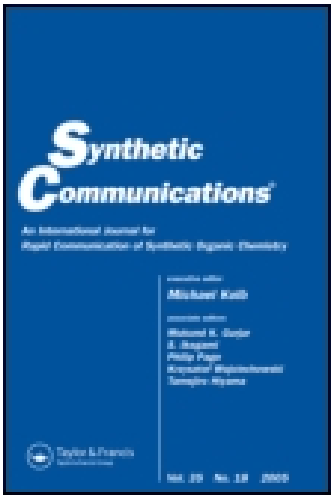

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Simplified Approach to the Regiospecific Synthesis of Trichloromethylpyrazolines Using Microwave Irradiation

Marcos A. P. Martins [a], Paulo Muraro [a], Paulo Beck [a], Pablo Machado [a], Clarissa P. Frizzo [a], Nilo Zanatta [a] & Helio G. Bonacorso [a]
[a] Department of Chemistry, Federal University of Santa Maria, Santa Maria, Brazil
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Simplified Approach to the Regiospecific Synthesis of Trichloromethylpyrazolines Using Microwave Irradiation

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Department of Chemistry, Federal University of Santa Maria, Santa Maria, Brazil

Abstract: Twelve novel 3-alkyl[aryl]-1-carboxamides-5-trichloromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole have been synthesized in good yields (72–90%) using environmentally benign microwave-induced techniques. The compounds were synthesized from the cyclocondensation of 4-alkoxy-1,1,1-trichloro-3-alkyl [aryl]-2-ones [$Cl_3CC(O)C(R^2) = C(R^1)OR$, where R = Me, Et; R^1 = H, Me, Et, Pr, *i*-Pr, *i*-Bu, *t*-Bu, Ph, Ph-4-NO_2, Ph-4-F, Ph-4-Cl, Ph-4-Br; and R^2 = H, Me] with semicarbazide hydrochloride in the presence of pyridine and using methanol/water (3:1 v/v) as the solvent. The advantages of using microwave irradiation, rather than a conventional method, were demonstrated.

Keywords: Biological activity, enones, microwave irradiation, pyrazoles, trichloromethyl compounds

INTRODUCTION

The pyrazole ring is known to be an important framework for a large number of compounds possessing pharmaceutical and agrochemical properties.[1–6] Numerous methods for the synthesis of these compounds have been well documented in previous studies,[7,8] but the methods

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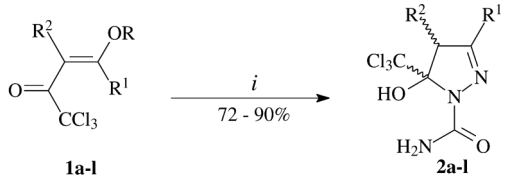
Address correspondence to Marcos A. P. Martins, Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, Santa Maria 97105-900 RS, Brazil. E-mail: mmartins@base.ufsm.br; www.ufsm.br/nuquimhe

usually entail the synthesis of nonhalogenated pyrazoles, and there are few methodologies for the preparation of trichloromethylated pyrazoles. General methods for the preparation of these compounds involve reactions of hydrazine derivatives with trichloromethylated precursors such as 1-trichloromethylated 1,3-diketones,[9] trichloroacetyl acetylenes,[10] β-alkoxyvinyl trichloromethyl ketones,[9,11] and β-trichloromethyl enaminones.[12] Over the past few years, we have developed a general procedure for preparing β-alkoxyvinyl halomethyl ketones from the β-haloacetylation of enol ethers using functionalized acyl groups CX_3CO (with X = F and Cl).[9,13] In addition, our research group has reported the synthesis and importance of β-alkoxyvinyl trichloromethyl ketones as versatile building blocks to be used in the construction of halomethyl-heterocyclic rings,[9,13–15] (e.g., isoxazoles, pyrazoles, pyrazolium chlorides, pyrrolidinones, pyrimidines, pyrimidinones, pyridines, thiazolo pyrimidinones, selenazoles, quinolines, and diazepines). In spite of the importance of trichloromethylpyrazoles, improvements in methods for their preparation have been quite limited in the literature in recent years.[16] Developing concise and effective methodologies for preparing combinatorial libraries of small molecules for drug discovery research remains an important challenge. In this context, our research group has recently reported the biological effect of novel trichloromethyl-substituted pyrazoles in animal models of inflammation, fever, and pain.[17] It was demonstrated that dihydropyrazoles **2b** and **2h** (Scheme 1) caused rapid antipyresis and antinociception after their systemic administration in mice.[17] The compounds demonstrated an antipyretic action similar to that of dypirone, a classical nonsteroidal anti-inflammatory drug (NSAID) and pyrazole compound. It was further ascertained that the mechanisms of antinociception for **2b** did not involve opioid receptors but rather spinal 5-HT receptors and α_2-adrenoceptors, which



1a-l **2a-l**

i : $NH_2NHCONH_2 \cdot HCl$, $MeOH/H_2O$ (3:1), Pyridine, 4 min, 70°C, MW, 100W, 2.2 bar

1,2	a	b	c	d	e	f	g	h	i	j	k	L
R^1	H	Me	Et	Pr	*i*-Pr	*i*-Bu	*t*-Bu	Ph	Ph-4-NO_2	Ph-4-F	Ph-4-Cl	Ph-4-Br
R^2	H	H	H	H	H	H	H	H	Me	H	H	H
R	Et	Me	Me	Me	Me	Me	Me	Me	Et	Me	Me	Me

Scheme 1.

also happened when **2h** induced antinociception.[17] In a more recent study,[18] we have demonstrated that fluorinated analogs such as 5-trifluoromethyl-4,5-dihydro-1H-pyrazoles decreased pain-related behavior during neurogenic and inflammatory phases of the formalin test in mice when administered subcutaneously. In addition, the more active analgesic compounds significantly decreased carrageenan-induced paw edema in mice. These results suggest that these pyrazolines could be promising candidates for the future development of novel analgesic and anti-inflammatory agents.

Microwave irradiation has been used to accelerate organic reactions because of it is high heating efficiency, providing remarkable rate enhancement and dramatic reduction in reaction times. Reactions that require hours or even days by conventional heating can often be accomplished in seconds or minutes by microwave heating.[19] In addition, there is increasing interest in the medicinal chemistry community in technologies and concepts that facilitate a more rapid synthesis and, consequently, the screening of novel chemical substances to identify compounds with appropriate pharmacological qualities.[20] In recent years, we have reported the application of microwave irradiation for the synthesis of halomethyl-substituted azoles.[21] Considering the pharmacological importance observed for compounds **2b** and **2h**,[17] the aim of this study is to demonstrate the advantages obtained by using microwave irradiation, as compared to the conventional method reported[22] for the synthesis of a series of 5-trichloromethyl-4,5-dihydro-1*H*-1-pyrazole methyl esters **2** (Scheme 1).

RESULTS AND DISCUSSION

4-Methoxy-1,1,1-trichloro-3-alken-2-ones **1a–l** were synthesized from the reaction of trichloroacetyl chloride with enol ether or acetal in the presence of pyridine, according to the methodology developed in our laboratory.[22] The cyclocondensation reactions of enones **1** with semicarbazide hydrochloride were carried out at a molar ratio of 1:1:3, respectively, in the presence of pyridine and using methanol/water (3:1 v/v) as solvent (Scheme 1).

The solution was submitted to microwave irradiation (100 W) for 4 min, at a temperature of 70 °C and at 2.2 bar of pressure, to produce 5-trichloromethyl-4,5-dihydro-1*H*-pyrazoles **2** with 72–90% yields (Table 1). The new method for forming 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles **2** under microwave irradiation offers several advantages, including faster reaction rates, fewer by products, and high yields, while the conventional method entails moderate yields and a long process (ca. 24 h).[22] Table 1 shows that the average yields of products

Table 1. Yields[a] and reaction conditions for microwave-assisted synthesis of **2a–l**

	Microwave method[b]		Conventional method[c]	
Product	Reaction time (min)	Yield (%)	Reaction time (h)	Yield (%)
2a	4	85	16	65
2b	4	72	17	71
2c	4	75	20	64
2d	4	75	20	63
2e	4	85	20	70
2f	4	76	20	60
2g	4	80	20	75
2h	4	83	20	89
2i	4	90	20	82
2j	4	85	20	73
2k	4	80	20	70
2l	4	90	20	84

[a]Yields of isolated products.
[b]Reaction conditions: methanol/water (3:1 v/v), pyridine, 70 °C, MW, 100 W, 2.2 bar.
[c]Reaction conditions: methanol/water (3:1 v/v), 30–85 °C (**2a–b**, **2h–i**, **2l**; see Ref. 22).

obtained by the microwave method are ca. 10% higher than those obtained by the conventional method.[22] ^{1}H and ^{13}C NMR and mass spectral data of all compounds are in full agreement with the proposed structures (see the Experimental section).

The reaction time for the microwave method is the main advantage of this method over other methods, where the average time ratio between the two methods is 1:300.[22] Furthermore, the new method of forming of 3-alkyl-5-hydroxy-5-trichloro-methyl-4,5-dihydro-1*H*-pyrazole-1-carboxamides supplies a synthesis of compounds with promising analgesic and antipyretic activities in mice. It also brings new structure variations at the pyrazole ring, thus allowing for a future study of structure–activity relationships to obtain a pharmacological profile for this species of compounds.

EXPERIMENTAL

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. Yields listed are of isolated compounds. ^{1}H, ^{13}C, and spectra were recorded on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and

^{13}C at 100.63 MHz), 298 K, digital resolution of ±0.01 ppm, 0.5 M, in $CDCl_3$-d_6 using tetramethylsilane (TMS) as internal standard. All spectra were acquired in a 5-mm tube, at natural abundance. Mass spectra were registered in a HP 5973 mass spectrometer detector (MSD) connected to an HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split–splitless, injector, auto sampler, and cross-linked HP-5 capillary column (30 m and 0.32 mm of internal diameter), and helium was used as the carrier gas. Melting points were determined with an Electrothermal Mel-Temp 3.0 (Laboratory Devices Inc., USA). Elemental analyses were performed on a Perkin-Elmer CHN elemental analyzer. Microwave irradiation was conducted in a multimode microwave Ethos 1 (Milestone Inc.) with a twin magnetron with maximum delivered power of 1300 W. The temperature was set to 70 °C, and the irradiation was automatically stopped at this temperature. The temperature and the pressure were measured throughout with an ATC-400 CE and APC-55 detector, respectively.

Preparation of 1-Carboxamide-5-trichloromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole 2a (Microwave Method): Typical Procedure

A solution of **1a** (2.0 mmol), semicarbazide hydrochloride (0.268 g, 2.4 mmol) in methanol/water 3:1 v/v (6 mL), and pyridine (2 mL) was stirred for a few minutes. The mixture was irradiated in a microwave Ethos 1 (Milestone Inc.) at 100 W and 2.2 bar of pressure for 4 min. The multimode microwave has a twin magnetron with maximum delivered power of 1300 W. The temperature was set to 70 °C, and the irradiation was automatically stopped at this temperature. The temperature and the pressure were measured throughout with ATC-400 CE and APC-55 detectors, respectively. After cooling to room temperature, the solution was extracted with chloroform (2 × 20 mL) and ethyl acetate (2 × 20 mL). The organic layers were washed with distilled water (2 × 20 mL) and dried with magnesium sulfate. The solvent was removed in a rotatory evaporator, and 5-hydroxy-5-trichloromethyl-4,5-dihydro-1*H*-1-carboxamidepyrazole **2a** was obtained in high purity. When necessary, products **2** were recrystallized from hexane.

1-Carboxamide-5-trichloromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole 2a (Conventional Method) [22]: Typical Procedure

To a stirred solution of **1a** (5.0 mmol) in methanol (6 mL), a solution of semicarbazide hydrochloride (5.0 mmol) in water (2 mL) was added at 20–25 °C. The mixture was stirred for 16 h at 50–55 °C. The product

precipitated by the addition of cool water (15 mL) to the reaction. The crystalline solids were filtered off and recrystallized from methanol.

Data

1-Carboxamide-5-trichloromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (2a)

$C_5H_6Cl_3N_3O_2$; mw 246.47; mp 129–130 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ($J_{H\text{-}H}$, Hz) 7.02 (d, 1H, H3), 3.32 (d, 1H, $^2J = 18$, H4a), 3.65 (d, 1H, $^2J = 18$, H4b). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.5 (C = O), 145.4 (C3), 104.7 (CCl_3), 99.0 (C5), 45.1 (C4). MS m/z (%) 128 (M +, $-CCl_3$ 16), 85 (100). Anal. calcd.: C, 24.37; H, 2.45; N, 17.05%. Found: C, 24.44; H, 2.60; N, 16.98%.

1-Carboxamide-5-trichloromethyl-3-methyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (2b)

$C_6H_8Cl_3N_3O_2$; mw 260.50; mp 141–143°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ($J_{H\text{-}H}$, Hz) 3.26 (d, 1H, $^2J = 19$, H4a), 3.51 (d, 1H, $^2J = 19$, H4b), 2.00 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.8 (C = O), 155.5 (C3), 104.2 (CCl_3), 100.5 (C5), 50.1 (C4), 15.6 (CH_3). MS m/z (%) 142 (M +, $-CCl_3$, 45), 117 (16), 99 (100), 82 (12). Anal. calcd.: C, 27.66, H, 3.10; N, 16.13%. Found: C, 27.75; H, 3.02; N, 16.65%.

1-Carboxamide-5-trichloromethyl-3-ethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (2c)

$C_7H_{10}Cl_3N_3O_2$; mw 274.53; mp 127–128 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ($J_{H\text{-}H}$, Hz) 1.18 (t, 3H, CH_3), 2.38 (q, 2H, CH_2), 3.25 (d, 1H, $^2J = 19$, H4a), 3.52 (d, 1H, $^2J = 19$, H4b), 2.00 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.9 (C = O), 157.9 (C3), 104.3 (CCl_3), 100.3 (C5), 48.6 (C4), 23.3 (C8), 10.3 (C9). MS m/z (%) 156 (M +, $-CCl_3$, 17), 113 (MH^+, $-CCl_3$, $-CONH_2$, 100), 85 (22). Anal. calcd.: C, 30.63; H, 3.67; N, 15.31%. Found: C, 30.48, H, 3.65, N, 15.24%.

1-Carboxamide-5-trichloromethyl-5-hydroxy-3-propyl-4,5-dihydro-1*H*-pyrazole (2d)

$C_8H_{12}Cl_3N_3O_2$; mw 288.56; mp 95–97 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ($J_{H\text{-}H}$, Hz) 0.99 (t, 3H, CH_3), 1.61–1.64 (m, 2H, CH_2), 2.33 (t, 2H, CH_2),

3.23 (d, 1H, $^2J = 19$, H4a), 3.52 (d, 1H, $^2J = 19$, H4b). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.7 (C = O), 158.1 (C3), 104.2 (CCl_3), 100.1 (C5), 48.7 (C4), 31.6 (C8), 19.2 (C9), 13.5 (C10). MS m/z (%) 170 (M +, $-CCl_3$, 25), 98 (14), 85 (44). Anal. calcd.: C, 33.30; H, 4.19; N, 14.56%. Found: C, 33.15; H, 4.17; N, 14.50%.

1-Carboxamide-5-trichloromethyl-5-hydroxy-3-(1-methylethyl)-4,5-dihydro-1*H*-pyrazole (2e)

$C_8H_{12}Cl_3N_3O_2$; mw 288.56; mp 92–95 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ($J_{H\text{-}H}$, Hz) 1.18 (d, 6H, $2CH_3$), 2.63–2.70 (m, 1H, CH), 3.24 (d, 1H, $^2J = 19$, H4a), 3.55 (d, 1H, $^2J = 19$, H4b). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.1 (C = O), 158.1 (C3), 104.3 (CCl_3), 100.2 (C5), 46.7 (C4), 29.5 (C8), 19.5 (C9). MS m/z (%) 170 (M +, $-CCl_3$, 19), 127 (MH^+, $-CCl_3$, $_2$, 100), 111 (8), 85 (65). Anal. calcd.: C, 33.30; H, 4.19; N, 14.56%. Found: C, 33.10; H, 4.18; N, 14.45%.

1-Carboxamide-5-trichloromethyl-5-hydroxy-3-(2-methylpropyl)-4,5-dihydro-1*H*-pyrazole (2f)

$C_9H_{14}Cl_3N_3O_2$; mw 302.59; mp 124–126 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ($J_{H\text{-}H}$, Hz) 0.99 (t, 6H, $2CH_3$), 1.92–2.02 (m, 1H, CH), 2.69 (d, 2H, CH_2), 3.23 (d, 1H, $^2J = 18$, H4a), 3.53 (d, 1H, $^2J = 18$, H4b). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.9 (C = O), 157.3 (C3), 104.4 (CCl_3), 100.0 (C5), 48.7 (C4), 38.0 (C8), 25.3 (C9), 22.3 (C10). MS m/z (%) 184 (M +, $-CCl_3$, 41), 141 (MH^+, $-CCl_3$, $-CONH_2$, 100), 125 (17), 85 (82). Anal. calcd: C, 35.73; H, 4.66; N, 13.89%. Found: C, 35.53, H, 4.62; N, 13.81%.

1-Carboxamide-5-trichloromethyl-5-hydroxy-3-(1,1-dimethylethyl)-4,5-dihydro-1*H*-pyrazole (2g)

$C_9H_{14}Cl_3N_3O_2$; mw 302.59; mp 122–125 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ($J_{H\text{-}H}$, Hz) 1.20 (s, 9H, $3CH_3$), 3.27 (d, 1H, $^2J = 18$, H4a), 3.60 (d, 1H, $^2J = 18$, H4b). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4 (C = O), 158.2 (C3), 104.3 (CCl_3), 100.5 (C5), 45.9 (C4), 34.1 (C8), 27.2 (C9). MS m/z (%) 184 (M +, $-CCl_3$, 41), 141 (MH^+, $-CCl_3$, $-CONH_2$, 100), 125 (17), 85 (82), 57 (78). Anal. calcd.: C, 35.73; H, 4.66; N, 13.89%. Found: C, 35.57; H, 4.59; N, 13.78%.

1-Carboxamide-5-trichloromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazole (2h)

$C_{11}H_{10}Cl_3N_3O_2$; mw 322.57; mp 158–160 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ($J_{H\text{-}H}$, Hz) 3.77 (d, 1H, $^2J = 18$, H4a), 3.94 (d, 1H, $^2J = 18$, H4b), 7.44–7.82 (5H, phenyl). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.6 (C = O), 152.6 (C3), 104.6 (CCl_3), 100.8 (C5), 46.3 (C4), 126.7, 128.7, 130.1, 130.5 (6 C, phenyl). Anal. calcd.: C, 40.96; H, 3.12; N, 13.03%. Found: C, 40.94; H, 3.26; N, 13.37%.

1-Carboxamide-5-trichloromethyl-3-(4-fluorophenyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazole (2i)

$C_{11}H_9Cl_3FN_3O_2$; mw 340.57; mp 184–186 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ($J_{H\text{-}H}$, Hz) 3.71 (d, 1H, $^2J = 18$, H4a), 3.98 (d, 1H, $^2J = 18$, H4b), 7.26–7.87 (m, 4H, aryl). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.3 (C = O), 151.8 (C3), 103.3 (CCl_3), 101.1 (C5), 46.8 (C4), 115.7, 127.0, 128.8, 163.2 (6C, aryl). MS m/z (%) 222 (M +, $-CCl_3$), 236 (42), 191 (36), 163 (18), 147 (10), 120 (100), 101 (50). Anal. calcd.: C, 38.80; H, 2.66; N, 12.34%. Found: C, 38.58; H, 2.65; N, 12.27%.

1-Carboxamide-5-trichloromethyl-3-(4-chlorophenyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazole (2j)

$C_{11}H_9Cl_4N_3O_2$; mw 357.02; mp 188–190 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ($J_{H\text{-}H}$, Hz) 3.89 (d, 1H, $^2J = 18$, H4a), 3.98 (d, 1H, $^2J = 18$, H4b), 7.42–7.68 (m, 4H, aryl). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.0 (C = O), 153.8 (C3), 103.4 (CCl_3), 100.7 (C5), 46.1 (C4), 127.9, 128.4, 129.1, 137.1 (6 C, aryl). MS m/z (%) 194 (M^+, $-CCl_3$, $-CONH_2$, 100), 163 (13), 137 (85), 101 (60). Anal. calcd.: C, 37.01; H, 2.54; N, 11.77%. Found: C, 36.68; H, 2.50; N, 11.66%.

1-Carboxamide-5-trichloromethyl-3-(4-bromophenyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazole (2k)

$C_{11}H_9Cl_3BrN_3O_2$; mw 401.47; mp 188–190 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ($J_{H\text{-}H}$, Hz) 3.78 (d, 1H, $^2J = 18$, H4a), 3.78 (d, 1H, $^2J = 18$, H4b), 7.70–7.73 (m, 4H, aryl). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.2 (C = O), 151.8 (C3), 103.3 (CCl_3), 101.1 (C5), 46.6 (C4), 123.9, 128.3, 129.4, 131.7 (6 C, aryl). MS m/z (%) 282 (M^+, $-CCl_3$, 6), 253 (100), 225 (97), 183 (63), 157 (40), 102 (35). Anal. calcd.: C, 32.91; H, 2.26; N, 10.47%. Found: C, 32.53; H, 2.34; N, 10.37%.

1-Carboxamide-5-trichloromethyl-5-hydroxy-3-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole (2l)

$C_{11}H_9Cl_3N_4O_4$; mw 367.56; mp 214–217 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ ($J_{H\text{-}H}$, Hz) 8.30 (s, 1H, OH), 8.28–8.15 (m, 4H, aryl), 7.30 (s, 2H, NH_2), 4.10 (d, 1H, $^2J = 19$, H4a), 3.80 (d, 1H, $^2J = 19$, H4b). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.9 (C = O), 150.4 (C3), 104.3 (CCl_3), 101.4 (C5), 46.3 (C4), 123.8, 128.5, 132.4, 148.2 (6 C, aryl). Anal. calcd.: C, 35.95; H, 2.47; N, 15.24%. Found: C, 36.12; H, 2.60; N, 15.17%.

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