AMINO COMPOUNDS AND BENZIMIDAZOLES DERIVED FROM TRIFLURALIN AND FLUMETRALIN

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ABSTRACT

In this work, we describe the synthesis of the amino compounds (**5a**) and (**5b**), and the benzimidazoles (**6a**), (**6b**) and (**6c**). These amino compounds and the benzimidazoles were obtained by catalytic hydrogenation of two widely used pesticides – flumetralin (**4a**) and trifluralin (**4b**). The reactions described are simple to perform, and generate no chemical wastes. The structures of the compounds were determined through MS and NMR data.

Keywords: Trifluralin, flumetralin, benzimidazoles, catalytic hydrogenation.

RESUMEN

En este trabajo se describe la síntesis de los compuestos amino (**5a**) y (**5b**), y los benzimidazoles (**6a**), (**6b**) y (**6c**). Estos compuestos fueron obtenidos por hidrogenación catalítica de dos plaguicidas ampliamente utilizados - flumetralin (**4a**) y trifluralina (**4b**). Las reacciones descritas son simples de realizar, y no generan desechos químicos. Las estructuras de los compuestos se determinaron através de MS y los datos de RMN.

INTRODUCTION

Amino compounds account for a substantial fraction of the world market of pharmaceuticals and pesticides. Commercially important pesticides that are amino compounds include chloramben, dicloran, and fluroxypyr (Feuer, 1970; Schach *et al.*, 1996). Benzimidazoles are recognised as a most interesting class of heterocyclic compounds. Their applications include their widespread use as anthelmentic drugs in human and veterinary medicine. Examples include fenbendazole, thiabendazole, albendazole, and oxibendazole (Balizs, 1999; Ruyck *et al.*, 2000).

The importance of amino compounds in the world market for chemicals, in particular pesticides and pharmaceuticals, is driving the constant search for better means to their production, where 'better' must now take account of environmental concerns. Benzimidazoles frequently show biological activity, and the synthesis of new members

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of this class may lead to the development of commercial products.

Various methods exist for the production of amino compounds from the corresponding nitro compounds; these include selective reduction by sulphite (Nickson, 1986), sodium borohydride-transition metal salt system (Satoh *et al.*, 1969), activated metal catalysis (Pyo *et al.*, 1995) and catalytic hydrogenation (Downing *et al.*, 1997). The latter has attracted the attention of industry, because the transformation can be performed without the generation of wastes, and a number of patents have been issued for the reduction of aromatic nitro compounds (Nason, 1970; Boudakian, 1986; Baasner *et al.*, 1986).

Benzimidazoles can also be obtained starting from nitro compounds. Andersch and Sickler have reported the synthesis of benzimidazoles containing hydrophilic chiral chains, which possess anthelmintic activity (Andersch and Sickler, 1999). In their method, catalytic hydrogenation was followed by treatment with acid, which lead to the undesirable accumulation of acidic wastes.

In the present work, we report the synthesis of the amino compounds N^2-(2-chloro-6-fluorobenzyl)-N^2-ethyl-5-(trifluoromethyl)benzene-1,2,3-triamine (**5a**) and N^2, N^2-dipropyl-5-(trifluoromethyl)benzene-1,2,3-triamine (**5b**), and the benzimidazoles 2-(2-chloro-6-fluorophenyl)-1-ethyl-5-(trifluoromethyl)-1H-benzimidazol-7-amine (6a), 1-(2-chloro-6-fluorobenzyl)-2-methyl-5-(trifluoromethyl)-1H-benzimidazole-7-amine (6b) and 2-ethyl-1-propyl-5-(trifluoromethyl)-1H-benzimidazol-7-amine (6c). Syntheses of these compounds have not previously been reported in the literature. The structures of the synthesised compounds were determined on the basis of their MS, IR and NMR (1H and 13C) spectral data.

MATERIALS AND METHODS

General

The melting points were determined on equipment Microquímica, model MQAPF-301. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Gemini 2000 spectrometer (operating at 300.06 MHz for ^{1}H and 75.45 MHz for ^{13}C). Low resolution mass spectra were obtained with a HP 5972 – MSD mass spectrometer, with electron impact (70 eV) ionisation. Samples could be introduced directly into the source, or via a gas chromatograph. The GC instrument was a HP 5890, equipped with a HP 1 capillary column. The carrier gas was helium, with a flow rate of 1 mL/min. Injected volumes were of the order of 0.1 mL, with a split ratio of 100:1. The column programme was: 50°C (4 min) followed by a 30°C/min ramp to a maximum temperature of 230°C, which was then held for 45 min. The temperatures of the injector and of the detector were 240°C and 280°C, respectively. The high resolution mass spectra were obtained with a VG Autospec spectrometer, with 70 eV electron impact ionisation. Separations by column chromatography were performed using type 60 G silica gel (0.063 – 0.200 mm).

Nitration and amination reactions were carried out in a jacketed 500 mL glass reactor (FGG). The reactor was equipped with a temperature sensor, together with facilities for heating, cooling, and mechanical shaking and stirring. The catalytic hydrogenations were performed in a jacketed 500 mL stainless steel reactor (Buchi type 316 L). This reactor was fitted with temperature and pressure monitors. It was equipped with facilities for heating and mechanical shaking, together with an anti-explosion system.

Synthesis

1-chloro-2-nitro-4-(trifluorome-thyl)benzene (**2**).

A mixture of concentrated nitric acid (95.5 g, 1.5 mol) and concentrated sulphu-

ric acid (100.0 g, 1.0 mol) was slowly added to 1-chloro-4-(trifluoromethyl)benzene (**1**) (182.3 g, 1.0 mol), with constant stirring and maintaining a temperature of 80°C. Once addition of the reagents was completed, constant stirring of the reaction mixture was continued and the temperature was held at 80°C for a period of 90 minutes. At the end of this period, the temperature was decreased to 60°C, water (41.4 g, 2.3 mol) was then added to the reaction mixture, and the reaction vessel and contents were allowed to stand, while the mixture separated into an organic phase and an acid phase. The organic phase was concentrated with a rotary evaporator. Yellow oil. Yield: 91.3%. ^{1}H NMR ($CDCl_3$): δ 7.76 (d, H-6, 1H, *J*=8.4 Hz), 7.83 (dd, 1H, 5-H, *J*=8.4 and 1.8 Hz), 8.16 (d, 1H, H-3, *J*=1.8 Hz); ^{13}C NMR ($CDCl_3$): δ 122.8 (q, CF_3, *J*=272.7 Hz), 123.3 (q, C-3, *J*=3.4 Hz), 130.1 (q, C-5, *J*=3.4 Hz), 130.8 (q, C-4, *J*=35.5 Hz), 131.5 (s, C-1), 133,4 (s, C-6), 148.4 (s, C-2). MS (70 eV, electron impact): m/z 225 (molecular ion).

2-chloro-1,3-dinitro-5-(trifluormethyl) benzene (3). A mixture of concentrated nitric acid (76.4 g, 1.2 mol) and concentrated sulphuric acid containing 23% SO_3 (264.9g, 2.0 mol) was added slowly to 1-chloro-2-nitro-4-(trifluoromethyl)benzene (**2**) (227.8 g, 1.0 mol), with constant stirring and maintaining a temperature of 70°C. Over a period of 6 hours the temperature was gradually raised to 140°C, with constant stirring. The reaction mixture was then maintained at 140°C, with constant stirring, for 2 hours. The temperature of the reaction mixture was lowered to 80°C, and it was then allowed to stand and separate into an organic phase and an acid phase. The organic phase was concentrated with a rotary evaporator. Yellow solid. Yield: 82.2%. ^{1}H NMR ($CDCl_3$): δ 8.26 (s, 2H, H-4/H-6); ^{13}C NMR ($CDCl_3$): δ 121.5 (*q*, CF_3, *J*=274.1 Hz), 124.8 (*s*, C-2), 125.0 (*s*, C-4/C-6), 131.3 (*q*, C-5, *J*=36.7 Hz), 150.0 (*s*, C-1/C-3). MS (70 eV, electron impact): m/z 270 (molecular ion).

***N*²-(2-chloro-6-fluorobenzyl)-*N*²-[2,6-dinitro-4-(trifluoromethyl)phenyl]-*N*²-ethylamine (4a)** *N*²-ethyl-2-chloro-6-fluorobenzylamine (60.6 g, 0.32 mol) and 50% sodium hydroxide (21.4 g, 0.32 mol) were added simultaneously, with constant stirring, to 2-chloro-1,3-dintro-5-(trifluoromethyl)benzene (**3**) (72.3 g, 0.26 mol). Following the addition of the reagents, the temperature was adjusted to 115°C. The reaction mixture was maintained at this temperature, with stirring, for a period of 2 hours and 30 minutes. At the end of this period water (50 mL) was added, the mixture was allowed to stand and separate into an organic phase and an aqueous phase. Yellow solid. Yield: 78.9%. ^{1}H NMR ($CDCl_3$): δ 1.28 (*t*, 3H, H-2", *J*=6.9 Hz), 2.97 (*q*, 2H, H-1", *J*=6.9 Hz), 4.34 (*d*, 2H, H-7', *J*=1.2 Hz), 7.02 (*qd*, 1H, H-5', *J*=9.3 and 0.9 Hz), 7.19 (*dd*, 1H, H-3', *J*=8.1 and 0.9 Hz), 7.27 (*td*, 1H, H-4', *J*=8.1 and 5.7 Hz), 8.16 (*s*, 2H, H-3/H-5). ^{13}C NMR ($CDCl_3$): δ 12.9 (*s*, C-2"), 46.7 (*s*, C-1"), 46.8 (*d*, C-7, *J*=2.3 Hz), 114.2 (*d*, C-5', *J*=22.9 Hz), 121.4 (*d*, C-1', *J*=18.3 Hz), 122.3 (*q*, CF_3, *J*=272.5 Hz), 123.0 (*q*, C-4, *J*=35.4 Hz), 125.7 (*d*, C-3', *J*=3.5 Hz), 127.0 (*q*, C-3/C-5, *J*=4.6 Hz), 130.4 (*d*, C-4', *J*=10.2 Hz), 136.3 (*d*, C-2', *J*=5.7 Hz), 141.8 (*s*, C-1), 146.1 (*s*, C-2/C-6), 162.3 (*d*, C-6', *J*=250.7 Hz). MS (70 eV, electron impact): m/z 421 (molecular ion).

***N*²-[2,6-dinitro-4-(trifluoromethyl)phenyl]-*N*², *N*²-dipropylamine (4b)** Dipropylamine (34.2 g, 0.34 mol) and 20% sodium hydroxide (46.2 mL, 0.25 mol) were added simultaneously, with constant stirring, to 2-chloro-1,3-dinitro-5-(trifluoromethyl)benzene (**3**) (77.6 g, 0.28 mol). Following the addition of the reagents, the temperature was adjusted to 60°C. The reaction mixture was maintained at this temperature, with stirring, for a period of 2 hours and 30 minutes. At the end of this period water (180 mL) was added, the mixture was allowed to stand and separate into an organic phase and an aqueous

phase. Maintaining the temperature at 60°C, the organic phase was diluted with ethanol (250.0 mL). Red solid. Yield: 74.6%. ^{1}H NMR ($CDCl_3$): δ 0.88 (*t*, 6H, H-3', *J*=7.5 Hz), 1.62 (*m*, 4H, H-2'), 2.98 (*t*, 4H, H-1', *J*=7.5 Hz), 8.07 (*s*, 2H, H-3/H-5). ^{13}C NMR ($CDCl_3$): δ 11.0 (*s*, C-3'), 20.6 (*s*, C-2'), 54.0 (*s*, C-1'), 118.7 (*q*, CF_3, *J*=272.5 Hz), 121.4 (*q*, C-4, *J*=36.7 Hz), 126.9 (*q*, C-3/C-5, *J*=3.5 Hz), 141.4 (*s*, C-1), 145.4 (*s*, C-2/C-6). MS (70 eV, electron impact): m/z 335 (molecular ion).

N^2-(2-chloro-6'-fluorobenzyl)-*N*^{2}-ethyl-5-(trifluoromethyl)benzene-1,2,3-triamine (**5a**), 1-(2-chloro-6-fluorobenzyl)-2-methyl-5-(trifluoromethyl)-1*H*-benzimidazol-7-amine (**6a**) and 2-(2-chloro-6-fluorophenyl)-1-ethyl-5-(trifluoromethyl)-1*H*-benzimidazol-7-amine (**6b**).

Methanol (200 mL) and 10% platinum on charcoal (9.75 g, 0.5 mmol) were added to (**4a**) (43.9 g, 0.10 mol). The system was purged with nitrogen gas, and the temperature was raised to 80°C. The reaction vessel was pressurised with hydrogen (5 bar), and reaction was allowed to occur for 5 hours at 80°C under a constant pressure of 5 bar of hydrogen, with constant shaking. Following depressurisation, the catalyst was recovered by filtration, and the solvent was evaporated. A portion (2.91 g) of the raw products from the reaction was chromatographed with gradient elution (hexane/ethyl acetate mixture, increasing polarity) on a silica gel column.

The amino compound (**5a**) (410.1 mg, 58.3%) was obtained as a red solid upon eluting the column with hexane/ethyl acetate 20%, m.p. = 120.0-121.9 °C. MS (70 eV, electron impact, high resolution): m/z 361.08978 (molecular ion, 30.1 %), 332.04680 (19.5 %), 218.08351 (100 %). ^{1}H and ^{13}C NMR, see Table 1.

Benzimidazole (**6a**) (46.3 mg, 6.5%) was obtained as a red solid upon eluting the column with hexane/ethyl acetate 30%, m.p. = 179.1-182.2. MS (70 eV, electron impact, high resolution): m/z 357.07162 (molecular ion, 100 %), 214.05179 (35.9 %), 143.00045 (81.0 %). NMR, see Table 2 (^{1}H) and Table 3 (^{13}C).

Benzimidazole (**6b**) (116.1 mg, 16.3%) was obtained as a red solid upon eluting the column with hexane/ethyl acetate 25%, m.p = 80.3–81.6. MS (70 eV, electron impact, high resolution): m/z 357.05463 (molecular ion, 100 %), 342.0461 (33.6 %). NMR, see Table 2 (^{1}H) and Table 3 (^{13}C).

N,*N*-dipropyl-5-(trifluoromethyl)benzene-1,2,3-triamine (**5b**) and 2-ethyl-1-propyl-5-(trifluoromethyl)-1*H*-benzimidazol-7-amine (**6c**).

Methanol (200 mL) and 10% platinum on charcoal (0.98 g, 0.05 mmol) were added to (**4b**) (33.8 g, 0.10 mol). The system was purged with nitrogen gas, and the temperature was raised to 80°C. The reaction vessel was pressurised with hydrogen (3 bar), and reaction was allowed to occur for 8 hours at 80°C under a constant pressure of 3 bar of hydrogen, with constant shaking. Following depressurisation, the catalyst was recovered by filtration, and the solvent was evaporated. A portion (2.12 g) of the raw products from the reaction was chromatographed with gradient elution (hexane/ethyl acetate mixture, increasing polarity) on a silica gel column.

The amino compound (**5b**) (575.3 mg, 66.3%) was obtained as a red solid upon elution of the column with hexane/ethyl acetate 35%, m.p. = 60.1-61.0. MS (70 eV, electron impact, high resolution): m/z 275.13711 (molecular ion, 37.0 %), 246.09874 (100 %), 202 (22.2 %). ^{1}H and ^{13}C NMR, see Table 1.

Benzimidazole (**6c**) (256.0 mg, 29.1%) was obtained as a red solid upon elution of the column with hexane/ethyl acetate 40%. m.p.= 159.5-160.8. MS (70 eV, electron impact): m/z 271 (molecular ion, 89.9 %), 242 (100 %), 229 (75.3 %). NMR, see Table 2 (^{1}H) and Table 3 (^{13}C).

RESULTS AND DISCUSSION

In this work the amino compounds **5a** and **5b** and the benzimidazoles **6a-6c** were prepared from the corresponding nitro compounds **4a** and **4b** through hydrogenation using a supported platinum catalyst, as shown in Figure 1. Flumetralin (**4a**) and trifluralin (**4b**) were obtained through amination reactions of **3** (Kwiatkowski, *et al.* 1998; Kwiatkowski, et al. 2000) which was itself prepared by stepwise nitration of compound **1**. The nitration of compound **2** required the use of a mixture of concentrated nitric and sulphuric acids, to which SO_3 was added.

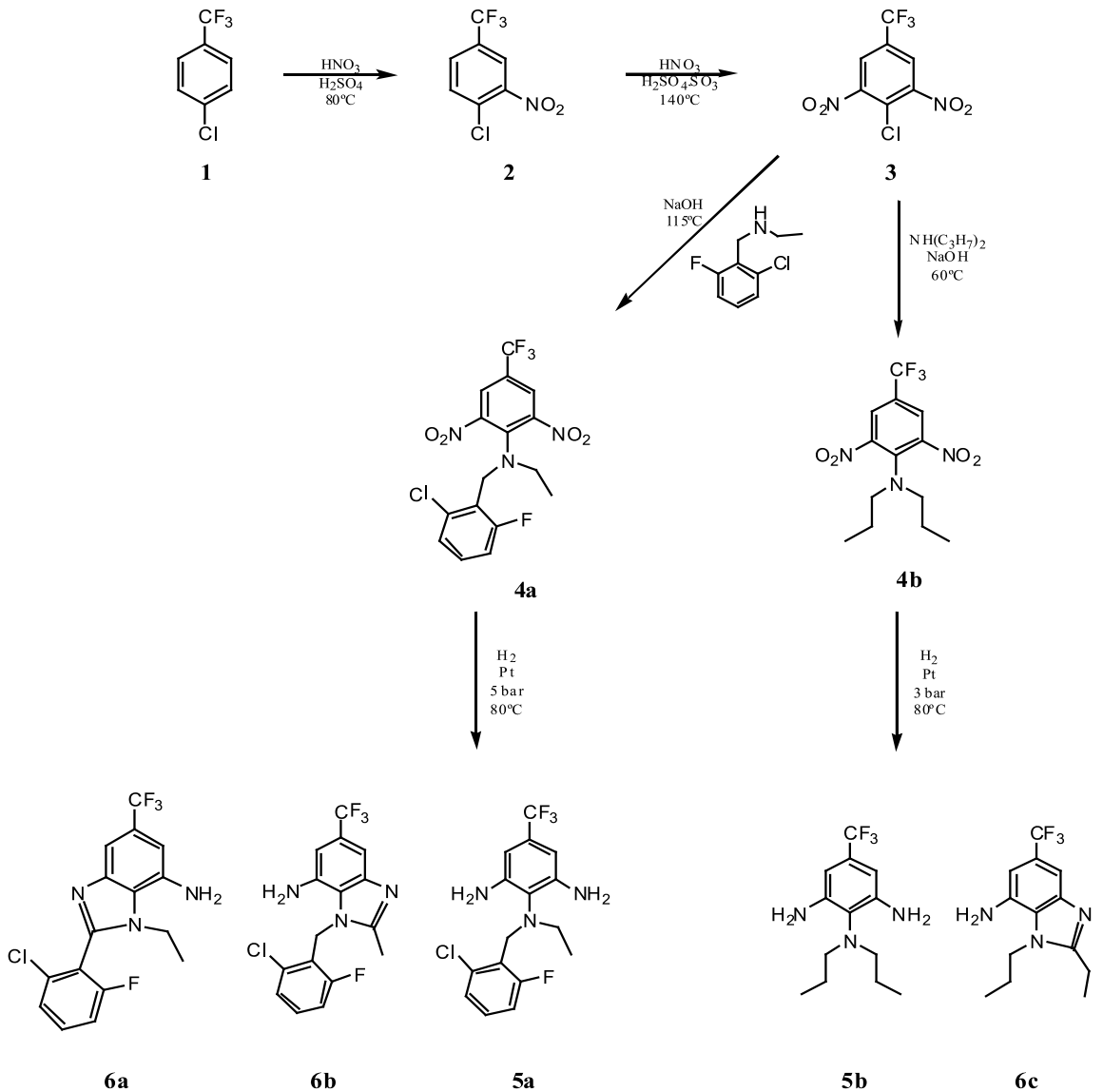

Figure 1: Synthetic route for amino compounds (**5a** and **5b**) and benzimidazoles (**6a-6c**).

The mass spectra of the amino compounds **5a** and **5b** showed the expected molecular ion peaks ($M^{+\bullet}$). The formation of these compounds was confirmed through the ^{1}H and ^{13}C NMR spectra. The presence of an aromatic ring bearing two NH_2 groups, a trifluoromethyl group and an amine group was revealed by the characteristic shielding of hydrogens H-4/H-6, and of carbons C-4/C-6 and C-2. Assignments were assisted by comparisons of the NMR spectra of **5a** and **5b** with those of nitro compounds **4a** and **4b**, which contain NO_2 groups in place of the two NH_2 groups. The NMR spectra of **5a** showed signals characteristic of a second aromatic ring bearing both a chlorine and a fluorine atom, while the spectra of **5b** demonstrated the presence of two *n*-propyl groups. For both molecules splittings of signals arising from ^{13}C-^{19}F coupling through one, two, three and four bonds were identified, and found to be consistent with the structures. Through an analysis of the ^{1}H and ^{13}C NMR spectra of **5a** and **5b**, it was possible to assign chemical shifts to each of the hydrogens and carbons in these molecules. The assignments are summarised in Table 1.

Table 1: ^{1}H (300 MHz, $CDCl_3$) and ^{13}C (75.5 MHz, $CDCl_3$) NMR data for **5a** and **5b**.

	5a		**5b**	
H/C	δ_H (mult. *J*, in Hertz)	δ_C(mult. *J*, in Hertz)	δ_H (mult. *J*, in Hertz)	δ_C (mult. *J*, in Hertz)
1	-	147.1 (s)	-	146.8 (s)
2	-	124.9 (s)	-	124.3 (s)
3	-	147.1 (s)	-	146.8 (s)
4	7.26 (s)	102.5 (d 1.8)	6.33 (s)	102.7 (q 3.5)
5	-	129.1 (q 33.2)	-	129.2 (q 32.0)
6	7.26 (s)	102.5 (d 1.8)	6.33 (s)	102.7 (q 3.5)
1'	-	120.8 (d 14.1)	2.96 (m)	55.3 (s)
2'	-	136.4 (d 4.8)	1.48 (sext 7.5)	23.0 (s)
3'	7.18 (m)	125.5 (d 3.3)	0.87 (t 7.5)	11.7 (s)
4'	7.19 (m)	129.4 (d 10.4)		
5'	6.95 (m)	114.1 (d 22.9)		
6'	-	160.7 (d 248.9)		
7'	4.36 (d 1.8)	46.3 (s)		
1"	3.13 (q 7.2)	45.9 (s)		
2"	1.03 (t 7.2)	14.1 (s)		
CF_3		122.1 (q 261.4)		124.6 (q 272.5)
NH_2	1.71 (s)		4.00 (s)	

The mass spectra of the benzimidazoles **6a**-**6c** showed the expected molecular ion peaks ($M^{+\bullet}$). Comparisons of the NMR spectra of **6a** and **6b** with **5a**, and of **6c** with **5b** assisted in demonstrating the presence of the benzimidazole system in **6a**-**6c**. A key structural difference between the amines and the benzimidazoles is the formal conversion of a CH_2 group attached to N in the amine to a C bearing no H atoms in the benzimidazole (carbon 2). Compared to the ^{13}C NMR spectra of **5a** and **5b**, the spectra of each of the benzimidazoles showed the anticipated loss of a single CH_2 signal and the appearance of a signal due to a carbon atom which did not bear hydrogen atoms; these new signals with δ_c 154.4, 146.9 and 159.6 were attributed to carbon C-2 in **6a**, **6b** and **6c**, respectively. The loss of the hydrogen atoms from the carbon which is incorporated into the heterocyclic ring of the benzimidazole was evident in the ^{1}H NMR spectra. There were characteristic changes in the shielding observed for carbons 3a and 7a, which are located at the junction of the two rings, compared to the

shielding of the related carbons in **5a** and **5b**. The ^{1}H NMR spectra demonstrated the inequivalence of protons H-4 and H-6 in the compounds **6a**, **6b** and **6c**, indicating that in these molecules the C-6 aromatic ring bearing the trifluoromethyl group is no longer symmetric. Other features of the structures of **6a**, **6b**, and **6c** which were readily confirmed by the identification of characteristic signals in the ^{1}H and ^{13}C NMR spectra were: an amino group and a trifluoromethyl group on the C-6 ring of the benzimidazole system (common to **6a**, **6b**, and **6c**), a C-6 aromatic ring bearing one chlorine and one fluorine atom (**6a** and **6b**), and alkyl chains (**6a**, **6b**, and **6c**). The observation of coupling to F atoms extending over one, two, three and four bonds allowed the bond connectivities proposed in the structures for **6a**, **6b**, and **6c** to be confirmed. Detailed assignments of the ^{1}H and ^{13}C NMR spectra, giving the chemical shifts for each hydrogen and carbon atom are given in Tables **2** and **3**.

Table 2: ^{1}H (300 MHz, $CDCl_3$) NMR data for 6a-6c.

	6a	**6b**	**6c**
H	δ_H (mult. *J*, in Hertz)	δ_H (mult. *J*, in Hertz)	δ_H (mult. *J*, in Hertz)
4	6.79 (d 1.2)	6.70 (d 0.6)	6.83 (d 1.8)
6	7.50 (d 1.2)	7.47 (d 0.6)	7.23 (d 1.8)
1’	-	4.09 (m)	4.28 (t 7.5)
2’	-	1.27 (t 7.5)	1.83 (sext 7.5)
3’	7.28 (m)	-	0.92 (t 7.5)
4’	7.30 (m)	-	
5’	6.99 (m)	-	
7’	5.85 (s)	-	
1”	2.46 (s)	-	2.88 (q 7.5)
2”	-	-	1.39 (t 7.5)
3”		7.20 (d 8.4)	
4”		7.31 (td 8.4 and 6.0)	
5”		7.00 (t 8.4)	
NH_2	3.78 (sl)	4,10 (s)	4.95 (s)

Table 3: ^{13}C (75.46 MHz, $CDCl_3$) NMR data for **6a-6c**.

	6a	**6b**	**6c**
C	δ_C(mult. *J*, in Hertz)	δ_C(mult. *J*, in Hertz)	δ_C(mult. *J*, in Hertz)
2	154.4 (s)	146.9 (s)	159.6 (s)
3a	132.1 (s)	133.2 (s)	136.2 (s)
4	109.2 (q 3.5)	107.2 (q 4.5)	106.8 (q 4.6)
5	124.8 (q 32.0)	125.5 (q 32.0)	126.4 (q 32.1)
6	109.6 (q 4.6)	109.1 (q 4.5)	107.6 (q 3.5)
7	143.4 (s)	144.4 (s)	144.4 (s)
7a	132.1 (s)	133. 2(s)	127.5 (s)
1'	121.9 (d 13.7)	41.0 (s)	47.4 (s)
2'	134.3 (d 3.7)	17.1 (s)	26.4 (s)
3'	126.3 (d 3.5)		10.9 (s)
4'	130.6 (d 10.3)		
5'	115.3 (d 23.0)		
6'	162.0 (d 250.8)		
7'	41.7(s)		
1"	14.1(s)	118.3 (d 19.5)	21.4 (s)
2"		135.9 (d 3.8)	12.2 (s)
3"		125.6 (d 3.4)	
4"		132.5 (d 10.3)	
5"		114.4 (d 21.7)	
6"		161.4 (d 251.9)	
CF_3	123.5 (q 270.8)	124.7 (q 272.5)	126.6 (q 270.4)

The hypothesis that can explain the formation of benzimidazoles **6a-6c** is based on a degradation process, with oxidation of methylene group (N-CH_2) in **5a** and **5b** via radical mechanism catalyzed by platinum, leading to the closure of the ring with subsequent aromatization.

CONCLUSION

Concluded, based on the data presented in this paper that the synthetic methodology of amino compounds and benzimidazoles by catalytic hydrogenation of pesticides trifluralin and flumetralin have high efficiency, demonstrating that this methodology is interesting to obtain the cited products.

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