined on a Buchi 510 melting points apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer. Chemical shifts are reported in ppm

from tetramethylsilane as internal standard. *J* values are given in Hz. EI-MS spectra were obtained at 70 eV using a Fisons Trio 1000 instrument. Elemental analyses were performed by the analytical department of CNRS, Vernaison, France. TLC was carried out using E. Merck silica gel F-254 plates (thickness 0.25 mm) and flash chromatography was accomplished using Merck silica gel 60, 200-400 mesh. All solvents were distilled prior to use. All chemicals and reagents used were obtained from either Aldrich or ACROS.

***N*-(3,5-Dimethoxyphenyl)trifluoroacetamide (1)**. To an ice cooled solution of 3,5-dimethoxyaniline (5 g, 32.64 mmol) in dichloromethane (100 mL) was added successively triethylamine (6.82 mL, 48.96 mmol) then trifluoroacetic anhydride (6.9 mL, 48.96 mmol). After completion of the reaction (1 h), it was quenched with ice cold water and to it was added 1N HCl until pH 6. The product was extracted with dichloromethane, and the organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated to furnish 7.96 g of pure **1** as a white solid. Yield 98%; mp 94 - 96 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.76 (6H, s), 6.32 (1H, t, *J* = 2 Hz), 6.76 (2H, d, *J* = 2 Hz), 8.04 (1H, s); MS: m/z 249 (M^+); Anal. Calcd for $C_{10}H_{10}NO_3F_3$: C, 48.20; H, 4.04; N, 5.62; F, 22.87. Found: C, 47.99; H, 4.01; N, 5.64; F, 22.71.

***N*-(Acetyl-3,5-dimethoxy)trifluoroacetamides (2) and (2a)**. To a solution of **1** (5 g, 20 mmol) in 1,2-dichloroethane (100 mL) was added dropwise a solution of $SnCl_4$ (10.46 g, 40 mmol) in 1,2-dichloroetane (5 mL) at 0°C within 45 min. After the addition, acetyl chloride (1.43 mL, 20 mmol) was added dropwise to the solution. The reaction was completed within 3 h and quenched by adding ice cold water. After extracting with dichloromethane (3 x 150 mL), the organic layer was washed with water (3 x 200 mL) and dried over Na_2SO_4. The solvent was evaporated and the crude compound was purified by column chromatography eluted with ethyl acetate:cyclohexane 1:3 to yield 3.43 g of **2** and 1.74 g of **2a** as white solids.

***N*-(2-Acetyl-3,5-dimethoxy)trifluoroacetamide (2)**. Yield 59%; mp 74 - 76 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.61 (3H, s), 3.87 (3H, s), 3.91 (3H, s), 6.31 (1H, d, *J* = 1.9 Hz), 6.77 (1H, d, *J* = 1.9 Hz), 7.89 (1H, s); MS: m/z 291 (M^+); Anal. Calcd for $C_{12}H_{12}NO_4F_3$: C, 49.49; H, 4.15; N, 4.81; F, 19.57. Found: C, 48.84; H, 4.06; N, 4.98; F, 21.18.

***N*-(4-Acetyl-3,5-dimethoxy)trifluoroacetamie (2a)**. Yield 30%; mp 155-157 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.45 (s, 3H), 3.73 (s, 6H), 6.81 (s, 2H), 8.57 (br s, 1H); MS: m/z 291 (M^+); Anal. Calcd for $C_{12}H_{12}NO_4F_3$: C, 49.49; H, 4.15; N, 4.81; F, 19.57. Found: C, 48.87; H, 4.04; N, 4.92; F, 20.07.

2-Acetyl-3,5-dimethoxyaniline (3). To a solution of **2** (9 g, 30.9 mmol) in methanol (150 mL) was added a solution of K_2CO_3 (6.4 g, 46.39 mmol). The reaction was refluxed for 3 h and on completion methanol was evaporated under reduced pressure. The solid obtained was washed with water to yield the crude product which was purified by column chromatography using ethyl acetate:cyclohexane 2:3 as a solvent system to afford 4 g of **3** as a yellow solid. Yield 66%; mp 98 - 100 °C (AcOEt); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.53 (3H, s), 3.77 (3H, s), 3.81 (3H, s), 5.71 (1H, d, *J* = 2 Hz), 5.75 (1H, d, *J* = 2 Hz); MS: m/z 195 (M^+); Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.03; H, 6.62; N, 7.11.

***N*-(2-Acetyl-3-hydroxy-5-methoxyphenyl)trifluoroacetamide (5).** To a solution of **2** (0.58 g, 2 mmol) in anhydrous dichloromethane (10 mL) was added BBr_3 (0.38 mL, 2 mmol). The solution was stirred 24 h at rt, poured into cold water, extracted with CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4 and concentrated. Column chromatography using ethyl acetate:cyclohexane (8:2) as eluent gave 0.33 g of **5** as amorphous yellow compound. Yield 60%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.63 (s, 3H), 3.91 (s, 3H), 6.32 (d, *J* = 2 Hz, 1H), 7.20 (d, *J* = 2 Hz, 1H), 11.90 (s, 1H); MS: m/z 277 (M^+, 100), 262 (83); Anal. Calcd for $C_{11}H_{10}NO_4F_3$: C, 47.66; H, 3.64; F, 20.56, N, 5.05. Found: C, 47.53; H, 3.59; F, 20.43; N, 4.98.

***N*-(4-Acetyl-3-hydroxy-5-methoxyphenyl)trifluoroacetamide (5a)**. The same procedure as **5**. Amorphous yellow compound; Yield 68%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.60 (s, 3H), 3.85 (s, 3H), 6.50 (d, *J* = 2.1 Hz, 1H), 7.00 (d, *J* = 2.1 Hz, 1H), 12.03 (s, 1H); MS: m/z 277 (M^+, 75), 262 (100); Anal. Calcd for $C_{11}H_{10}NO_4F_3$: C, 47.66; H, 3.64; F, 20.56, N, 5.05. Found: C, 47.50; H, 3.57; F, 20.48; N, 5.03.

5-Amino-7-methoxyflavone (7). To a solution of **5** (277 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added benzoyl chloride (0.14 mL, 1.1 mmol) followed by triethylamine (0.15 mL, 1.1 mmol). The solution was stirred at rt for 3 h and hydrolized by adding water, then extracted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4 and concentrated. The crude was dissolved in dry THF (10 mL) and treated with *t*-BuOK (0.33 g, 3 mmol) and refluxed overnight. After cooling, the solution was poured into water and extracted with ethyl acetate. The extract was dried over Na_2SO_4, evaporated and the crude was dissolved in MeOH (20 mL) and treated with K_2CO_3 (0.27 g, 2 mmol). The solution was heated at 70°C for 3 h, cooled to rt and MeOH was evaporated. The residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was separated, dried over Na_2SO_4 and concentrated. Column chromatography using ethyl:cyclohexane 8:2 as eluent gave 119 mg of **7**. Yield 25%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.85 (s, 3H), 6.00 (d, *J* = 2 Hz, 1H), 6.27 (d, *J* = 2 Hz, 1H), 6.58 (s, 1H), 7.51 (m, 3H), 7.87 (m, 2H); MS: *m/z* 267 (M^+, 100), 238 (45); Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.84; H, 4.86; N, 5.19.

7-Amino-5-methoxyflavone (7a). Prepared starting from 1 mmol of **5a** and following the same procedure as for **7**. 147 mg were obtained. Yield 31%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.92 (s, 3H), 4.25 (br s, 2H), 6.09 (d, *J* = 1.9 Hz, 1H), 6.31 (d, *J* = 1.9 Hz, 1H), 6.60 (s, 1H), 7.47 (m, 3H), 7.82 (m, 2H); MS: *m/z* 267 (M^+, 100), 238 (45), 221 (48), 120 (33); Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.80; H, 4.88; N, 5.21.

REFERENCES AND NOTES

1. M. Cushman, H. Zhu, R. L. Geahlen, and A. J. Kraker, *J. Med. Chem.*, 1994, **37**, 3334.
2. B. D. M. Cunningham, M. D. Threadgill, P. W. Groundwater, I. L. Dale, and J. A. Hickman, *Anti-Cancer Drug Design*, 1992, **7**, 365.
3. T. Akama, H. Ishida, U. Kimura, K. Gomi, and H. Saito, *J. Med. Chem.*, 1998, **41**, 2056.
4. H. K. Wang, Y. Xia, Z-Y. Yang, S. L. Morris-Natschke, and K-H. Lee, *Adv. Exp. Med. Biol.*, 1998, **439**, 191.
5. Y. Xia, Z-Y. Yang, P. Xia, K. F. Bastow, Y. Tachibana, S-C. Kuo, E. Hamel, T. Hackl, and K-H. Lee, *J. Med. Chem.*, 1998, **41**, 1155.
6. S.-X. Zhang, J. Feng, S-C. Kuo, A. Brossi, E. Hamel, A. Tropsha, and K-H. Lee, *J. Med. Chem.*, 2000, **43**, 167.
7. Z. Sui, V. N. Nguyen, J. Altom, J. Fernandez, J. J. Hilliard, J. I. Bernstein, J. F. Barrett, and K. A. Ohemeng, *Eur. J. Med. Chem.*, 1999, **34**, 381.
8. F. Bois, C. Beney, A. Boumendjel, A.-M. Mariotte, G. Conseil, and A. Di Pietro, *J. Med. Chem.*, 1998, **41**, 4161.
9. A. Boumendjel, F. Bois, C. Beney, A.-M. Mariotte, G. Conseil, and A. Di Pietro, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 75.
10. G. Conseil, H. Baubichon-Cortay, G. Dayan, J.-M. Jault, D. Barron, and A. Di Pietro, *Proc. Natl. Acad. Sci. USA.*, 1998, **95**, 9831.
11. F. W. De Azevedo, H. J. Mueller-Dieckmann, U. Schulze-Gahmen, P. J. Worland, and E. H. Sausville, *Proc. Natl. Acad. Sci. U.S.A.*, 1996, **93**, 2735.
12. F. Sicheri, I. Moarefi, and J. Kuriyan, *Nature*, 1997, **385**, 602.
13. M. Hadjeri, A.-M. Mariotte, and A. Boumendjel, *Chem. Pharm. Bull.*, 2001, **10**, 1352.
14. T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1981, pp. 88-92.