Tetrahedron 64 (2008) 5055–5060

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A simple and convenient synthesis of 4-methyl-3-nitro-2-trihalomethyl-2*H*-chromenes from *N*-unsubstituted imines of 2-hydroxyacetophenones and trichloro(trifluoro)ethylidene nitromethanes

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ARTICLE INFO

Article history:
Received 19 December 2007
Received in revised form 6 March 2008
Accepted 19 March 2008
Available online 22 March 2008

Keywords:
2-Hydroxyacetophenones imines
Nitroalkenes
Michael addition
4-Methyl-2*H*-chromenes
Trihalomethylated compounds

ABSTRACT

The reaction of *N*-unsubstituted imines of 2-hydroxyacetophenones with trichloro(trifluoro)ethylidene nitromethanes in the presence of DABCO proceeds via tandem oxa-Michael/aza-Henry additions (in dichloromethane) or aza-Michael addition (in benzene) to give 4-methyl-3-nitro-2-trichloro(trifluoro)-methyl-2*H*-chromenes or 1,1,1-trichloro(trifluoro)-3-nitro-*N*-[1-(2-hydroxyaryl)ethylidene]propan-2-amines, respectively.

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1. Introduction

Derivatives of 2*H*-1-benzopyran, also known as 2*H*-chromenes, are prominent natural products, which are widely distributed among many plants.[1] They have considerable biological importance, especially as potentially useful pesticides,[2] endothelin-A (ET_A) selective receptor antagonists,[3] and drug candidates in the field of potassium channel openers (e.g., cromakalim, a highly potent antihypertensive drug).[4] In addition, they are also useful intermediates in the synthesis of complex natural products, such as pterocarpans.[5] The synthesis of 2*H*-chromenes is of considerable current interest. Most pertinent to the present research is synthetic method involving the base-catalyzed condensation of salicylaldehydes with various conjugated olefins[6–8] to give 4-unsubstituted 2*H*-chromenes having electron-withdrawing substituents at the 3-position. Although the biological benefits of the 2*H*-chromenes are widespread, there are very few general methods known to prepare 4-alkyl-2*H*-chromenes. Besides the classic synthesis by the Grignard reagent from chroman-4-ones,[5c] several groups have reported a palladium-catalyzed cyclization of *o*-allylic phenols[9] and thermal cyclization of aryl propargyl ethers[10] and allylic alcohols bearing 2-hydroxyaryl substituent.[11] In this paper we report a novel and convenient synthesis of 4-methyl-2*H*-chromenes involving the condensation of primary imines (*N*-unsubstituted imines) of 2-hydroxyacetophenones **1** with trihaloethylidene derivatives of nitromethane **2**, prepared from trichloro(trifluoro)acetaldehyde hydrates and nitromethane.[12] Although much attention has been paid to the chemistry of alkenes **2** mainly due to the possibility of using them as an excellent building blocks for the preparation of a variety of CX_3-containing compounds,[13] their reactions with primary imines were not described in the literature.

2. Results and discussion

It is well-known that the reactions of salicylaldehydes with nitroalkenes,[6] acrylate derivatives,[7] or α,β-unsaturated ketones[8] proceed via nucleophilic addition of phenolic hydroxyl to an activated C=C bond (oxa-Michael addition) with further cyclization at the formyl group (aldol condensation) leading to the corresponding 2*H*-chromene derivatives. When DABCO was used as a base, a sequence of the Baylis–Hillman reaction and a Michael addition was invoked.[8] We have recently[14] reported the synthesis of 3-nitro-2-trihalomethyl-2*H*-chromenes, which turned out to be highly reactive substrates in the reactions with *N*-, *S*-, and *C*-nucleophiles,[15]

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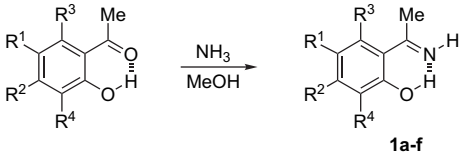
0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.03.065

by the tandem reaction (the Michael addition followed by intramolecular aldol condensation) of salicylaldehydes with (*E*)-3,3,3-trichloro- and 3,3,3-trifluoro-1-nitroprop-1-enes **2a**,**b** in the presence of triethylamine. This one-pot procedure is convenient and straightforward with simple product isolation. However, using 2-hydroxyacetophenone we failed to prepare 4-methyl-3-nitro-2-trihalomethyl-2*H*-chromenes due to the lack of the ketone reactivity to nucleophilic attack compared to salicylaldehyde. The 2-hydroxyacetophenone was recovered unchanged after the reaction. For the condensation with alkenes **2a**,**b** we decided to use *N*-unsubstituted ketimines **1a**–**f**, prepared from the corresponding 2-hydroxyacetophenones and ammonia in methanol at room temperature in excellent yield (Scheme 1, Table 1). These compounds are quite stable (no hydrolysis has been detected when stored in pure form) and can be regarded as useful precursors to a variety of pharmaceutically attractive chroman and chromene derivatives.



Scheme 1.

The presence of the *ortho*-hydroxy group stabilizes the imine function by enforcing a strong intramolecular hydrogen bonding. Indeed, the observed ^{1}H NMR chemical shift of the *ortho*-hydroxy proton for all the ketimines **1a**–**f** is higher (δ_{OH}=14.8–16.2 ppm) than the same chemical shift of the corresponding ketones (δ_{OH}=12.3–14.0 ppm) and thioketones (δ_{OH}=13.4–14.2 ppm).[17] This observation allows the conclusion that the intramolecular O–H···N=C hydrogen bonding in the ketimines is stronger than the corresponding hydrogen bonding in the parent ketones and thioketones.

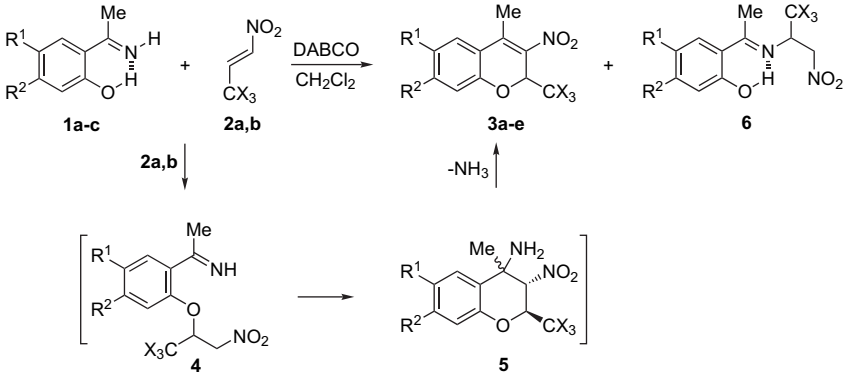
Table 1
Synthesis of ketimines **1a**–**f**

Imine	R^1	R^2	R^3	R^4	Yield (%)	Mp (°C)
1a	H	H	H	H	96	139–140[a]
1b	Me	H	H	H	86	168–169
1c	H	MeO	H	H	82	184–185
1d	Cl	H	H	H	86	195–196
1e	H	Me	Me	H	80	152–153
1f	Br	H	H	Br	90	259–260

[a] Lit.[16] mp 143 °C.

To the best of our knowledge, *N*-unsubstituted ketimines **1** have not been examined in a tandem process utilizing activated alkenes, although these compounds without isolation and purification were used for the condensation of *o*-hydroxyaryl ketones with Meldrum's acid.[18] On the other hand, there is no report dealing with 3-nitro-2*H*-chromene having an active methyl group at the 4-position except for a single description.[6e] This fact encouraged us to investigate the annulation reaction utilizing readily accessible ketimines **1** and nitroalkenes **2**, which appears to proceed through base-catalyzed tandem conjugate addition/Henry-type reaction and affords a convenient one-pot synthesis of biologically interesting 4-methyl-2*H*-chromenes **3** under mild reaction conditions. A plausible mechanism for this synthetically useful reaction is illustrated in Scheme 2. The key intermediate **4** generated from oxa-Michael addition of the aryl oxide to the activated olefin **2** apparently undergoes intramolecular aza-Henry cyclization to afford the 4-amino-4-methylchroman derivative **5** followed by deamination to the desired 4-methyl-2*H*-chromene **3**. However, when **2** reacts faster with the imino nitrogen atom than with phenolic hydroxyl, aza-Michael addition could also lead to the *N*-substituted imine **6**. Although this unwanted reaction appears to be fairly competitive, we still felt that we might be able to suppress it by adjusting the reaction conditions, for example, using different solvents to promote oxa-Michael addition followed by cyclization over aza-Michael reaction.

We first examined the reaction of ketimine **1a** and (*E*)-3,3,3-trichloro-1-nitropropene **2a** in the presence of DABCO (5 mol %) in benzene. After 5 h reaction at reflux, a 3:1 mixture of aza-Michael addition product **6a** and chromene **3a** was obtained, from which **6a** with *E*-configuration was isolated in 64% yield. When a similar experiment was carried out in ethanol, the ^{1}H NMR spectrum of the crude product showed a 3:1:1 mixture of chromenes **3a**, *E*-**6a**, and *Z*-**6b**, respectively. In both cases, some amount of 2-hydroxyacetophenone was observed, indicating that partial hydrolysis of **1a** had occurred. After some optimization, it was found that treatment of ketimines **1a**–**c** with alkenes **2a**,**b** (1.2 equiv) in the presence of DABCO (2–5 mol %) in refluxing CH_2Cl_2 for several hours gave 4-methyl-3-nitro-2-trihalomethyl-2*H*-chromenes **3a**–**e** in yields 55–71% (Scheme 2). Under these conditions, most of the product is chromene **3** with a small amount of imine **6** (*E*-isomer). The progress of the reaction was monitored by TLC, and the results are summarized in Table 2. Among different solvents (benzene, toluene, $CHCl_3$, EtOH), which have been tested to perform the reaction, CH_2Cl_2 appeared to give the best results. The reaction works well with DABCO as a base, while the use of Et_3N resulted in a lower yield of chromenes **3**. It should be noted that the reaction seems to depend on the electronic nature of the substituent on the benzene ring. Thus, when imines **1d**,**f** with electron-withdrawing halogen atoms were employed under the different reaction conditions, the corresponding chromenes were not obtained, probably due to the lower nucleophilicity of the phenolate anions. Efforts to carry out an analogous cyclization with non-halogenated substrate, such as ω-nitrostyrene, were unsuccessful. The reaction only gave undefined



Scheme 2.

Table 2
Synthesis of 4-methyl-2*H*-chromenes **3a**–**e** and chroman **5b**

Imine	Alkene	R^1	R^2	X	Product	Yield (%)	Time (h)	Mp (°C)
1a	**2a**	H	H	Cl	**3a**	66	5	114–115
1b	**2a**	Me	H	Cl	**3b**[a]	62	0.5	88–89
1c	**2a**	H	MeO	Cl	**3c**	55	8	87–88
1a	**2b**	H	H	F	**3d**	71	3	65–66
1b	**2b**	Me	H	F	**3e**	68	2	80–81
1b	**2a**	Me	H	Cl	**5b**[b]	60	3	122–123

[a] Obtained from **5b**.
[b] Obtained at 5 °C.

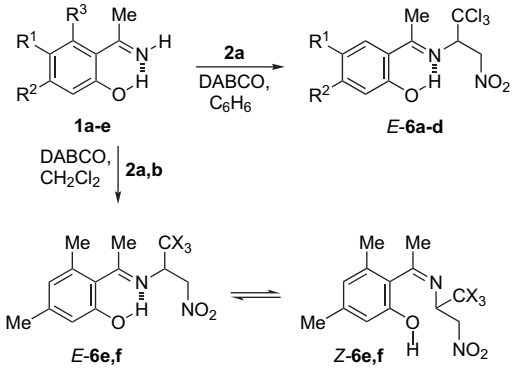
mixture of compounds that did not include the desired 4-methyl-3-nitro-2-phenyl-2*H*-chromene. It seems that the CX_3 group favors the initial oxa-Michael addition reaction due to its electron-withdrawing character, which lowers the LUMO level of the molecule.[19] In the light of the present interest in halogen-containing compounds as pharmaceutical intermediates,[20] this novel entry to halogenated derivatives of 2*H*-chromene with an active methyl group is noteworthy and will complement the published synthetic methods.

Except for **5b**, the intermediate 4-aminochromans **5** were not observed, indicating their immediate deamination to the corresponding 4-methyl-2*H*-chromenes **3**. However, when a similar experiment (DABCO, CH_2Cl_2) was carried out with ketimine **1b** and alkene **2a**, the ^{1}H NMR spectrum of the crude product showed an 80:15:5 mixture of **5b**, *E*-**6b**, and **3b**, respectively. Analytically pure 4,6-dimethyl-3-nitro-2-(trichloromethyl)chroman-4-amine **5b** (60%) was obtained in CH_2Cl_2 in the presence of DABCO or Et_3N at 5 °C as a mixture of two diastereomers in a ratio of 82:18, which was easily converted into chromene **3b** (62%) by refluxing in toluene for 0.5 h with a catalytic amount of concd H_2SO_4. Chromene **3b** can be prepared directly from **1b** and **2a** by refluxing in CH_2Cl_2 in the presence of Et_3N in low yield (20%). The configuration of the C-2 and C-3 atoms of **5b** was assigned based on the large coupling constants ($J_{2,3}$=8.1 Hz for major isomer and $J_{2,3}$=7.8 Hz for minor isomer), which are indicative of the axial positions of the H-2 and H-3 atoms and, consequently, the trans configuration of the equatorial substituents in a half-chair conformation.[15] The configuration at the C-4 atom was not determined.

The structures of compounds **3** compare well with the results of elemental analysis, ^{1}H NMR, ^{19}F NMR, and IR spectroscopies. A characteristic feature of the ^{1}H NMR spectra of **3a**–**e** is the appearance of doublet at δ 2.50–2.63 ppm for the Me group and quartet at δ 6.11–6.31 ppm for H-2 proton (quartet of quartets for **3d**,**e**) due to the long-range coupling constants $^5J_{H,H}$=0.7–0.9 Hz. In the ^{19}F NMR spectra CF_3 group of **3d**,**e** manifest itself as a doublet at 84.2–84.3 ppm with $^3J_{F,H}$=6.6 Hz. The IR spectra of **3a**–**e** showed the absorption bands at 1629–1636 (C=C) and 1567–1578, 1320–1366 (NO_2) cm^{-1}. Since all of the 4-methyl-3-nitro-2*H*-chromenes prepared here are hitherto unknown, the chemical properties of these compounds intrigued us, and they will be used for synthesis of novel functionalized systems possessing a chromene ring.

Next, we investigated the reaction of alkenes **2a**,**b** with 4,6-dimethyl-2-hydroxyacetophenone imine **1e** under the same reaction conditions. It turned out that unlike imines **1a**–**c**, the presence of an *ortho*-substituent on the aryl ring inhibits the addition reaction between phenolic hydroxyl and activated double bond of **2a**,**b**. In this case, *N*-substituted imines **6e**,**f** were obtained as a mixture of *Z*- and *E*-isomers instead of the corresponding chromene derivatives. It is probable that the failure experienced with *ortho*-methyl group arises from steric requirements involved in ring closure and not from its inductive effect. The ^{1}H NMR spectrum of **6f** in DMSO-d_6 solution contained only one set of signals. The choice between *Z*-**6f** and *E*-**6f** was made in favor of the former on the basis of analysis of the data of 2D HSQC, HMBC, and NOESY experiments. In particular, the NOESY spectrum of **6f** exhibits a cross-peak between the proton of the OH group and one of the diastereotopic methylene protons, indicating that they are spatially close to each other and, hence, **6f** in DMSO-d_6 has *Z*-configuration.

When the reaction of **1a**–**d** with **2a** was carried out in refluxing benzene in the presence of DABCO (5 mol%) for several hours, *N*-substituted imines **6a**–**d** were obtained in low to moderate yields (Scheme 3). Due to the low reactivity of **1d**, the use of toluene instead of benzene was necessary; stable imine **1f** derived from 3,5-dibromo-2-hydroxyacetophenone was recovered unchanged. Only a small amount of (*E*)-1,1,1-trifluoro-3-nitro-*N*-[1-(2-hydroxyphenyl)ethylidene]propan-2-amine **6g** from the reaction of **1a** with CF_3–alkene **2b** has been detected by ^{1}H NMR spectroscopy, and no effort was made to isolate it in pure form. The progress of the reaction was monitored by TLC, and the results are summarized in Table 3. In the ^{1}H NMR spectra of **6a**–**d**, the ABX-system of the CH_2CH fragment (J_{AB}=13.6–13.8 Hz, J_{AX}=8.9–9.0 Hz, J_{BX}=2.3–2.5 Hz) is observed. The IR spectra of **6a**–**d** showed the absorption bands at 1605–1617 (C=N) and 1556–1557, 1374–1377 (NO_2) cm^{-1}. Thus, 4-methyl-2*H*-chromenes **3** and *N*-substituted imines **6** could be synthesized controllably from the same starting material just by choice of solvent.



Scheme 3.

All signals in the ^{1}H and ^{13}C NMR spectra of compound **6a** were assigned on the basis of 2D HSQC and HMBC experiments. To determine the stereochemistry of **6a** and to verify the assignment in other compounds of type **6**, NOESY spectrum of **6a** was recorded. It exhibits a cross-peak between the protons of the Me and CH groups and does not show any connectivities between the OH and CH_2 protons. This result clearly demonstrates that compound **6a** is the *E*-isomer. In the case of this configuration, the molecule can be stabilized due to the formation of an intramolecular hydrogen bond between the phenolic hydroxyl and the imine nitrogen atom. As expected, for compounds *E*-**6a**–**d** a strong intramolecular hydrogen bond was observed (δ_{OH}=13.8–14.7 ppm in both $CDCl_3$ and DMSO-d_6 solutions). This explains the formation of *E*-isomers **6a**–**d** preferentially.

In contrast, a weak intramolecular hydrogen bond was observed for *E*-**6e**,**f** in $CDCl_3$ (δ_{OH}=9.5–12.0 ppm) due to unfavorable interactions between the *ortho*- and ketimine Me groups, which

Table 3
Synthesis of *N*-substituted imines **6a**–**f**

Imine	Alkene	R^1	R^2	R^3	X	Product	Yield (%)	Time (h)	Mp (°C)
1a	**2a**	H	H	H	Cl	**6a**	64	5	74–75
1b	**2a**	Me	H	H	Cl	**6b**	25	3	95–96
1c	**2a**	H	MeO	H	Cl	**6c**	25	4	114–115
1d	**2a**	Cl	H	H	Cl	**6d**	17	2	104–105
1e	**2a**	Me	H	Me	Cl	**6e**	41	5	112–113
1e	**2b**	Me	H	Me	F	**6f**	60	3	171–172

hinder the formation of the planar conformation required for a strong hydrogen bond. As a result, the ^{1}H NMR spectra of **6e**,**f** in $CDCl_3$ solution contained two sets of signals, one of which belonged to *E*-isomer (95% for **6e** and 45% for **6f**) and another set was attributed to the *Z*-isomer. In DMSO-d_6 solution of **6e**,**f**, the *Z*-configuration was the prevailing form (80% for **6e** and 100% for **6f**) since a weak intramolecular OH···N=C hydrogen bond, which stabilizes *E*-isomer in $CDCl_3$, is broken under the action of basic dimethyl sulfoxide molecules and another intermolecular OH···DMSO hydrogen bond is formed (δ_{OH}=9.8 ppm). These results indicate that the *ortho*-Me group in **1e** has an important role in the (*E*)→(*Z*) isomerization of imines **6e**,**f**. The determination of the geometrical isomers ratio that is influenced by the nature of the CX_3 group can easily be performed by ^{1}H NMR spectroscopic analysis. A characteristic difference between two stereoisomers is based on chemical shift of the CH proton, which shifted downfield by 0.6–0.7 ppm in *E*-isomer compared with *Z*-isomer. In the crystalline state, these compounds exist mainly in *Z*-form as evidenced by their IR spectra recorded in KBr: the absorption band of the non-bonded and non-conjugated C=N group at 1636–1651 cm^{-1} is present.

3. Conclusion

The reaction of *N*-unsubstituted imines of 2-hydroxyacetophenones with activated trihalomethyl substituted nitroalkenes provides a simple and convenient preparative procedure from readily available starting materials to 4-methyl-3-nitro-2-trihalomethyl-2*H*-chromenes, which may be considered as new precursors in the synthesis of other highly functionalized biologically and medicinally important products. Although two competitive routes were observed, the reaction pathways could be controlled with respect to prevailing 4-methyl-2*H*-chromene derivatives. This method is simple, proceeds in good yields, and the isolation of intermediates is not necessary.

4. Experimental

4.1. General

^{1}H (400 MHz), ^{13}C (100 MHz) and ^{19}F (376 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer in DMSO-d_6 with TMS and C_6F_6 as internal standards, respectively. IR spectra were recorded on a Perkin–Elmer Spectrum BX-II instrument as KBr discs. Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Melting points are uncorrected. All solvents used were dried and distilled as per standard procedures. The starting nitroalkenes **2a**,**b** were prepared according to described procedure.[14]

4.2. General procedure for ketimines 1a–f

A mixture, prepared by passing dry ammonia into a solution of the corresponding 2-hydroxyacetophenone (2.0 mmol) in dry methanol (3 mL) until saturated (ca. 15 min), was kept for 24 h at ~20 °C. The precipitate formed was filtered, washed with hexane, and dried in air to give ketimines **1a**–**f** as yellow powder (Table 1).

*4.2.1. 2-Hydroxyacetophenone imine (**1a**)*

Yield 96%, mp 139–140 °C (lit.[16] mp 143 °C); IR (KBr) 3200–2400, 1607, 1523, 1470 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H, Me), 6.80 (td, 1H, H-5, *J*=7.7, 1.2 Hz), 6.97 (dd, 1H, H-3, *J*=8.4, 1.1 Hz), 7.34 (ddd, 1H, H-4, *J*=8.5, 7.2, 1.7 Hz), 7.49 (dd, 1H, H-6, *J*=8.0, 1.7 Hz), 9.19 (br s, 1H, NH), 15.17 (br s, 1H, OH).

*4.2.2. 2-Hydroxy-5-methylacetophenone imine (**1b**)*

Yield 86%, mp 168–169 °C; IR (KBr) 3100–2400, 1620, 1522, 1481 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H, Me), 2.47 (s, 3H, Me), 6.88 (d, 1H, H-3, *J*=8.4 Hz), 7.15 (dd, 1H, H-4, *J*=8.4, 2.0 Hz), 7.27 (br d, 1H, H-6, *J*=1.5 Hz), 9.16 (br s, 1H, NH), 14.83 (br s, 1H, OH). Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.51; H, 7.48; N, 9.30.

*4.2.3. 2-Hydroxy-4-methoxyacetophenone imine (**1c**)*

Yield 82%, mp 184–185 °C; IR (KBr) 3200–2500, 1614, 1549, 1517, 1462 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (d, 3H, Me, *J*=0.9 Hz), 3.80 (s, 3H, MeO), 6.27 (dd, 1H, H-5, *J*=9.0, 2.5 Hz), 6.35 (d, 1H, H-3, *J*=2.5 Hz), 7.32 (d, 1H, H-6, *J*=9.0 Hz), 8.04 (br s, 1H, NH), 15.46 (s, 1H, OH). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.24; H, 6.79; N, 8.55.

*4.2.4. 5-Chloro-2-hydroxyacetophenone imine (**1d**)*

Yield 86%, mp 195–196 °C; IR (KBr) 3100–2500, 1601, 1538, 1513, 1473 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (d, 3H, Me, *J*=1.4 Hz), 6.92 (d, 1H, H-3, *J*=8.9 Hz), 7.28 (dd, 1H, H-4, *J*=8.9, 2.6 Hz), 7.45 (d, 1H, H-6, *J*=2.6 Hz), 9.26 (br s, 1H, NH), 15.12 (br s, 1H, OH). Anal. Calcd for C_8H_8ClNO: C, 56.65; H, 4.75; N, 8.26. Found: C, 56.64; H, 4.54; N, 8.13.

*4.2.5. 4,6-Dimethyl-2-hydroxyacetophenone imine (**1e**)*

Yield 80%, mp 152–153 °C; IR (KBr) 3500–2700, 1593, 1523, 1474 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H, Me), 2.47 (s, 3H, Me), 2.54 (s, 3H, Me), 6.44 (s, 1H, H-5), 6.66 (s, 1H, H-3), 7.5–13.5 (br s, 2H, NH, OH). Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N 8.58. Found: C, 73.43; H, 7.89; N, 8.26.

*4.2.6. 3,5-Dibromo-2-hydroxyacetophenone imine (**1f**)*

Yield 90%, mp 259–260 °C; IR (KBr) 3200–2800, 1614, 1584, 1531, 1499 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H, Me), 7.54 (d, 1H, H-4, *J*=2.4 Hz), 7.75 (d, 1H, H-6, *J*=2.4 Hz), 8.73 (br s, 1H, NH), 16.21 (br s, 1H, OH); (DMSO-d_6) δ 2.55 (s, 3H, Me), 7.62 (d, 1H, H-4, *J*=2.6 Hz), 7.73 (d, 1H, H-6, *J*=2.6 Hz), 10.81 (br s, 1H, NH), 14.83 (br s, 1H, OH). Anal. Calcd for $C_8H_7Br_2NO$: C, 32.80; H, 2.41; N, 4.78. Found: C, 32.87; H, 2.40; N, 4.57.

4.3. General procedure for 4-methyl-2*H*-chromenes 3a–e

A solution of the corresponding imine (1.0 mmol), nitroalkene (1.2 mmol), and DABCO (2–5 mol %) in dry dichloromethane (4 mL) was refluxed until the reaction was completed (TLC, Table 2). The reaction mixture was then evaporated, and the residue was washed with ethanol (1 mL). The solid product was recrystallized from hexane to give pure product **3** as yellow powder or needles.

*4.3.1. 4-Methyl-3-nitro-2-(trichloromethyl)-2H-chromene (**3a**)*

Yield 66%, mp 114–115 °C; IR (KBr) 1632, 1605, 1571, 1521, 1486, 1335 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (d, 3H, Me, *J*=0.9 Hz), 6.27 (q, 1H, H-2, *J*=0.8 Hz), 7.09 (dd, 1H, H-8, *J*=8.2, 1.2 Hz), 7.11 (td, 1H, H-6, *J*=7.6, 1.2 Hz), 7.41 (ddd, 1H, H-7, *J*=8.2, 7.4, 1.6 Hz), 7.50 (dd, 1H, H-5, *J*=7.8, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.37 (Me), 80.73 (C2), 99.28 (CCl_3), 116.48 (C8), 120.34 (C4a), 123.14 (C6), 126.68 (C5), 133.35 (C7), 135.77 (C3), 138.36 (C4), 152.37 (C8a). Anal. Calcd for $C_{11}H_8Cl_3NO_3$: C, 42.87; H, 2.61; N, 4.54. Found: C, 42.62; H, 2.58; N, 4.55.

*4.3.2. 4,6-Dimethyl-3-nitro-2-(trichloromethyl)-2H-chromene (**3b**)*

A mixture of 4,6-dimethyl-3-nitro-2-(trichloromethyl)chroman-4-amine **5b** (0.33 g, 1.0 mmol) and concd H_2SO_4 (10 mol %) was refluxed in toluene (4 mL) for 0.5 h. The resulting solution was cooled, filtered, concentrated under reduced pressure, and the precipitate that formed was recrystallized from hexane to give pure

product **3b** as yellow powder. Yield 0.20 g (62%), mp 88–89 °C; IR (KBr) 1636, 1614, 1578, 1523, 1489, 1336 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H, Me), 2.50 (d, 3H, Me, J=0.7 Hz), 6.25 (q, 1H, H-2, J=0.7 Hz), 6.99 (d, 1H, H-8, J=8.3 Hz), 7.21 (dd, 1H, H-7, J=8.3, 1.6 Hz), 7.27 (br d, 1H, H-5, J=1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.40 (Me), 20.76 (Me), 80.71 (C2), 99.37 (CCl_3), 116.20 (C8), 120.04 (C4a), 126.85 (C5), 132.57 (C6), 134.08 (C7), 135.77 (C3), 138.58 (C4), 150.29 (C8a). Anal. Calcd for $C_{12}H_{10}Cl_3NO_3$: C, 44.68; H, 3.12; N, 4.34. Found: C, 44.71; H, 3.06; N, 4.20.

4.3.3. 7-Methoxy-4-methyl-3-nitro-2-(trichloromethyl)-2H-chromene (**3c**)

Yield 55%, mp 87–88 °C; IR (KBr) 1636, 1604, 1569, 1509, 1330 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.52 (d, 3H, Me, J=0.8 Hz), 3.86 (s, 1H, MeO), 6.31 (q, 1H, H-2, J=0.8 Hz), 6.61 (d, 1H, H-8, J=2.5 Hz), 6.66 (dd, 1H, H-6, J=8.7, 2.5 Hz), 7.42 (d, 1H, H-5, J=8.7 Hz). Anal. Calcd for $C_{12}H_{10}Cl_3NO_4$: C, 42.57; H, 2.98; N, 4.14. Found: C, 42.52; H, 2.97; N, 4.11.

4.3.4. 4-Methyl-3-nitro-2-(trifluoromethyl)-2H-chromene (**3d**)

Yield 71%, mp 65–66 °C; IR (KBr) 1629, 1605, 1567, 1506, 1486, 1452, 1366, 1320 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.63 (d, 3H, Me, J=0.9 Hz), 6.14 (qq, 1H, H-2, J=6.6, 0.9 Hz), 7.06 (dd, 1H, H-8, J=8.2, 1.2 Hz), 7.14 (td, 1H, H-6, J=7.7, 1.2 Hz), 7.42 (ddd, 1H, H-7, J=8.2, 7.4, 1.5 Hz), 7.56 (dd, 1H, H-5, J=7.9, 1.5 Hz); (DMSO-d_6) δ 2.61 (d, 3H, Me, J=0.8 Hz), 6.57 (qq, 1H, H-2, J=7.0, 0.8 Hz), 7.17 (dd, 1H, H-8, J=8.2, 1.0 Hz), 7.23 (td, 1H, H-6, J=7.9, 1.0 Hz), 7.53 (ddd, 1H, H-7, J=8.2, 7.9, 1.5 Hz), 7.80 (dd, 1H, H-5, J=7.9, 1.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 84.19 (d, CF_3, J=6.6 Hz); (DMSO-d_6) δ 86.38 (d, CF_3, J=7.0 Hz); MS m/z (EI, 70 eV) 259 $[M]^+$ (18), 190 $[M-CF_3]^+$ (100), 144 $[M-CF_3-NO_2]^+$ (85), 115 (60), 89 (25), 69 $[CF_3]^+$ (8). Anal. Calcd for $C_{11}H_8F_3NO_3$: C, 50.98; H, 3.11; N, 5.40. Found: C, 50.74; H, 3.16; N, 5.40.

4.3.5. 4,6-Dimethyl-3-nitro-2-(trifluoromethyl)-2H-chromene (**3e**)

Yield 68%, mp 80–81 °C; IR (KBr) 1632, 1576, 1511, 1490, 1362, 1320 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H, Me), 2.62 (d, 3H, Me, J=0.7 Hz), 6.11 (qq, 1H, H-2, J=6.6, 0.7 Hz), 6.95 (d, 1H, H-8, J=8.3 Hz), 7.22 (dd, 1H, H-7, J=8.3, 1.8 Hz), 7.33 (d, 1H, H-5, J=1.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 84.26 (d, CF_3, J=6.6 Hz). Anal. Calcd for $C_{12}H_{10}F_3NO_3$: C, 52.75; H, 3.69; N, 5.13. Found: C, 52.44; H, 3.39; N, 5.33.

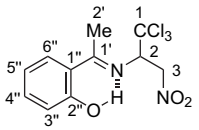
4.3.6. 4,6-Dimethyl-3-nitro-2-(trichloromethyl)chroman-4-amine (**5b**)

A mixture of 2-hydroxy-5-methylacetophenone imine **1b** (0.15 g, 1.0 mmol), 3,3,3-trichloro-1-nitropropene **2a** (0.23 g, 1.2 mmol), and DABCO or Et_3N (5 mol %) was dissolved in dry dichloromethane or ethanol (4 mL) and kept for 3 h at ~5 °C. The precipitated crystals were filtered and recrystallized from hexane. Yield 0.20 g (60%), mp 122–123 °C, colorless powder; IR (KBr) 3398, 3335, 1632, 1555, 1494, 1359 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (major isomer, 82%) 1.41 (s, 3H, Me), 1.70 (br s, 2H, NH_2), 2.34 (s, 3H, Me), 4.74 (d, 1H, H-3, J=8.1 Hz), 5.64 (d, 1H, H-2, J=8.1 Hz), 6.95 (d, 1H, H-8, J=8.2 Hz), 7.09 (dd, 1H, H-7, J=8.2, 1.7 Hz), 7.47 (d, 1H, H-5, J=1.7 Hz); (minor isomer, 18%) 1.66 (s, 3H, Me), 1.70 (br s, 2H, NH_2), 2.34 (s, 3H, Me), 5.00 (d, 1H, H-3, J=7.8 Hz), 5.44 (d, 1H, H-2, J=7.8 Hz), 7.01 (d, 1H, H-8, J=8.2 Hz), 7.12 (br d, 1H, H-7, J=8.2 Hz), 7.23 (br s, 1H, H-5, J=1.7 Hz). Anal. Calcd for $C_{12}H_{13}Cl_3N_2O_3$: C, 42.44; H, 3.86; N, 8.25. Found: C, 42.50; H, 3.90; N, 8.25.

4.4. General procedure for *N*-substituted imines 6a–d

A mixture of the corresponding imine **1** (1.0 mmol), 3,3,3-trichloro-1-nitropropene **2a** (0.23 g, 1.2 mmol), and DABCO (5 mol %) in dry benzene (4 mL) (toluene for **1d**) was refluxed until the reaction was completed (TLC, Table 3). The resulting solution was concentrated under reduced pressure, and the precipitate that formed was recrystallized from hexane–benzene (2:1) or purified by simple short silica gel column chromatography to give pure product **6** as light-yellow or colorless powder.

4.4.1. (E)-1,1,1-Trichloro-3-nitro-N-[1-(2-hydroxyphenyl)-ethylidene]propan-2-amine (**6a**)



Yield 64%, mp 74–75 °C; IR (KBr) 1613, 1557, 1522, 1501, 1376 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H, Me), 4.87 (dd, 1H, C*H*H, J=13.7, 8.9 Hz), 5.26 (dd, 1H, CH*H*, J=13.7, 2.5 Hz), 5.39 (dd, 1H, CH, J=8.9, 2.5 Hz), 6.89 (ddd, 1H, H-5, J=8.1, 7.2, 1.1), 6.98 (dd, 1H, H-3, J=8.4, 1.1 Hz), 7.38 (ddd, 1H, H-4, J=8.4, 7.2, 1.6 Hz), 7.63 (dd, 1H, H-6, J=8.1, 1.6 Hz), 14.05 (br s, 1H, OH); (DMSO-d_6) δ 2.58 (s, 3H, Me), 5.05 (dd, 1H, C*H*H, J=13.9, 8.2 Hz), 5.52 (dd, 1H, CH*H*, J=13.9, 3.3 Hz), 5.67 (dd, 1H, CH, J=8.2, 3.3 Hz), 6.89 (dd, 1H, H-3, J=8.3, 1.2 Hz), 6.91 (ddd, 1H, H-5, J=8.0, 7.2, 1.2 Hz), 7.41 (ddd, 1H, H-4, J=8.3, 7.2, 1.6 Hz), 7.80 (dd, 1H, H-6, J=8.0, 1.6 Hz), 14.17 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.33 (C2′), 69.95 (C2), 77.10 (C3), 98.73 (C1), 117.67 (C3″), 118.38 (C5″), 119.30 (C1″), 130.16 (C6″), 133.66 (C4″), 161.17 (C2″), 178.49 (C1′). Anal. Calcd for $C_{11}H_{11}Cl_3N_2O_3$: C, 40.58; H, 3.41; N, 8.60. Found: C, 40.58; H, 3.49; N, 8.36.

4.4.2. (E)-1,1,1-Trichloro-3-nitro-N-[1-(2-hydroxy-5-methylphenyl)-ethylidene]propan-2-amine (**6b**)

Yield 25%, mp 95–96 °C; IR (KBr) 1605, 1572, 1557, 1493, 1374 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H, Me), 2.55 (s, 3H, Me), 4.86 (dd, 1H, C*H*H, J=13.7, 8.9 Hz), 5.25 (dd, 1H, CH*H*, J=13.7, 2.3 Hz), 5.38 (dd, 1H, CH, J=8.9, 2.3 Hz), 6.89 (d, 1H, H-3, J=8.4 Hz), 7.19 (dd, 1H, H-4, J=8.4, 2.0 Hz), 7.41 (br s, 1H, H-6), 13.84 (br s, 1H, OH); (DMSO-d_6) δ 2.27 (s, 3H, Me), 2.56 (s, 3H, Me), 5.02 (dd, 1H, C*H*H, J=13.8, 8.3 Hz), 5.52 (dd, 1H, CH*H*, J=13.8, 3.3 Hz), 5.64 (dd, 1H, CH, J=8.3, 3.3 Hz), 6.78 (d, 1H, H-3, J=8.4 Hz), 7.22 (dd, 1H, H-4, J=8.4, 2.0 Hz), 7.60 (br d, 1H, H-6, J=1.6 Hz), 13.89 (s, 1H, OH). Anal. Calcd for $C_{12}H_{13}Cl_3N_2O_3$: C, 42.44; H, 3.86; N, 8.25. Found: C, 42.30; H, 3.67; N, 8.12.

4.4.3. (E)-1,1,1-Trichloro-3-nitro-N-[1-(2-hydroxy-4-methoxyphenyl)ethylidene]propan-2-amine (**6c**)

Yield 25%, mp 114–115 °C; IR (KBr) 1617, 1599, 1557, 1515, 1377 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H, Me), 3.83 (s, 3H, MeO), 4.86 (dd, 1H, C*H*H, J=13.6, 9.0 Hz), 5.24 (dd, 1H, CH*H*, J=13.6, 2.5 Hz), 5.36 (dd, 1H, CH, J=9.0, 2.5 Hz), 6.43–6.46 (m, 2H, H-3, H-5), 7.52 (d, 1H, H-6, J=9.0 Hz), 14.63 (br s, 1H, OH); (DMSO-d_6) δ 2.52 (s, 3H, Me), 3.78 (s, 3H, OMe), 5.00 (dd, 1H, C*H*H, J=13.7, 8.4 Hz), 5.51 (dd, 1H, CH*H*, J=13.7, 3.3 Hz), 5.60 (dd, 1H, CH, J=8.4, 3.3 Hz), 6.39 (d, 1H, H-3, J=2.6 Hz), 6.47 (dd, 1H, H-5, J=9.0, 2.6 Hz), 7.71 (d, 1H, H-6, J=9.0 Hz), 14.72 (s, 1H, OH). Anal. Calcd for $C_{12}H_{13}Cl_3N_2O_4$: C, 40.53; H, 3.68; N, 7.88. Found: C, 40.55; H, 3.69; N, 7.68.

4.4.4. (E)-1,1,1-Trichloro-3-nitro-N-[1-(5-chloro-2-hydroxyphenyl)ethylidene]propan-2-amine (**6d**)

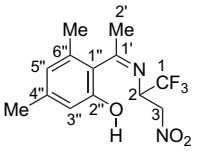
Yield 17%, mp 104–105 °C; IR (KBr) 1607, 1556, 1483, 1374 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 3H, Me), 4.87 (dd, 1H, C*H*H, J=13.8, 9.0 Hz), 5.26 (dd, 1H, CH*H*, J=13.8, 2.4 Hz), 5.37 (dd, 1H, CH, J=9.0, 2.4 Hz), 6.93 (d, 1H, H-3, J=8.9 Hz), 7.33 (dd, 1H, H-4, J=8.9, 2.5 Hz), 7.59 (d, 1H, H-6, J=2.5 Hz); (DMSO-d_6) δ 2.59 (s, 3H, Me), 5.07 (dd, 1H, C*H*H, J=13.9, 8.2 Hz), 5.51 (dd, 1H, CH*H*, J=13.9, 3.3 Hz), 5.69 (dd, 1H, CH, J=8.2, 3.3 Hz), 6.93 (d, 1H, H-3, J=8.8 Hz),

7.45 (dd, 1H, H-4, J=8.8, 2.6 Hz), 7.83 (d, 1H, H-6, J=2.6 Hz), 14.19 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.62 (C2′), 69.94 (C2), 76.92 (C3), 98.55 (C1), 119.58 (C1″), 120.46 (C3″), 121.95 (C5″), 129.32 (C6″), 133.24 (C4″), 159.79 (C2″), 177.84 (C1′). Anal. Calcd for $C_{11}H_{10}Cl_4N_2O_3$: C, 36.70; H, 2.80; N, 7.78. Found: C, 36.66; H, 2.56; N, 7.57.

4.4.5. 1,1,1-Trichloro-3-nitro-N-[1-(4,6-dimethyl-2-hydroxyphenyl)-ethylidene]propan-2-amine (**6e**)

Yield 41%, mp 112–113 °C. This compound was obtained according to the procedure for chromenes **3**. IR (KBr) 1636, 1558, 1386 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (*Z*-isomer, 80%) δ 2.15 (s, 3H, Me-6), 2.21 (s, 3H, Me-4), 2.23 (s, 3H, Me), 4.60 (dd, 1H, CH, J=6.9, 1.9 Hz), 4.68 (dd, 1H, C*H*H, J=15.9, 1.9 Hz), 5.03 (dd, 1H, CH*H*, J=15.9, 6.9 Hz), 6.52 (s, 1H, H-3), 6.58 (s, 1H, H-5), 9.82 (s, 1H, OH); (*E*-isomer, 20%) δ 2.06 (s, 3H, Me-6), 2.16 (s, 3H, Me-4), 2.26 (s, 3H, Me), 4.78 (dd, 1H, C*H*H, J=13.5, 8.8 Hz), 5.28 (dd, 1H, CH, J=8.8, 2.8 Hz), 5.50 (dd, 1H, CH*H*, J=13.5, 2.8 Hz), 6.45 (s, 1H, H-3), 6.46 (s, 1H, H-5), 9.36 (s, 1H, OH); ($CDCl_3$) (*E*-isomer, 95%) δ 2.26 (s, 3H, Me), 2.36 (s, 3H, Me), 2.51 (s, 3H, Me), 4.88 (dd, 1H, C*H*H, J=13.6, 9.0 Hz), 5.22 (dd, 1H, CH*H*, J=13.6, 2.4 Hz), 5.33 (dd, 1H, CH, J=9.0, 2.4 Hz), 6.57 (s, 1H, H-3), 6.63 (s, 1H, H-5), 9.5–12.0 (br s, 1H, OH); (*Z*-isomer, 5%) δ 2.23 (s, 3H, Me), 2.29 (s, 3H, Me), 2.34 (s, 3H, Me), 4.66 (dd, 1H, C*H*H, J=15.6, 2.0 Hz), 4.78 (dd, 1H, CH, J=6.3, 2.0 Hz), 4.95 (dd, 1H, CH*H*, J=15.6, 6.3 Hz), 6.44 (s, 1H, H-3), 6.69 (s, 1H, H-5). Anal. Calcd for $C_{13}H_{15}Cl_3N_2O_3$: C, 44.15; H, 4.28; N, 7.92. Found: C, 44.10; H, 4.12; N, 7.87.

4.4.6. 1,1,1-Trifluoro-3-nitro-N-[1-(4,6-dimethyl-2-hydroxyphenyl)-ethylidene]propan-2-amine (**6f**)



This compound was obtained according to the procedure for chromenes **3**. Yield 60%, mp 171–172 °C; IR (KBr) 1651, 1614, 1565, 1388, 1374 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (*Z*-isomer, 100%) δ 2.05 (s, 3H, Me-6), 2.21 (s, 3H, Me-4), 2.22 (s, 3H, Me), 4.29 (dqd, 1H, CH, J=7.8, 7.2, 3.4 Hz), 4.61 (dd, 1H, C*H*H, J=14.3, 3.4 Hz), 5.04 (dd, 1H, CH*H*, J=14.3, 7.8 Hz), 6.57 (s, 1H, H-3), 6.58 (s, 1H, H-5), 9.81 (s, 1H, OH); ($CDCl_3$) (*Z*-isomer, 55%) δ 2.14 (s, 3H, Me), 2.29 (s, 3H, Me), 2.33 (s, 3H, Me), 4.45 (dqd, 1H, CH, J=7.3, 6.7, 3.8 Hz), 4.57 (dd, 1H, C*H*H, J=13.7, 3.8 Hz), 4.78 (dd, 1H, CH*H*, J=13.7, 7.3 Hz), 5.01 (s, 1H, OH), 6.47 (s, 1H, H-3), 6.69 (s, 1H, H-5); (*E*-isomer, 45%) δ 2.26 (s, 3H, Me), 2.34 (s, 3H, Me), 2.44 (s, 3H, Me), 4.87 (dd, 1H, C*H*H, J=13.8, 5.5 Hz), 4.90 (dd, 1H, CH*H*, J=13.8, 3.8 Hz), 5.10–5.20 (m, 1H, CH), 6.57 (s, 1H, H-3), 6.62 (s, 1H, H-5), 9.5–11.0 (br s, 1H, OH); ^{19}F NMR (376 MHz, DMSO-d_6) (*Z*-isomer) δ 89.48 (d, CF_3, J=7.2 Hz); (*E*-isomer) δ 90.81 (d, CF_3, J=7.2 Hz); ($CDCl_3$) (*Z*-isomer) δ 87.42 (d, CF_3, J=6.7 Hz); (*E*-isomer) δ 88.68 (d, CF_3, J=6.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 18.14 (Me-C6″), 20.84 (Me-C4″), 27.98 (C2′), 61.44 (q, C2, $^2J_{C,F}$=28.4 Hz), 73.62 (C3), 113.29 (C3″), 121.10 (C1″), 121.85 (C5″), 124.62 (q, C1, $^1J_{C,F}$=280.7 Hz), 133.75 (C6″), 139.30 (C4″), 152.42 (C2″), 177.25 (C1′). Anal. Calcd for $C_{13}H_{15}F_3N_2O_3$: C, 51.32; H, 4.97; N, 9.21. Found: C, 51.15; H, 5.05; N, 9.10.

4.4.7. (E)-1,1,1-Trifluoro-3-nitro-N-[1-(2-hydroxyphenyl)-ethylidene]propan-2-amine (**6g**)

This compound was observed in the ^{1}H NMR spectrum of the crude chromene **3d**; it was not obtained as pure and was not fully characterized. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.56 (s, 3H, Me), 5.18 (dd, 1H, C*H*H, J=14.2, 7.8 Hz), 5.32 (dd, 1H, CH*H*, J=14.2, 4.3 Hz), 5.64 (dqd, 1H, CH, J=7.8, 7.0, 4.3 Hz), 6.87–6.93 (m, 2H, H-6, H-8), 7.38–7.41 (m, 1H, H-7), 7.78 (dd, 1H, H-5, J=8.0, 1.5 Hz), 13.95 (br s, 1H, NH); ^{19}F NMR (376 MHz, DMSO-d_6) δ 90.12 (d, CF_3, J=7.0 Hz).

Acknowledgements

This work was financially supported by the Russian Foundation for Basic Research (Grant 06-03-04004).

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