Regioselective 3-Nitration of Flavones: A New Synthesis of 3-Nitro- and 3-Aminoflavones

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Abstract: A new, general, and regioselective method for the 3-nitration of flavones have been developed. The nitration reaction is solvent dependent, proceeds via a nitro radical pathway, and the corresponding 3-nitroflavones have been obtained in moderate to very good yields (up to 81%). The reduction of 3-nitroflavones allowed the preparation of the corresponding 3-aminoflavones in very good yields (up to 96%).

Key words: flavones, nitration, regioselectivity, reduction, radical reaction

Flavones are a group of oxygen heterocyclic compounds found in a wide variety of plants where they participate in a variety of biological funtions.[1] Their chemistry as well as their biological and pharmacological properties have been widely studied and reviewed in the last decades.[1,2] Among the various pharmacological activities, those related with inflammation, cancer, and heart diseases have aroused substantial interest.[2]

More recently, it has also been demonstrated that nitro- and aminoflavones possess important biological applications. 3′-Nitroflavones are specific high-affinity ligands for central benzodiazepine receptors, having an anxiolitic action in mice and blocking the muscle-relaxant effect of a full benzodiazepine receptor agonist.[3,4] 3′-Methoxy-4′-nitroflavone is an aryl hydrocarbon receptor antagonist[5] and 2′,3′-dinitroflavone-8-acetic acid proved to be noncytotoxic with the human U937 cell line, exhibiting an exclusive inhibitory aminopeptidase N/CD13 activity, by reversible binding to the catalytic site of the enzyme.[6] 5,4′-Diaminoflavones exhibit potent antitumor activity against certain types of human cell lines both in vitro and in vivo,[7] and 6-aminoflavones are inhibitors of protein-tyrosine kinases[8] and α-glucosidase.[9] Certain 3-nitro- and 3-aminoflavones were found to be highly mutagenic through two different mechanisms and might be used as cancer chemopreventive agents.[10] Furthermore, some of these flavones inhibit the formation of colon aberrant crypt foci of rats[11] and they have also shown antiproliferative properties.[12]

Flavones bearing nitro groups in the A and B rings can be synthesized by the Baker–Venkataraman procedure,[6,8,13–15] starting from the appropriate nitroacetophenones and/or nitrobenzoyl halides, by nitration at the more activated positions of the flavone with nitric acid,[3,8,9] or by cyclodehydrogenation of the corresponding nitro-2′-hydroxychalcones.[16] Routes for the synthesis of 3-nitro derivatives are scarce, only three methods are known. The first centers on the synthesis of 3-nitroflavone (**3a**) in poor yield (42%), by a multistep procedure starting from flavanone.[17] The second follows a three-step procedure via 3-nitroflavanones, starting from 2′-hydroxy-2-nitroacetophenones and aryl aldehydes and producing 3-nitroflavones in moderate yields.[18] The third and the most utilized procedure was established by Dauzonne and co-workers wherein salicylaldehydes and (*Z*)-β-chloro-β-nitrostyrenes are used as starting materials.[6,10–12,19,20] The condensation of these reagents in the presence of triethylamine affords 2-aryl-3-chloro-3,4-dihydro-4-hydroxy-3-nitro-2*H*-1-benzopyrans, which are then oxidized to 2-aryl-3-chloro-2,3-dihydro-3-nitro-4*H*-1-benzopyran-4-ones by pyridinium chlorochromate under sonochemical conditions. These intermediates are easily converted into 3-nitroflavones by a DBU-assisted elimination of hydrogen chloride.

Aminoflavones and their 3-amino derivatives are normally synthesized by reduction of the corresponding nitroflavones with hydrogen/palladium on charcoal or tin/HCl systems.[6,8,9,12,20,21] However, there are other methods for the synthesis of specific derivatives, such as a palladium-catalyzed 7-amination of 7-triflyloxyflavones,[22] direct amination of 3-tosyloxy- or 3-mesyloxyflavones with ammonia or primary amines,[23] and a Claisen condensation of the appropriate aminoacetophenones and ethyl aminobenzoates followed by a cyclization of the obtained 1,3-diketones in acid medium.[7]

The potential applications of 3-nitro- and 3-aminoflavones and the paucity of routes for their synthesis led us to initiate a program to study their synthesis. Several methods are known for nitrating aromatic compounds but they usually require harsh reaction conditions and possess low selectivity, with mixtures of nitrated and dinitrated compounds being obtained depending on substitution of the substrate.[24] Mixtures of inorganic nitrate salts and strong organic acids or anhydrides have been shown to be a selective and mild system for nitration of aromatic compounds and *ipso*-nitration of arylboronic acids.[25] This method was firstly introduced by Crivello,[26] using ammonium nitrate and trifluoroacetic anhydride (TFAA), at 25 °C, to nitrate benzene and other aromatic substrates producing the corresponding nitro derivatives in good

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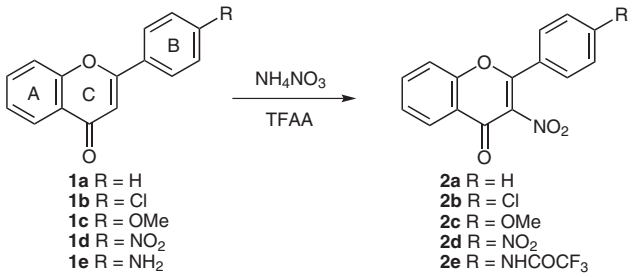
yields. Latter Njoroge and co-workers[2,7] showed that aromatic nitration with tetrabutylammonium nitrate–TFAA proceed by a free-radical method. These results led us to apply this method to the nitration of flavones **1a–e** (Scheme 1).

In a first attempt 4′-chloroflavone (**1b**) was treated with an excess of ammonium nitrate (3 equiv) and TFAA (10 equiv), in a $CHCl_3$–MeCN (1:1) mixture, at 40 °C for 24 hours (Table 1, entry 1), with 4′-chloro-3-nitroflavone (**2b**) being obtained in 53% yield. We then studied the reaction conditions in terms of solvent, amount of TFAA, and reaction time with the best yield of **2b** (72%) being obtained with ammonium nitrate (3 equiv), TFAA (7 equiv), in a CH_2Cl_2–MeCN (1:1) mixture at 40 °C for 1 h (Table 1, entry 3). 4′-Chloro-6-nitroflavone (**3b**) was obtained as a byproduct, resulting from aromatic nitration at one of the most activated positions of the flavone A ring.

We extended our study to the nitration of flavones **1a**,**c**,**d**[28] with the corresponding 3-nitro derivatives **2a**,**c**,**d** being obtained in moderate to good yields (Scheme 1, Table 1). From the range of reaction conditions (amounts of reactants and mixture of solvents) attempted, only those giving better yields in the formation of **2a–d** are presented in Table 1. These results show a regioselective 3-nitration of flavones even in the presence of an activated aromatic B ring (e.g., **1c**).



Scheme 1 Regioselective 3-nitration of flavones **1a–e**

The formation of **2a–e** is dependent on the B-ring substituents of the starting materials **1a–e**. Compound **1c**, bearing an electron-donating substituent (OMe), is very reactive, requiring only one molar equivalent of ammonium nitrate to obtain the 3-nitro derivative **2c** in good yield (50%), together with byproducts 4′-methoxy-3′-nitroflavone (**4c**) and 4′-methoxy-3,3′-dinitroflavone (**5c**, Figure 1), resulting from the nitration at their activated aromatic positions (Table 1, entry 6). Using a slight excess of nitrating agent and other solvent mixtures than $CHCl_3$–MeCN the results did not give better results (Table 1, entries 7, 8). Flavone **2d**, having an electron-withdrawing substituent (4′-NO_2), is less reactive, requiring a great excess (several batches) of nitrating agent for a short reaction time (1 h) to obtain 3,4′-dinitroflavone **1d** in moderate yield (33%, Table 1, entry 11). A small amount of nitrating agent and longer reaction times results in a smaller yield of **2d** and higher yields of byproducts **3d** and **6d** (Table 1, entries 9, 10).

Since the result obtained in the nitration of **1d** was unsatisfactory and the reduction of dinitro derivative **2d** to the corresponding 3-amino derivative was unselective, we decided to perform the reduction of 4′-nitroflavone (**1d**) and to study the nitration of the 4′-aminoflavone (**1e**) so obtained. The nitration reaction of 4′-aminoflavone **1e** afforded the 3-nitro derivative trifluoroacetylated in the 4′-amino group in good yield[29] (73%, Table 1, entry 14), although the acetyl group was easily removed in quantitative yield by treatment with KOH in an H_2O–EtOH (1:1) mixture. The trifluoroacetylated 4′-aminoflavone derivative **7e**[30] was obtained as byproduct (entries 12–14). Since the 3-nitro-4′-aminoflavone was not found in the reaction mixture, the trifluoroacetylation probably occurs prior to the nitration.

From Table 1, one can also conclude that the solvent plays an important role in the reaction rate and selectivity, as mentioned by Crivello,[26] the rate of the reaction seems to be dependent on the solubility of the inorganic salt in reaction medium. In substrates bearing electron-withdrawing groups (deactivated substrates) the reactive species formation should be faster in order to be readily available to react with the substrate; thus a more polar solvent is preferred. On the other hand, in substrates bearing electron-donating substituents (activating substrates) a slow formation of the reactive species is better in order to have a more selective reaction and this is favored by a less polar solvent.

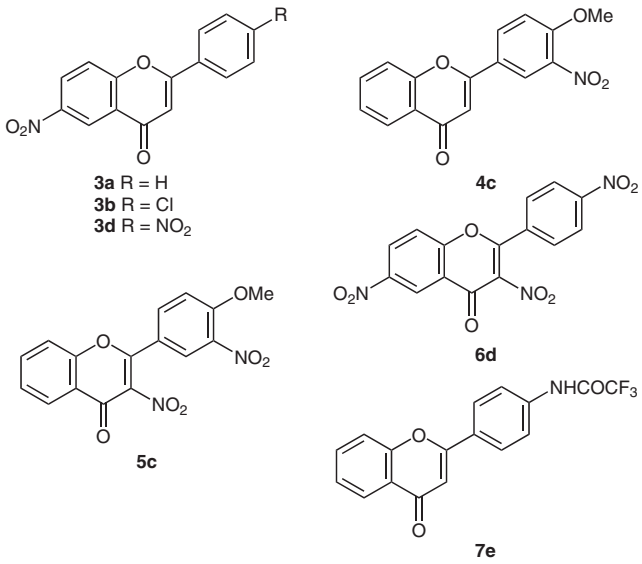


Figure 1 Byproducts obtained in the nitration of flavones **1a–e**

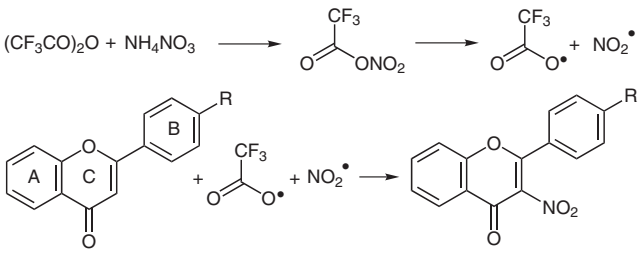
To determine whether the nitration reaction proceeds through a nitronium ion (NO_2^+) or a free-radical mechanism, the nitration of 4′-methoxyflavone (**1c**) was performed in the presence of a free-radical scavenger (TEMPO).[27,32] Analysis after 24 hours showed that no appreciable amount of 4′-methoxy-3-nitroflavone (**4c**, 4%) had been obtained and no side products were formed. These results imply that the reaction occurs through a free radical pathway. The proposed mechanism is similar to

Table 1 Regioselective 3-Nitration of Flavones **1a–e** with Ammonium Nitrate and TFAA

Entry	Substrate[a]	Reagents (equiv)	Solvents[b]	Temp (°C)	Time (h)	Yield of **2a–e** (%)	Yield of byproduct (%)
1	4′-ClFl **1b**	NH_4NO_2 (3) TFAA (10)	$CHCl_3$ MeCN	40	24	**2b**[19b] (53)[c]	**3b**[19b] (2)
2	4′-ClFl **1b**	NH_4NO_2 (3) TFAA (7)	CCl_4 MeCN	40	5	**2b**[19b] (60)[c]	**3b**[19b] (3)
3	4′-ClFl **1b**	NH_4NO_2 (3) TFAA (7)	CH_2Cl_2 MeCN	40	1	**2b**[19b] (72)[c]	**3b**[19b] (2)
4	Fl **1a**	NH_4NO_2 (3) TFAA (7)	CH_2Cl_2 MeCN	40	3	**2a**[19b] (57)[c]	**3a**[12] (2)
5	Fl **1a**	NH_4NO_2 (3) TFAA (7)	CCl_4 MeCN	40	7	**2a**[19b] (81)	**3a**[12] (4)
6	4′-OMeFl **1c**	NH_4NO_2 (1.1) TFAA (2.5)	CH_2Cl_2 MeCN	r.t.	7	**2c**[19b] (50)	**4c**[31] (31), **5c**[12] (7)
7	4′-OMeFl **1c**	NH_4NO_2 (1.1+0.5) TFAA (2.5)	CCl_4 MeCN	r.t.	5	**2c**[19b] (53)	**4c**[31] (27), **5c**[12] (4)
8	4′-OMeFl **1c**	NH_4NO_2 (1.1 + 0.5) TFAA (2.5)	TCB MeCN	r.t.	5	**2c** (29)	**4c**[31] (31), **5c**[12] (3)
9	4′-NO_2Fl **1d**	NH_4NO_2 (4) TFAA (10)	CH_2Cl_2 MeCN	40	4	**2d**[19b] (16)	**6d**[12] (25)
10	4′-NO_2Fl **1d**	NH_4NO_2 (4) TFAA (10)	CCl_4 MeCN	40	22	**2d**[19b] (16)	**3d**[15] (14), **6d**[12] (29)
11	4′-NO_2Fl **1d**	NH_4NO_2 (7) TFAA (14)	MeCN	40	1	**2d**[19b] (33)	**6d**[12] (19)
12	4′-NH_2Fl **1e**	NH_4NO_2 (2.2) TFAA (5)	CCl_4 MeCN	40	1	**2e** (41)	**7e** (56)
13	4′-NH_2Fl **1e**	NH_4NO_2 (2.2) TFAA (5)	CH_2Cl_2 MeCN	40	1	**2e** (27)	**7e** (23)
14	4′-NH_2Fl **1e**	NH_4NO_2 (2.2) TFAA (5)	TCB MeCN	40	1	**2e** (73)	**7e** (6)

[a] Fl = flavone
[b] TCB = 1,2,4-trichlorobenzene.
[c] Some starting material was recovered.

that proposed by other authors,[27,32] involving the reaction of ammonium nitrate with TFAA to form nitronium trifluoroacetate which decomposes to trifluoroacetyl and nitro free radicals; the latter reacts with the substrate to give the nitro derivatives obtained (Scheme 2).



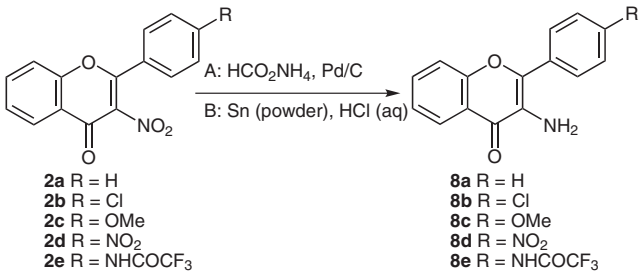
Scheme 2 Proposed mechanism for the regioselective 3-nitration of flavones **1a–e**

In the second part of this work, we studied the reduction of 3-nitroflavones **2a–e** to the corresponding 3-amino derivatives **8a–e** with ammonium formate in the presence of Pd/C (10%), in refluxing acetone (method A)[33] and/or by using tin (powder) with HCl (37%), in chloroform at room temperature (method B,[34] Table 2).

We started the reduction study with method A using methanol as solvent. We found that there was no reaction for a period of 5 minutes, and only after the addition of more catalyst did the reaction proceed. Although it has been stated that the catalytic cycle of this reaction is solvent dependent and occurs very quickly when using methanol as solvent;[35] in our case the methanol proved not to be a good solvent. However, when we changed to acetone, reaction occurred with no need of additional catalyst and 3-aminoflavones **8a–c** were obtained in good yields (87–96%,

Table 2). Method A did not work for substrates **2d** and **2e**, where only degradation products have been obtained.

The reduction of the 3-nitroflavones **2a–e** using method B afforded the expected 3-aminoflavones **8a–e**[36] in good yields (60–88%), reaction being favored by the presence of an electron-donating group on ring B (Scheme 3, Table 2).



Scheme 3 Synthesis of 3-aminoflavones **8a–e**

Table 2 Synthesis of 3-Aminoflavones **8a–e** by Reduction of 3-Nitroflavones **2a–e**

Entry	Substrate	Method[a]	Time (h)	Yield of **8** (%)
1	3-nitroflavone **2a**	A	3	**8a**[12] (88)
2	3-nitroflavone **2a**	B	1	**8a**[12] (80)
3	4′-Cl-3-nitroflavone **2b**	A	3	**8b**[12] (96)
4	4′-Cl-3-nitroflavone **2b**	B	1.5	**8b**[12] (71)
5	4′-OMe-3-nitroflavone **2c**	A	1	**8c**[12] (87)
6	4′-OMe-3-nitroflavone **2c**	B	1	**8c**[12] (88)
7	3,4′-dinitroflavone **2d**	A	3.5	–
8	3,4′-dinitroflavone **2d**	B	1	**8d**[12] (60)
9	4′-($NHCOCF_3$)-3-nitroflavone **2e**	A	5	–
10	4′-($NHCOCF_3$)-3-nitroflavone **2e**	B	1	**8e** (83)

[a] Method A: ammonium formate, Pd/C (10%), acetone, reflux. Method B: Sn (powder), HCl (37%), $CHCl_3$, r.t.

In summary we have developed a new, general, and regioselective method for the radical 3-nitration of flavones that allows the synthesis of 3-nitroflavones in moderate to very good yields (up to 81%). The reduction of these 3-nitroflavones permits the synthesis of the corresponding 3-aminoflavones in very good yields (up to 96%).

Acknowledgment

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References and Notes

(1) (a) *The Flavonoids – Advances in Research Since 1986*; Harborne, J. B., Ed.; Chapman and Hall: London, **1994**. (b) Harborne, J. B.; Williams, C. A. *Phytochemistry* **2000**, *55*, 481.
(2) (a) *Flavonoids in Health and Disease*; Rice-Evans, C.; Packer, L., Eds.; Marcel Dekker: New York, **1998**. (b) Middleton, E. Jr.; Kandaswami, C.; Theoharides, T. C. *Pharmacol. Rev.* **2000**, *52*, 673. (c) Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S. In *Targets in Heterocyclic Systems – Chemistry and Properties*, Vol. 4; Attanasi, O. A.; Spinelli, D., Eds.; Italian Society of Chemistry: Rome, **2001**, 231. (d) Rice-Evans, C. *Curr. Med. Chem.* **2001**, *8*, 797. (e) Manthey, J. A.; Guthrie, N.; Grohmann, K. *Curr. Med. Chem.* **2001**, *8*, 135.
(3) (a) Marder, M.; Viola, H.; Wasowski, C.; Wolfman, C.; Waterman, P. G.; Medina, J. H.; Paladini, A. C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2717. (b) Viola, H.; Marder, M.; Wolfman, C.; Wasowski, C.; Medina, J. H.; Paladini, A. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 373.
(4) Wolfman, C.; Viola, H.; Marder, M.; Wasowski, C.; Ardenghi, P.; Izquierdo, I.; Paladini, A. C.; Medina, J. H. *Eur. J. Pharmacol. Lett.* **1995**, *5*, 2717.
(5) Davis, J. W. II.; Burdick, A. D.; Lauer, F. T.; Burchiel, S. W. *Toxicol. Appl. Pharmacol.* **2003**, *188*, 42.
(6) Bauvois, B.; Puiffe, M.-L.; Bongui, J.-B.; Paillat, S.; Monneret, C.; Dauzonne, D. *J. Med. Chem.* **2003**, *46*, 3900.
(7) Akama, T.; Ishida, H.; Kimura, U.; Gomi, K.; Saito, H. *J. Med. Chem.* **1998**, *41*, 2056.
(8) Cushman, M.; Zhu, H.; Geahlen, R. L.; Kraker, A. J. *J. Med. Chem.* **1994**, *37*, 3353.
(9) Gao, H.; Kawabata, J. *Bioorg. Med. Chem.* **2005**, *13*, 1661.
(10) Beudot, C.; De Méo, M. P.; Dauzonne, D.; Elias, R.; Laget, M.; Guiraud, H.; Balansard, G.; Duménil, G. *Mutation Res.* **1998**, *417*, 141.
(11) Steele, V. E.; Boone, C. W.; Dauzonne, D.; Rao, C. V.; Bensasson, R. V. *Cancer Res.* **2002**, *62*, 6506.
(12) Dauzonne, D.; Folléas, B.; Martinez, L.; Chabot, G. G. *Eur. J. Med. Chem.* **1997**, 71.
(13) Tang, L.; Zhang, S.; Yang, J.; Gao, W.; Cui, J.; Zhuang, T. *Synth. Commun.* **2005**, *35*, 315.
(14) Marder, M.; Viola, H.; Bacigaluppo, J. A.; Colombo, M. I.; Wasowski, C.; Wolfman, C.; Medina, J. H.; Rúveda, J. H.; Paladini, A. C. *Biochem. Biophys. Res. Commun.* **1998**, *249*, 481.
(15) Anand, N.; Venkataraman, F. A. *Proc. Indian Acad. Sci. A* **1947**, *26*, 279.
(16) Barros, A. I. R. N. A.; Silva, A. M. S. *Monatsh. Chem.* **2006**, *137*, 1505.
(17) (a) Michalska, M. *Chem. Ind. (London)* **1966**, 628. (b) Michalska, M. *Bull. Acad. Pol. Sci., Ser. Sci. Chem.* **1968**, *16*, 567.
(18) Paparao, C.; Rao, K. V.; Sundaramurthy, V. *Synthesis* **1981**, 236.
(19) (a) Dauzonne, D.; Demerseman, P. *Synthesis* **1990**, 66. (b) Dauzonne, D.; Grandjean, C. *Synthesis* **1992**, 677.
(20) Dauzonne, D.; Martinez, L. *Tetrahedron Lett.* **1995**, *36*, 1845.

(21) (a) Barros, A. I. R. N. A.; Silva, A. M. S. *Magn. Reson. Chem.* **2006**, *44*, 1122. (b) Barros, A. I. R. N. A.; Dias, A. F. R.; Silva, A. M. S. *Monatsh. Chem.* **2007**, *138*, 585.
(22) Deng, B.-L.; Lepoivre, J. A.; Lumière, G. *Eur. J. Org. Chem.* **1999**, 2683.
(23) Takechi, A.; Takikawa, H.; Miyake, H.; Sasaki, M. *Chem. Lett.* **2006**, *35*, 128.
(24) (a) Olah, G. A.; Malhorta, R.; Narang, S. C. *Nitration – Methods and Mechanism*; VCH: New York, **1989**. (b) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, **2001**.
(25) (a) Salzbrunn, S.; Simon, J.; Prakash, G. K. R.; Petasis, N. A.; Olah, G. A. *Synlett* **2000**, 1485. (b) Prakash, G. K. R.; Panja, C.; Mathew, T.; Surampudi, V.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2004**, *6*, 2205. (c) Deghati, P. Y. F.; Bieraugel, H.; Wanner, M. J.; Koomen, G. J. *Tetrahedron Lett.* **2000**, *41*, 569. (d) Mellor, J. M.; Mittoo, S.; Parkes, R.; Millar, R. W. *Tetrahedron* **2000**, 8019.
(26) Crivello, J. V. *J. Org. Chem.* **1981**, *46*, 3056.
(27) Njoroge, F. G.; Vibulbhan, B.; Pinto, P.; Chang, T.-M.; Osterman, R.; Remiszewski, S.; Del Rosario, J.; Doll, R.; Girijavallabhan, V.; Ganguly, A. K. *J. Org. Chem.* **1998**, *63*, 445.
(28) **General Procedure for the Nitration of Flavones 1a–e: Synthesis of 3-Nitroflavones 2a–e**
To a solution of the appropriate flavone **1a–e** (0.38 mmol) in the requisite solvent (20 mL in total), cooled in an ice bath, NH_4NO_3 and TFAA were added, and the reaction mixture was stirred under conditions indicated in Table 1. After the appropriate reaction time, the reaction mixture was poured into H_2O (20 mL), and extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated to dryness. The mixture was purified by silica gel column chromatography eluting with mixtures of CH_2Cl_2–light PE of increasing polarity to afford the 3-nitroflavones and byproducts (Table 1).
(29) **Physical Data for 3-Nitro-4′-trifluoroacetamidoflavone (1e)**
Mp 228–230 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.65 (ddd, 1 H, *J* = 8.1, 7.0, 1.0 Hz, H-6), 7.84 (d, 2 H, *J* = 8.8 Hz, H-3′,5′), 7.86 (d, 1 H, *J* = 8.4 Hz, H-8), 7.95 (d, 2 H, *J* = 8.8 Hz, H-2′,6′), 7.98 (ddd, 2 H, *J* = 8.4, 7.0, 1.6 Hz, H-7), 8.19 (dd, 1 H, *J* = 8.1, 1.6 Hz, H-5), 11.69 (s, 1 H, 4′-NHCOCF$_3$) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 115.6 (C$_q$, *J* = 288.6 Hz, 4′-NHCO*C*F$_3$), 119.2 (C-8), 121.3 (C-3′,5′), 122.8 (C-10), 124.9 (C-5), 125.5 (C-6), 126.9 (C-1′), 129.2 (C-2′,6′), 136.0 (C-7), 137.5 (C-3), 140.5 (C-4′), 155.0 (C$_q$, *J* = 37.0 Hz, 4′-NH*C*OCF$_3$), 155.2 (C-9), 159.4 (C-2), 168.5 (C-4) ppm. ^{19}F NMR (282.40 MHz, DMSO-d_6): δ = –97.46 (4′-NHCOCF$_3$) ppm. ESI-MS (+): *m/z* (%) = 417 (22) [M + K]$^+$, 401 (100) [M + Na]$^+$, 379 (88) [M + H]$^+$. Anal. Calcd for $C_{17}H_9F_3N_2O_5$: C, 53.96; H, 2.40; N, 7.41. Found: C, 54.02; H, 2.26; N, 7.25.
(30) **Physical Data for 4′-Trifluoroacetamidoflavone (7e)**
Mp 280–282 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.05 (s, 1 H, H-3), 7.51 (ddd, 1 H, *J* = 8.1, 6.9, 1.4 Hz, H-6), 7.79 (dd, 1 H, *J* = 8.4, 1.0 Hz, H-8), 7.85 (ddd, 1 H, *J* = 8.4, 6.8, 1.6 Hz, H-7), 7.90 (d, 2 H, *J* = 8.9 Hz, H-3′,5′), 8.06 (dd, 1 H, *J* = 7.9, 1.4 Hz, H-5), 8.18 (d, 2 H, *J* = 8.9 Hz, H-2′,6′), 11.60 (s, 1 H, 4′-NHCOCF$_3$) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 106.6 (C-3), 115.7 (C$_q$, *J* = 288.7 Hz, 4′-NHCO*C*F$_3$), 118.6 (C-8), 121.1 (C-3′,5′), 123.4 (C-10), 124.9 (C-6), 125.6 (C-5), 127.4 (C-2′,6′), 127.9 (C-1′), 134.4 (C-7), 139.6 (C-4′), 154.8 (C$_q$, *J* = 37.3 Hz, 4′-NH*C*OCF$_3$), 155.7 (C-9), 162.0 (C-2), 177.2 (C-4) ppm. ^{19}F NMR (282.40 MHz, DMSO-d_6): δ = –97.39 (4′-NHCOCF$_3$) ppm. ESI-MS (+): *m/z* (%) = 356 (21) [M + Na]$^+$, 334 (100) [M + 1]$^+$. Anal. Calcd for $C_{17}H_{10}F_3NO_3$: C, 61.27; H, 3.02; N, 4.20. Found: C, 61.06; H, 2.67; N, 4.43.
(31) Cunningham, B. D.; Threadgill, M. D.; Groundwater, P. W.; Dale, I. L.; Hickman, J. A. *Anticancer Drug Des.* **1992**, *7*, 365.
(32) Evans, P. A.; Longmire, J. M. *Tetrahedron Lett.* **1994**, *35*, 8345.
(33) **General Procedure for the Reduction of 3-Nitroflavones 2a–c (Method A): Synthesis of 3-Aminoflavones 8a–c**
Ammonium formate (215 mg; 3.30 mmol) and Pd/C (33 mg) were added to a solution of the 3-nitroflavone **2a–c** (0.33 mmol) in acetone (5 mL), and the reaction mixture was heated at 80 °C for 1 h. After cooling to r.t., the reaction mixture was filtered through Celite, and the organic layer was evaporated to dryness. The residue was purified by column chromatography on silica gel and eluted with CH_2Cl_2 to give the 3-aminoflavones **8a–c** (for yield, see Table 2).
(34) **General Procedure for the Reduction of 3-Nitroflavones 2a–e (Method B): Synthesis of 3-Aminoflavones 8a–e**
To a solution of the 3-nitroflavone **2a–e** (0.33 mmol) in $CHCl_3$ (40 mL), tin(powder) (3.3 g), and HCl (37%, w/v; 11 mL) were added, and the reaction mixture was stirred vigorously for 1 h at r.t. After this period, the reaction mixture was neutralized with $NaHCO_3$, filtered through Celite, and the solid residue washed with H_2O and $CHCl_3$. The filtrate was extracted with $CHCl_3$, the organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The mixture was purified by silica gel column chromatography, eluting with CH_2Cl_2, giving 3-aminoflavones (for yield, see Table 2).
(35) (a) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1986**, 133. (b) Haldar, P.; Mahajani, V. V. *Chem. Eng. J.* **2004**, *104*, 27. (c) Byun, E.; Hong, B.; De Castro, K. A.; Kim, M.; Rhee, H. *J. Org. Chem.* **2007**, *72*, 9815.
(36) **Physical Data for 3-Amino-4′-trifluoroacetamidoflavone (8e)**
Mp 195–196 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.80 (s, 2 H, 3-NH$_2$), 7.43 (ddd, 1 H, *J* = 8.1, 6.9, 1.2 Hz, H-6), 7.67 (ddd, 1 H, *J* = 8.6, 1.2, 0.5 Hz, H-8), 7.76 (ddd, 1 H, *J* = 8.6, 6.9, 1.7 Hz, H-7), 8.04 (d, 2 H, *J* = 9.0 Hz, H-3′,5′), 7.89 (d, 2 H, *J* = 9.1 Hz, H-2′,6′), 8.10 (ddd, 1 H, *J* = 8.1, 1.7, 0.5 Hz, H-5), 11.51 (s, 1 H, 4′-NHCOCF$_3$) ppm. ^{13}C NMR (125.67 MHz, DMSO-d_6): δ = 115.8 (quart, *J* = 288.6 Hz, 4′-NHCO*C*F$_3$), 118.3 (C-8), 120.1 (C-10), 121.0 (C-2′,6′), 124.3 (C-6), 125.0 (C-5), 128.2 (C-3′,5′), 128.6 (C-3), 129.6 (C-1′), 133.3 (C-7), 137.2 (C-4′), 142.3 (C-2), 154.7 (quart, *J* = 37.1 Hz, 4′NH*C*OCF$_3$), 154.7 (C-9), 172.7 (C-4) ppm. ^{19}F NMR (282.40 MHz, DMSO-d_6): δ = –97.36 (s, 4′-NHCOC*F*$_3$) ppm. ESI-MS (+): *m/z* (%) = 371 (21) [M + Na]$^+$, 349 (100) [M + 1]$^+$. Anal. Calcd for $C_{17}H_{11}F_3N_2O_3$: C, 58.63; H, 3.18; N, 8.04. Found: C, 58.42; H, 3.49; N, 7.85.