Pergamon

Tetrahedron 57 (2001) 7685–7692

TETRAHEDRON

Synthesis of 3-chloroanthranilates from α,γ,γ-trichloro-β-iminoesters

Christian V. Stevens,* Bart Kesteleyn, Erick Rosas Alonso and Norbert De Kimpe*

Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure links 653, B-9000 Ghent, Belgium

Received 7 May 2001; accepted 16 July 2001

Abstract—3-Chloroanthranilates have been prepared by a short pathway involving dehydrohalogenation of α,γ,γ-trichloro-β-iminoesters, which were obtained by trihalogenation of the corresponding enaminoesters. This route opens the way to a number of previously unknown functionalised anthranilates, which are potential starting materials for a variety of heterocyclic and biologically interesting compounds.

1. Introduction

Chloroanthranilates and dichloroanthranilates proved to be versatile building blocks for the synthesis of a variety of heterocyclic compounds. They are used for the synthesis of 1,2,3,4-tetrahydroquinoline-2,3,4-trione 3-oximes (NMDA-glycine site antagonists),[1] several kinds of 1,2,3,4-tetrahydro-1,4-benzodiazepines,[2,3] 4-hydroxycarbostyril-3-alkylcarboxylic acids and their esters (aldosterone antagonists),[4] benzo-separated xanthines,[5] 2-amino-3,1-benzoxazin-4-ones (serine protease C1r inhibitors)[6] and 9-oxo-9,10-dihydroacridine-4-carboxylic acids.[7]

Despite the utility of chloroanthranilates in general, little attention was paid to the synthesis of 3-chloroanthranilates, which were seldomly reported in the literature.[2] The lack of straightforward synthetic methods probably led to the absence of 3-chloro substituted derivatives in the screening of the corresponding heterocyclic compounds reported. In this communication, a straightforward method for regiospecifically chlorinated anthranilates, i.e. 3-chloroanthranilates **4**, from α,γ,γ-trichloro-β-iminoesters **3** is reported.

2. Results and discussion

The synthesis of 3-chloroanthranilates is described via halogenation of *N*-alkyl enaminoesters, followed by base induced dehydrohalogenation.

Alkoxycarbonylation of cyclohexanones was performed by treatment with sodium hydride and reaction with two equivalents of dimethyl carbonate in benzene. The reaction with dimethyl carbonate proceeds smoothly for cyclohexanone itself, but results in the formation of a considerable amount of side-products (about 18%) for the 4-*t*-butyl derivative which had to be removed by a short path high vacuum distillation. Distillation of all the alkoxycarbonyl cyclohexanones **1** is recommended before condensation with primary amines in the next step.[8]

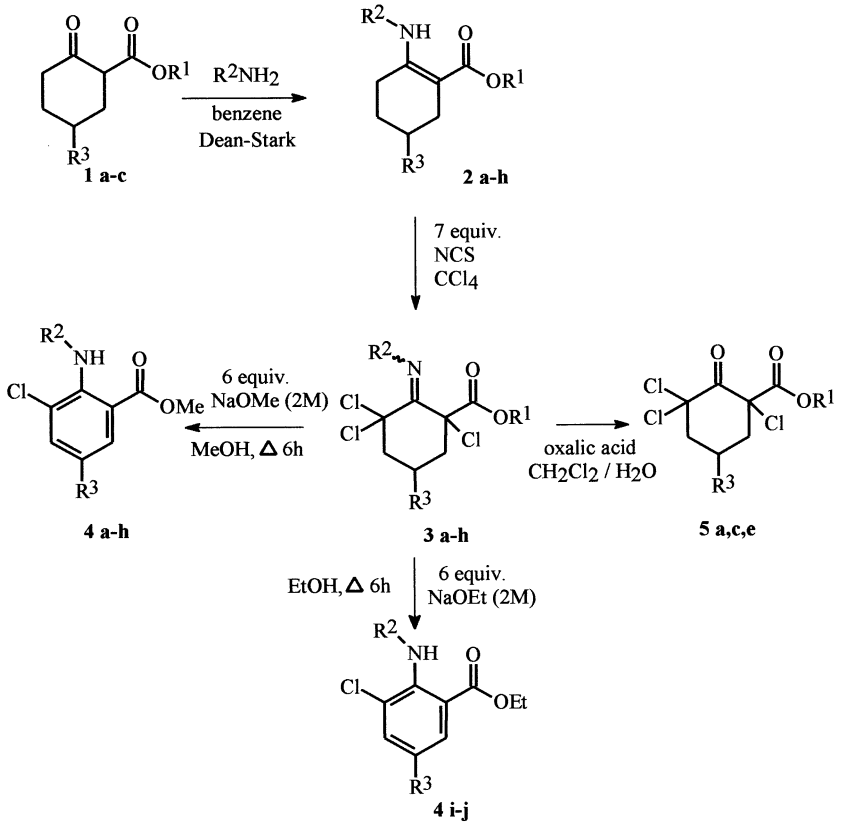
β-Keto esters **1** were then condensed with an excess of a primary amine in refluxing benzene under azeotropic removal of water and acid catalysis (*p*-toluenesulfonic acid) to obtain the *N*-alkyl enaminoesters **2** (Scheme 1).[9,10] An excess of amine was necessary when using volatile amines, whereas 1.2 equiv. were sufficient for less volatile amines, e.g. cyclohexylamine. The selectively formed β-enaminoesters[11,12] were obtained in almost quantitative yield (98–100%) and can be used as such in the following reaction step. However, when the compounds need to be stored for a longer period, purification is advisable since small traces of *p*-toluenesulfonic acid stimulates hydrolysis. The purified β-enaminoesters **2** can be obtained in reasonable to good yields (45–97%).

Since very little work has been performed on chlorinated β-enaminoesters or β-iminoesters,[13–16] the chlorination of **2** was evaluated using different conditions suitable for the chlorination of imines. During this study, it was observed that the chlorination of **2** with NCS in tetrachloromethane often produced complex mixtures of chlorinated products.

Even an attempt to selectively chlorinate the monochloro iminoester **8**, synthesised by imination of α-chloro-β-ketoester **6** and thermal rearrangement, similar to the allylic rearrangement of α-chloro-β-ketoesters to γ-chloro-β-ketoesters, did not lead to a good synthesis of the dichloro

Keywords: anthranilates; chloroanthranilates; iminoesters; chloroimines.
* Corresponding authors. Fax: +32-9-264-6243; e-mail: chris.stevens@rug.ac.be; Fax: +32-9-264-6243; e-mail: norbert.dekimpe@rug.ac.be

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00750-5



Scheme 1.

derivative **9** (Scheme 2). Only mixtures could be obtained containing up to 70% of the α,γ-dichloro-β-iminoester **9**. However, if an excess of chlorinating agent (7 equiv. NCS) was applied to **8**, the trichloro derivative **3** could be obtained but the reaction mixture was contaminated with some starting material and some hydrolyzed starting material (purity: 70%).

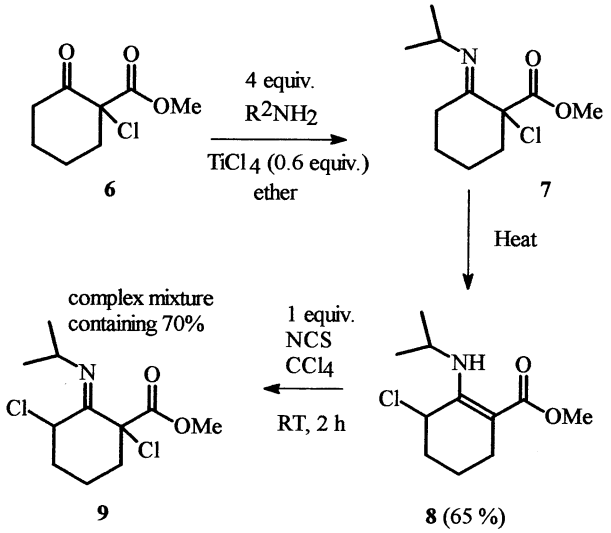
When the enaminoesters **2** were treated with an excess of chlorinating reagent, a single reaction product could be isolated. Therefore, the enaminoesters were dissolved in tetrachloromethane and reacted with 5 equiv. of *N*-chlorosuccinimide (NCS) during 20 h of reflux in order to obtain the trichlorinated derivative **3**.

The same result could be achieved by adding 7 equiv. of NCS and heating the reaction mixture vigorously by a bunzen flame for 30 s. The trichlorinated iminoesters **3** were obtained in almost quantitative yield (98–100%) and could be used without further purification. Because of the *E*/*Z*-isomerism of the trichlorinated β-iminoesters, the reaction mixtures always contained two isomers in a ratio approximately 2:1, which cause the occurrence of two sets of signals in the ^{13}C NMR.

Treatment of the α,γ,γ-trichloro-β-iminoesters with sodium alkoxides in the corresponding alcohols led to the synthesis of alkyl 3-chloroanthranilates **4** (or alkyl 3-chloro-2-aminobenzoates) in moderate to good yields (Table 1). The purity of the reaction mixtures is better when using methyl benzoates compared to ethyl benzoates, which also results in higher yields after the chromatographic purification.

Because of considerable loss of material during flash chromatography of the anthranilates, the solvent mixtures for purification were choosen so that the R_f-value of the compounds **4** were high. However, in the case of the *t*-butyl derivative **4e**, the aromatised compound was present but could not be obtained pure.

The mechanism of the formation of 3-chloroanthranilates **4** (Scheme 3) consists of a double dehydrochlorination leading to a (chlorocyclohexadienylidene)amine **10**,

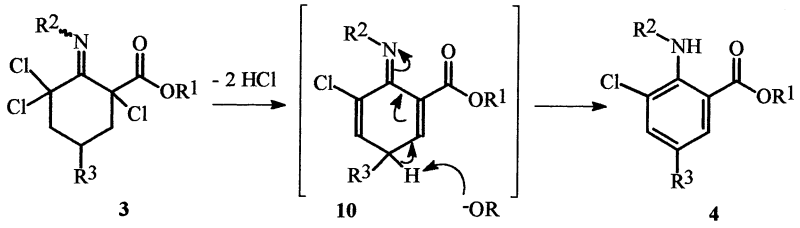


Scheme 2.

Table 1. Yields for the synthesis of enaminoesters **2**, α,γ,γ-trichloro-β-iminoesters **3** and 3-chloroanthranilates **4**

Substituent compound	R^1	R^2	R^3	Yield **2**	Yield **3**	Yield **4**
a	Me	*i*-Pr	H	81	>98	65 (45)[a]
b	Me	*c*-Hex	H	87	>98	71 (53)[a]
c	Et	*i*-Pr	H	79	98	66 (26)[a]
d	Et	*c*-Hex	H	45	>98	39 (17)[a]
e	Me	*i*-Pr	*t*-Bu	77	>98	–[b]
f	Me	$CH_2CH_2C_6H_5$	H	90	>98	–
g	Me	*s*-Bu	H	97	99	66
h	Me	Cyclopent.	H	70	97	58
i	Et	Cyclopent.	H	–	–	52[c]
j	Et	*s*-Bu	H	–	–	35[c]

[a] Isolated yield after flash chromatography.
[b] The compound was present in the mixture, but could not be obtained pure.
[c] Products obtained by dehydrohalogenation and transesterification.



3 10 4

Scheme 3.

followed by proton abstraction giving rise to the formation of the aromatic nucleus. A similar reactivity has been reported during the formation of 2,6-dichloroanilines from the imines derived from 2,2,6,6-tetrachlorocyclohexanone.[17,18]

Also, interesterification could be performed during the aromatisation when sodium methoxide or ethoxide was used on the ethyl or methyl benzoate derivatives, respectively (conversion of **3g**, **3h** into **4j**, **4i**). The aromatisation of the *N*-phenylethyl derivative **3f** could not be performed using different sodium alkoxides (sodium methoxide, potassium *t*-butoxide) and led to complicated reaction mixtures, which were not characterised further.

The α,γ,γ-trichloro-β-iminoesters **3** were also hydrolysed to the α,γ,γ-trichloro-β-ketoesters **5** after prolonged heating (minimum 20 h) in a two phase system dichloromethane/water in the presence of oxalic acid (yield: 76–82%). These derivatives could not be prepared by direct chlorination of the β-ketoesters **1** since their treatment with an excess of sulfuryl chloride (3.3 equiv., reflux 20 h) only allowed the introduction of one chlorine atom. Therefore, the synthesis of trichlorocyclohexanones was only possible by chlorination of the iminoesters followed by hydrolysis.

In conclusion, this paper describes a convenient three-step synthesis of 3-chloroanthranilates by dehydrohalogenation of α,γ,γ-trichloro-β-iminoesters prepared by a straightforward halogenation of the easily accessible enaminoesters.

3. Experimental

^{1}H NMR spectra were recorded at 60 MHz (Jeol PMX 60 SI) and at 270 MHz (Jeol PMX 270 SI) with $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded at 20 MHz (Varian FT-80) with $CDCl_3$ as solvent. Mass spectra were obtained on a Varian MAT 112 mass spectrometer (70 eV) using direct inlet or GC-MS coupling (RSL 200, 20 m capillary column, i.d. 0.53 mm, He carrier gas). Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl.

3.1. General procedure for the synthesis of enaminoesters 2

In a round bottom flask of 250 ml, equipped with a Dean–Stark aparatus and a reflux condenser, 50 mmol of alkoxycarbonylcyclohexanone **1** was dissolved in benzene and 100 mg of *p*-toluenesulphonic acid was added. The reaction mixture was heated under reflux and 250 mmol of the primary amine was added during one hour. After 4 h of reflux, the solvent was evaporated in vacuo. Purification of the reaction mixture was performed by high vacuum distillation (yield: 45–87%).

3.1.1. Methyl 2-(isopropylamino)-1-cyclohexen-1-carboxylate (2a). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.18 (6H, d, *J*=6.6 Hz, $CH(Me)_2$); 1.54–1.69 (4H, m, $(CH_2)_2$); 2.26 (2H, t, *J*=6 Hz, CH_2); 2.35 (2H, t, *J*=6 Hz, CH_2); 3.65 (3H, s, OCH_3); 3.72 (1H, m, $CH(CH_3)_2$); 8.93 (1H, broad d, *J*=5.9 Hz, NH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 22.39 and 22.82 and 23.83 and 26.24 (4×CH_2); 24.34 ($CH(CH_3)_2$); 43.23 ($CH(CH_3)_2$); 50.21 (OCH_3); 88.82 (C=CN); 158.88 (C=CN); 171.21 (C=O). IR (NaCl, ν, cm^{-1}): 1650 (CO), 1600 (C=C). MS *m/z* (%): 197 (M^+, 68); 182 (43); 166 (42); 156 (46); 150 (100); 138 (62); 122 (34); 110 (13); 96 (27); 81 (27); 67 (21); 58 (26); 41 (38). Bp: 67°C/

0.02 mmHg. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.84; H, 9.86; N, 7.15.

3.1.2. Methyl 2-(cyclohexylamino)-1-cyclohexen-1-carboxylate (2b). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.23–1.35 (6H, m, $(CH_2)_3$); 1.53–1.87 (8H, m, $(CH_2)_4$); 2.26 (2H, t, J=6.3 Hz, CH_2); 2.35 (2H, t, J=6.3 Hz, CH_2); 3.31 (1H, m, NHC*H*); 3.65 (3H, s, OCH_3); 9.06 (1H, broad d, J=8.6 Hz, NH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 22.39 and 22.84 and 23.85 (2C) and 24.82 (2C) and 25.57 (2C) and 26.27 (9×CH_2); 34.59 (*C*HN); 50.22 (OCH_3); 88.62 (*C*=CN); 158.88 (C=CN); 171.21 (C=O). IR (NaCl, ν, cm^{-1}): 1645 (CO), 1580 (C=C). MS *m/z* (%): 237 (M^+, 100); 222 (12); 206 (33); 204 (20); 194 (37); 178 (67); 162 (60); 156 (82); 154 (42); 124 (45); 96 (63); 81 (30); 55 (46); 41 (49). Crystallised from diethyl ether/pentane; Mp: 63°C. Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.99; H, 9.64; N, 5.82.

3.1.3. Ethyl 2-(isopropylamino)-1-cyclohexen-1-carboxylate (2c). See Ref. 19 for details.

3.1.4. Ethyl 2-(cyclohexylamino)-1-cyclohexen-1-carboxylate (2d).[20] ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.19–1.34 (6H, m, $(CH_2)_3$); 1.26 (3H, t, J=7.3 Hz, *Me*CH_2O); 1.55–1.87 (10H, m, $(CH_2)_{5+}(CH_2)_2$); 2.27 (2H, t, J=6 Hz, CH_2); 2.35 (2H, t, J=6 Hz, CH_2); 3.31 (1H, m, NHC*H*); 4.11 (2H, q, J=7.3 Hz, OCH_2); 9.05 (1H, broad d, J=7.9 Hz, NH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 14.74 (*Me*CH_2O); 22.43 (2C) and 22.84 and 23.88 and 24.87 (2C) and 25.57 and 26.29 and 34.63 (9×CH_2); 50.30 (CHN); 58.53 (Me*C*H_2O); 88.86 (*C*=CN); 158.69 (C=CN); 170.90 (C=O). IR (NaCl, ν, cm^{-1}): 1645 (CO), 1595 (C=C). MS *m/z* (%): 251 (M^+, 100); 222 (28); 208 (34); 206 (37); 104 (34); 178 (80); 170 (70); 168 (49); 162 (60); 124 (50); 122 (32); 98 (29); 96 (67); 81 (31); 55 (21); 41 (52). Bp: 125–127/0.001 mmHg. Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.53; H, 10.13; N, 5.69.

3.1.5. Methyl 5-*tert*-butyl-2-(isopropylamino)-1-cyclohexen-1-carboxylate (2e). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.90 (9H, s, C(*C*H_3)$_3$); 1.17 (3H, d, J=6.6 Hz, CH(*Me*)$_2$); 1.19 (3H, d, J=6.6 Hz, CH(*Me*)$_2$); 1.13–1.25 (2H, m, CH_2); 1.82–1.94 (2H, m, CH_2); 2.22–2.60 (3H, m); 3.67 (3H, s, OCH_3); 3.64–3.76 (1H, m, C*H*$(CH_3)_2$); 8.88 (1H, broad d, J=8.3 Hz, NH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 24.40 and 24.37 (CH(*C*H_3)$_2$; 23.50 and 25.18 and 27.53 and 32.29 (3×CH_2, 1×CH); 27.32 (C(*C*H_3)$_3$); 43.38 (*C*H$(CH_3)_2$); 44.29 (*C*(Me)$_3$), 50.24 (OCH_3); 88.80 (*C*=CN); 158.81 (C=CN); 171.31 (C=O). IR (NaCl, ν, cm^{-1}): 1650 (CO), 1595 (C=C). MS *m/z* (%): 253 (M^+, 63); 238 (82); 222 (27); 210 (25); 206 (30); 196 (33); 194 (27); 169 (34); 154 (100); 122 (34); 110 (46); 94 (25); 57 (28); 43 (22); 41 (40). Bp: 85–90°C/0.01 mmHg. Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.23; H, 10.64; N, 5.45.

3.1.6. Methyl 2-(phenetylamino)-1-cyclohexen-1-carboxylate (2f). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.51–1.63 (4H, m, $(CH_2)_2$); 2.22–2.26 (4H, m, $(CH_2)_2$); 2.84 (2H, t, J=7.6 Hz, NCH_2CH_2); 3.41 (2H, t, J=7.6 Hz, NCH_2); 3.66 (3H, s, OCH_3); 7.19–7.36 (5H, m, C_6H_5); 9.01 (1H, broad s, NH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 22.28 and 22.69 and 23.81 and 26.33 (4×CH_2); 37.34 (CH_2CH_2N); 44.06 (CH_2N); 50.26 (OCH_3); 89.52 (*C*=CN); 126.47 (CH); 128.53 (2C); 128.75 (2C)(=CH); 138.99 (=Cquat); 159.37 (C=CN); 171.10 (C=O). IR (NaCl, ν, cm^{-1}): 1645 (CO), 1595 (C=C). MS *m/z* (%): 259 (M^+, 26); 244 (10); 230 (40); 228 (31); 212 (18); 198 (23); 168 (16); 122 (10); 91 (99); 77 (14); 67 (31); 55 (12); 41 (32); 39 (24). This compound was not distilled and used as such (purity > 95%) in the next chlorination step.

3.1.7. Methyl 2-(1-*sec*-butylamino)-1-cyclohexen-1-carboxylate (2g). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.92 (3H, t, J=7.4 Hz, CH_2CH_3); 1.14 (3H, d, J=6.6 Hz, CH*C*H_3); 1.47 (2H, m, *C*H_2CH_3); 1.48–1.69 (4H, m, $(CH_2)_2$); 2.24–2.38 (4H, m, $(CH_2)_2$); 3.38–3.49 (1H, m, C*H*CH_3); 3.66 (3H, s, OCH_3); 8.95 (1H, broad s, NH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 10.39 (CH_2CH_3); 21.89 (CH*C*H_3); 22.30 and 22.72 and 23.76 and 26.33 (4×CH_2); 30.97 (*C*H_2CH_3); 48.66 (OCH_3); 50.06 (CHN); 88.50 (*C*=CN); 159.12 (C=*C*N); 171.10 (C=O). IR (NaCl, ν, cm^{-1}) 1645 (CO), 1595 (C=C). MS *m/z* (%): 211 (M^+, 24); 182 (46); 180 (27); 164 (13); 150 (100); 122 (11); 96 (11); 81 (10); 40 (24). Bp: 70°C/0.05 mmHg. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.14; H, 9.94; N, 6.57.

3.1.8. Methyl 2-(cyclopentylamino)-1-cyclohexen-1-carboxylate (2h). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.43–1.78 and 1.81–1.98 (12H, m, $(CH_2)_2$ and $(CH_2)_4$-cyclopentyl); 2.26 (2H, ~t, CH_2); 2.37 (2H, ~t, CH_2); 3.65 (3H, s, OCH_3); 3.81–3.91 (1H, m, NCH); 9.06 (1H, broad s, NH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 22.25 and 22.66 and 23.65 and 23.72 (2C) and 26.63 and 34.39 (2C) $(CH_2)_2$-cyclopentyl and 4×CH_2); 50.06 (OCH_3); 53.26 (NCH); 88.72 (*C*=CN); 159.26 (C=*C*N); 171.03 (C=O). IR (NaCl, ν, cm^{-1}): 3252 (NH); 1709 (CO); 1645 (C=C). MS *m/z* (%): 224 (M^+ +1, 15); 223 (M^+, 100); 222 (18); 192 (38); 190 (24); 178 (15); 164 (95); 162 (28); 156 (55); 149 (32); 136 (15); 124 (38); 122 (33); 96 (66); 81 (32); 79 (34); 67 (43); 55 (30); 41 (85). This compound was not distilled and used as such (purity > 95%) in the next chlorination step.

3.2. General procedure for the synthesis of α,γ,γ-trichloro-β-iminoesters 3

To a solution of 25 mmol enaminoester **2** in 10 ml of tetrachloromethane, 175 mmol (7 equiv.) of *N*-chlorosuccinimide was added. The flask was equipped with a reflux condenser and the solution was refluxed by means of a bunzen flame for 30 s. After cooling the reaction mixture to 0°C, succinimide was filtered and washed with cold tetrachloromethane. After evaporation of the solvent, the trichloroiminoesters were obtained in almost quantitative yield (96–100%) and with high purity (>96%).

3.2.1. Methyl 1,3,3-trichloro-2-(isopropylimino)cyclohexanecarboxylate (3a). (Ratio *E*/*Z*: 65/35) ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.13 (6H, d, J=5.9 Hz, CH(*Me*)$_2$, major); 1.18 (6H, d, J=5.9 Hz, CH(*Me*)$_2$, minor); 1.96–2.06 (2H, m, CH_2); 2.24–2.34 (1H, m, C*H*(H)); 2.58–2.87 (2H, m, CH_2); 3.20–3.31 (1H, m, CH(*H*)); 3.69 (1H, sept., J=5.9 Hz, C*H*(Me)$_2$, minor); 3.78 (3H, s, OCH_3, major); 3.84 (3H, s, OCH_3, minor); 4.84 (1H, sept., J=5.9 Hz,

C*H*(Me)$_2$, major). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: Major: 16.19 (CH_2); 21.98 (CH(*Me*)$_2$); 22.28 (CH(*Me*)$_2$); 31.19 (*C*H_2CCl); 43.52 (*C*H_2CCl$_2$); 51.81 (*C*H(Me)$_2$); 53.31 (OCH_3); 74.09 (CCl); 78.44 (CCl_2); 155.43 (C=N); 168.91 (C=O). Minor: 16.73 (CH_2); 21.51 (CH(*Me*)$_2$); 22.43 (CH(*Me*)$_2$); 36.32 (*C*H_2CCl); 42.39 (*C*H_2CCl$_2$); 52.94 (*C*H(Me)$_2$); 53.96 (OCH_3); 64.06 (CCl); 87.69 (CCl_2); 154.61 (C=N); 169.95 (C=O). IR (NaCl, ν, cm^{-1}) 1750 (CO). MS *m*/*z* (%): no M^+; 284/86 (6); 264/66 (10); 257/59 (27); 225/27/29 (33); 190/92/94 (9); 177 (4); 135 (10); 89 (8); 59 (19); 43 (100). Anal. Calcd for $C_{11}H_{16}Cl_3NO_2$: C, 43.95; H, 5.36; N, 4.66. Found: C, 43.92; H, 5.33; N, 4.68.

3.2.2. Methyl 1,3,3-trichloro-2-(cyclohexylimino)cyclohexanecarboxylate (3b). (Ratio *E*/*Z*: 65/35) ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.28–1.83 (10H, m, (C*H*$_2$)$_5$-cyclohex.); 1.96–2.32 (3H, m); 2.61–2.87 (2H, m); 3.31–3.33 (1H, m, CH(*H*)); 3.36 (1H, br.s., C*H*N); 3.78 (3H, s, OCH_3, major); 3.83 (3H, s, OCH_3, minor); 4.52 (1H, br.s., C*H*N). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: Major: 16.23 (CH_2); 31.25 (2×CH_2); 31.57 (2×CH_2); 23.58 (CH_2); 31.95 (*C*H_2CCl); 43.54 (*C*H_2CCl$_2$); 53.35 (H*C*N); 59.69 (OCH_3); 74.14 (CCl); 78.31 (CCl_2); 155.74 (C=N); 169.00 (C=O). Minor: 16.77 (CH_2); 25.76 (2×CH_2); 31.34 (2×CH_2); 23.76 (CH_2); 36.30 (*C*H_2CCl); 42.41 (*C*H_2CCl$_2$); 53.89 (H*C*N); 41.40 (OCH_3); 64.00 (CCl); 87.87 (CCl_2); 154.50 (C=N); 170.00 (C=O). IR (NaCl, ν, cm^{-1}) 1755 (CO). MS *m*/*z* (%): no M^+; 304/06/08 (34); 257/59/61 (14); 225/27/29 (6); 121 (5); 83 (100); 55 (62); 41 (32).

3.2.3. Ethyl 1,3,3-trichloro-2-(isopropylimino)cyclohexanecarboxylate (3c). (Ratio *E*/*Z*: 62/38) ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.15 (3H, d, *J*=5.9 Hz, CH(*Me*)$_2$, major); 1.18 (3H, d, *J*=5.9 Hz, CH(*Me*)$_2$, major); 1.14 (3H, d, *J*=5.9 Hz, CH(*Me*)$_2$, minor); 1.19 (3H, d, *J*=5.9 Hz, CH(*Me*)$_2$, minor); 1.29 (3H, t, *J*=7.3 Hz, OCH_2*Me*, major); 1.32 (3H, t, *J*=7.3 Hz, OCH_2*Me*, minor); 1.94–2.33 (3H, m); 2.58–2.89 (2H, m, CH_2); 3.18–3.29 (3H, m); 3.74 (1H, sept., *J*=5.9 Hz, C*H*(Me)$_2$, minor); 4.23 (2H, m, OC*H*$_2$Me, major); 4.33 (2H, m, OC*H*$_2$Me, minor); 4.86 (1H, sept., *J*=5.9 Hz, C*H*(Me)$_2$, major). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: Major: 13.99 (OCH_2*Me*); 16.30 (CH_2); 22.01 (CH(*Me*)$_2$); 22.23 (CH(*Me*)$_2$); 31.43 (*C*H_2CCl); 43.72 (*C*H_2CCl$_2$); 51.82 (*C*H(Me)$_2$); 62.60 (O*C*H_2Me); 73.82 (CCl); 78.54 (CCl_2); 155.36 (C=N); 168.28 (C=O). Minor: 13.82 (OCH_2*Me*); 16.71 (CH_2); 21.56 (CH(*Me*)$_2$); 22.43 (CH(*Me*)$_2$); 36.21 (*C*H_2CCl); 42.25 (*C*H_2CCl$_2$); 52.79 (*C*H(Me)$_2$); 63.38 (O*C*H_2Me); 64.26 (CCl); 87.81 (CCl_2); 154.62 (C=N); 169.31 (C=O). IR (NaCl, ν, cm^{-1}) 1750 (CO), 1650 (C=N, w). MS *m*/*z* (%): no M^+; 298/00/02/04 (7); 278/80/82 (31); 271/73/75 (23); 242/44/46 (18); 225/27/29 (41); 190 (23); 164 (18); 135 (31); 107 (20); 89 (18); 77 (19); 43 (100). Anal. Calcd for $C_{12}H_{18}Cl_3NO_2$: C, 45.81; H, 5.77; N, 4.45. Found: C, 45.78; H, 5.82; N, 4.41.

3.2.4. Ethyl 1,3,3-trichloro-2-(cyclohexylimino)cyclohexanecarboxylate (3d). (Ratio *E*/*Z*: 62/38) ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.29 (3H, t, *J*=6.9 Hz, OCH_2*Me*, major); 1.33 (3H, t, *J*=6.9 Hz, OCH_2*Me*, minor); 1.30–1.78 (10H, m, (C*H*$_2$)$_5$-cyclohex.); 1.94–2.33 (3H, m); 2.57–2.90 (2H, m); 3.22–3.30 (3H, m); 4.21 (2H, m, OCH_2Me, major); 4.25 (2H, m, OCH_2Me, minor); 4.54 (1H, br.s., C*H*N). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: Major: 14.03 (OCH_2*Me*);16.32 (CH_2); 25.75 (2×CH_2); 31.63 (2×CH_2))(cyclohex.); 23.70 (CH_2); 31.91 (*C*H_2CCl); 43.70 (*C*H_2CCl$_2$); 59.93 (H*C*N); 62.62 (O*C*H_2CH$_3$); 73.89 (CCl); 78.40 (CCl_2); 155.65 (C=N); 168.37 (C=O). Minor: 13.89 (OCH_2*Me*); 16.75 (CH_2); 25.66 (2×CH_2); 31.36 (2×CH_2)(cyclohex.); 23.81 (CH_2); 36.21 (CH_2CCl); 42.25 (*C*H_2CCl$_2$); 61.24 (H*C*N); 63.36 (O*C*H_2CH$_3$); 64.24 (CCl); 87.99 (CCl_2); 154.82 (C=N); 169.45 (C=O). IR (NaCl, ν, cm^{-1}) 1750 (CO); 1650 (C=N). MS *m*/*z* (%): no M^+; 318/20/22 (36); 271/73/75 (13); 225/27/29 (9); 192 (4); 164 (4); 135 (6); 101 (3); 83 (100); 55 (64); 41 (31).

3.2.5. Methyl 5-*tert*-butyl-1,3,3-trichloro-2-(isopropylimino)cyclohexanecarboxylate (3e). (Ratio *E*/*Z*: 59/41) ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.95 (9H, s, C(*C*H$_3$)$_3$); 1.15 (6H, d, *J*=5.9 Hz, CH(*Me*)$_2$, major); 1.19 (6H, d, *J*=5.9 Hz, CH(*Me*)$_2$, minor); 2.12–2.19 and 2.28–2.48 and 2.86–3.02 (5H, each m, (C*H*$_2$)$_2$+CH$_{ring}$); 3.66 (1H, sept., *J*=5.9 Hz, C*H*(Me)$_2$, major); 3.79 (3H, s, OCH_3, minor); 3.84 (3H, s, OCH_3, major); 4.95 (1H, sept., *J*=5.9 Hz, C*H*(Me)$_2$, minor). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: Major: 21.42 (CH(*Me*)$_2$); 21.98 (CH(*Me*)$_2$); 27.13 (C(*C*H$_3$)$_3$); 31.95 and 38.74 and 41.78 and 48.30 (*C*(CH$_3$)$_3$+*C*H$_2$*C*H*C*H$_2$); 53.14 (*C*H(Me)$_2$); 53.99 (OCH_3); 64.29 (CCl); 88.41 (CCl_2); 155.43 (C=N); 170.40 (C=O). Minor: 21.64 (CH(*Me*)$_2$); 22.21 (CH(*Me*)$_2$); 27.13 (C(*C*H$_3$)$_3$); 31.88 and 39.17 and 39.30 and 51.36 (*C*(CH$_3$)$_3$+*C*H$_2$*C*H*C*H$_2$); 51.64 (*C*H(Me)$_2$); 53.48 (OCH_3); 75.47 (CCl); 79.57 (CCl_2); 155.29 (C=N); 169.81 (C=O). IR (NaCl, ν, cm^{-1}) 1750 (CO). MS *m*/*z* (%): no M^+; 340/42/44/46 (19); 320/22/24 (39); 304/06/08 (12); 272/74 (18); 248 (8); 228 (8); 177/79 (20); 154 (9); 135 (12); 121/3 (54); 112 (13); 97(19); 83 (20); 70 (27); 44 (29); 43 (40); 41 (32); 40 (100).

3.2.6. Methyl 1,3,3-trichloro-2-(benzylimino)cyclohexanecarboxylate (3f). (Ratio *E*/*Z*: 64/36) ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.96–2.07 (2H, m, CH_2); 2.23–2.33 (1H, m, C*H*(H)); 2.59–3.09 (4H, m, CH_2 and NCH_2CH_2); 3.20–3.23 (1H, m, CH(*H*)); 3.74 (3H, s, OCH_3, major); 3.78 (3H, s, OCH_3, minor); 4.25–4.35 (2H, m, NCH_2); 7.16–7.30 (5H, m, C_6H_5). ^{13}C NMR (67.9 MHz, $CDCl_3$)? δ: Major: 16.09 (CH_2); 31.39 (NCH_2CH_2); 36.48 (CH_2CCl); 43.43 (*C*H_2CCl$_2$); 53.15 (NCH_2); 53.82 (OCH_3); 73.51 (CCl); 87.67 (CCl_2); 125.84 and 2×127.99 and 2×128.66 (=CH); 139.53 (=Cquat); 157.45 (C=N); 168.43 (C=O). Minor: 16.57 (CH_2); 35.65 (NCH_2CH_2); 36.19 (CH_2CCl); 41.99 (*C*H_2CCl$_2$); 46.92 (NCH_2); 53.59 (OCH_3); 71.34 (CCl); 87.37 (CCl_2); 126.01 and 2×127.99 and 2×128.75 (=CH); 139.26 (=Cquat); 157.14 (C=N); 169.04 (C=O). IR (NaCl, ν, cm^{-1}) 1745 (CO), 1655 (C=N). MS *m*/*z* (%): no M^+; 254 (10); 242/44 (39); 210/12 (100); 182 (18); 154 (32); 149/50 (81); 126/27 (25); 105 (17); 99 (11); 91 (21); 85 (11); 77 (15); 70 (15); 63 (12); 57 (30); 43 (20); 41 (22). Anal. Calcd for $C_{15}H_{16}Cl_3NO_2$: C, 51.67; H, 4.63; N, 4.02. Found: C, 51.62; H, 4.68; N, 3.98.

3.2.7. Methyl 1,3,3-trichloro-2-(1-*sec*-butylimino)cyclohexanecarboxylate (3g). (Ratio *E*/*Z*: 53/47) ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.85–0.96 (3H, m, CH_2CH_3); 1.09–1.27 (CHC*H*$_3$); 1.48–1.69 (2H, m, C*H*$_2$CH$_3$); 1.88–2.07 (2H, m, CH_2); 2.24–2.33 (1H, m, CH(*H*)); 2.59–2.89 (2H,

m, CH_2); 3.17–3.28 (1H, m, C*H*(H)); 3.77 (3H, s, OCH_3, major); 3.85 (3H, s, OCH_3, minor); 4.58–4.64 (1H, m, NCH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: Major: 10.52 (CH_2CH_3); 16.23 (CH_2); 19.75 ($CHCH_3$): 30.77 (CH_2CH_3); 31.00 (CH_2); 43.42 (CH_2); 53.39 (OCH_3); 57.34 (NCH); 74.50 (CCl); 88.11 (CCl_2); 156.14 (C=N); 168.98 (C=O). Minor: 10.42 (CH_2CH_3); 16.68 (CH_2); 19.66 ($CHCH_3$): 30.29(CH_2CH_3); 32.42 (CH_2); 44.71 (CH_2); 53.94 (OCH_3); 57.13 (NCH); 74.57 (CCl); 87.69 (CCl_2); 155.87 (C=N); 169.16 (C=O). IR (NaCl, ν, cm^{-1}): 1746 (C=O); 1653 (C=N). MS *m/z* (%): 314 (M^+, 1); 285/87 (26); 283/85/87 (28); 259/61 (22); 257 (25); 229 (13); 227 (30); 225 (33); 189 (12); 121/23 (13); 59 (19); 57 (100); 56 (13); 55 (13); 41 (56). (Purity: 65%).

3.2.8. Methyl 1,3,3-trichloro-2-(cyclopentylimino)cyclohexanecarboxylate (3h). (Ratio *E*/*Z*: 68/32) ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.49–2.06 (10H, m, CH_2 and $(CH_2)_4$-cyclopentyl); 2.24–2.34 (1H, m, CH(*H*)); 2.61–2.93 (2H, m, CH_2); 3.21–3.33 (1H, m, C*H*(H)); 3.77 (3H, s, OCH_3, major); 3.83 (3H, s, OCH_3, minor); 4.98–5.10 (1H, m, NCH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: Major: 16.18 (CH_2); 24.78 (2×CH_2-cyclohexyl); 31.25 (CH_2); 34.11 (2×CH_2-cyclohexyl); 43.51 (CH_2); 53.25 (OCH_3); 61.62 (NCH); 65.77 (CCl); 74.13 (CCl_2); 155.08 (C=N); 168.91 (C=O). Minor: 16.73 (CH_2); 24.99 (2×CH_2-cyclohexyl); 32.92 (CH_2); 33.68 (2×CH_2-cyclohexyl); 42.28 (CH_2); 53.86 (OCH_3); 62.46 (NCH); 65.77 (CCl); 74.13 (CCl_2); 154.21 (C=N); 169.97 (C=O). IR (NaCl, ν, cm^{-1}): 1756 (CO); 1638 (C=N). MS *m/z* (%): no M^+; 290/92/94 (31); 261 (10); 259 (26); 257 (27); 254 (10); 227 (27); 225 (28); 121/23 (35); 101 (10); 77 (12); 69 (99); 68 (18); 66 (36); 65 (19); 59 (16); 51 (13); 41 (100).

3.3. General procedure for the synthesis of 3-chloroanthranilates 4

To a flask, equiped with a reflux condenser and a drying tube, 0.88 mmol of the α,γ,γ-trichloro-β-iminoester **3** was treated with 5.28 mmol of sodium methoxide (2 M) in methanol (or sodium ethoxide (2 M), in case of transesterification **4i** and **4j**). The reaction mixture was refluxed for 6 h, then poured into 20 ml of water and extracted three times with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The crude products were purified by flash chromatography (EtOAc/hex.:mostly 20/80) in order to obtain the pure 3-chloroanthranilates **4**.

3.3.1. Methyl 3-chloro-2-isopropylaminoanthranilate (4a). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.17 (6H, d, *J*=6.6 Hz, $CH(CH_3)_2$); 3.87 (3H, s,OMe); 4.14 (1H, sept., *J*=6.6 Hz, $CH(CH_3)_2$); 6.73 (1H, dd, J_1=8.1, J_2=7.8 Hz, =CH); 6.87 (1H, broad s, NH); 7.41 (1H, dd, J_1=7.8, J_2=1.7 Hz, =CH); 7.83 (1H, dd, J_1=8.1, J_2=1.7 Hz, =CH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 23.74 ($CH(CH_3)_2$); 47.64 ($CH(CH_3)_2$); 52.04 (OCH_3); 118.88 (*C*COOMe); 119.10 (=CH); 124.98 (=CCl); 130.17 (=CH); 135.74 (=CH); 148.68 (=*C*NH); 168.35 (C=O). IR (NaCl, ν, cm^{-1}): 3330 (NH); 1695 (CO); 1590; 1515; 1450. MS *m/z* (%): 227/29 (M^+, 31); 212/14 (54); 194/96 (20); 180/82 (100); 153/55 (19); 117 (10); 90 (17); 58 (19). R_f=0.6 (EtOAc/hex.:20/80). Anal. Calcd for $C_{11}H_{14}ClNO_2$: C, 58.03; H, 6.20; N, 6.15. Found: C, 58.21; H, 6.11; N, 6.06.

3.3.2. Methyl 3-chloro-2-cyclohexylaminoanthranilate (4b). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.14–1.37 (6H, m, cyclohex.); 1.57–1.73 (2H, m, cyclohex.); 1.94–1.98 (2H, m, cyclohex.); 3.70–3.81 (1H, m, *C*HN); 3.87 (3H, s,OMe); 6.72 (1H, dd, J_1=8.1, J_2=7.4 Hz, =CH); 7.02 (1H, broad s, NH); 7.41 (1H, dd, J_1=7.8, J_2=1.7 Hz, =CH); 7.82 (1H, dd, J_1=8.1, J_2=1.7 Hz, =CH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 25.05 (2×CH_2); 25.79 (2×CH_2); 34.29 (2×CH_2); 52.04 (*C*HN); 54.75 (OCH_3); 118.61 (*C*COOMe); 118.81 (=CH); 124.72 (=CCl); 130.15 (=CH); 135.74 (=CH); 148.50 (=*C*NH); 168.39 (C=O). IR (NaCl, ν, cm^{-1}): 3325 (NH); 1690 (CO); 1585; 1510; 1450. MS *m/z* (%): 267/69 (M^+, 62); 252/54 (51); 236/38 (19); 224/26 (89); 192 (100); 166 (21); 153 (41); 98 (29); 90 (17); 55 (26); 41 (32). R_f=0.59 (EtOAc/Hex.: 20/80). Anal. Calcd for $C_{14}H_{18}ClNO_2$: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.68; H, 6.88; N, 5.35.

3.3.3. Ethyl 3-chloro-2-isopropylaminoanthranilate (4c). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.17 (6H, d, *J*=6.3 Hz, $CH(CH_3)_2$); 1.39 (3H, t, *J*=6.9 Hz, OCH_2Me); 4.15 (1H, sept., *J*=6.3 Hz, $CH(CH_3)_2$); 4.34 (2H, q, *J*=6.9 Hz, OCH_2Me); 6.75 (1H, t, *J*=7.9 Hz, CH); 6.77 (1H, broad s, NH); 7.42 (1H, dd, J_1=7.9, J_2=1.7 Hz, =CH); 7.85 (1H, dd, J_1=7.9, J_2=1.7 Hz, =CH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 14.25 (OCH_2Me); 23.74 ($CH(CH_3)_2$); 47.65 ($CH(CH_3)_2$); 61.02 (OCH_2CH_3); 118.96 (*C*COOMe); 119.60 (=CH); 125.10 (=CCl); 130.13 (=CH); 135.61 (=CH); 148.64 (=*C*NH); 167.92 (C=O). IR (NaCl, ν, cm^{-1}): 3315 (NH); 1690 (CO); 1580; 1505; 1450. MS *m/z* (%): 241/43 (M^+, 24); 226/28 (24); 212/14 (24); 196 (14); 194 (27); 180/82 (100); 153 (11); 117 (5); 90 (9); 58 (12), 43 (3). R_f=0.59 (EtOAc/Hex.: 20/80). Anal. Calcd for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.75; H, 6.63; N, 5.82.

3.3.4. Ethyl 3-chloro-2-cyclohexylaminoanthranilate (4d). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.12–1.34 (6H, m, cHex.); 1.56–1.64 (1H, m, cHex.); 1.70–1.75 (1H, m, cHex.); 1.93–1.98 (2H, m, cHex.); 1.38 (3H,t, *J*=7 Hz, OCH_2CH_3); 3.77 (1H, m, *C*HN); 4.34 (2H, q, *J*=7 Hz, OCH_2Me); 6.72 (1H, t, *J*=7.9 Hz, =CH); 7.00 (1H, broad s, NH); 7.40 (1H, dd, J_1=7.9, J_2=1.6 Hz, =CH); 7.83 (1H, dd, J_1=7.9, J_2=1.7 Hz, =CH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 14.27 (OCH_2Me); 25.07 (2×CH_2); 25.82 (2×CH_2); 34.29 (2×CH_2); 54.75 (*C*HN); 60.99 (OCH_2CH_3); 118.63 (*C*COOMe); 119.28 (=CH); 124.81 (=CCl); 130.11 (=CH); 135.59 (=CH); 148.46 (=*C*NH); 167.94 (C=O). IR (NaCl, ν, cm^{-1}): 3320 (NH); 1690 (CO); 1580; 1510; 1450 (arom.). MS *m/z* (%): 281/83 (M^+, 42); 252/54 (86); 238/40 (59); 234/36 (32); 192/94 (100); 153 (29); 55 (16); 41 (22). R_f=0.65 (EtOAc/hex.:20/80). Anal. Calcd for $C_{15}H_{20}ClNO_2$: C, 63.94; H, 7.15; N, 4.97. Found: C, 63.82; H, 7.14; N, 5.10.

3.3.5. Methyl 5-*tert*-butyl-3-chloro-2-isopropylaminoanthranilate (4e). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.15 (6H, d, *J*=6.3 Hz, $CH(CH_3)_2$); 1.29 (9H, s, $C(CH_3)_3$); 3.89 (3H, s,OMe); 4.07 (1H, sept., *J*=6.3 Hz, $CH(CH_3)_2$); 6.80 (1H, broad s, NH); 7.46 (1H, d, *J*=2.3 Hz); 7.82 (1H, d,

J=2.3 Hz, =CH). IR (NaCl, ν, cm^{-1}): 3320 (NH); 1690 (CO); 1530; 1430 (arom.). MS *m/z* (%): 283/85 (M^+, 45); 268/70 (100); 252 (14); 250 (22); 238 (35); 237 (19); 236 (98); 226 (15); 196 (20); 194 (20); 166 (8); 126 (9); 117 (9); 103 (8); 97 (13); 58 (25); 57 (25). This anthranilate could not be obtained pure despite all chromatographic efforts, this compound was only obtained with a purity of about 50%.

3.3.6. Methyl 3-chloro-2-(*sec*-butylamino)anthranilate (4g). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.93 (3H, t, J= 7.4 Hz, CH_2CH_3); 1.13 (3H, d, J=6.3 Hz, $CHCH_3$); 1.43–1.61 (2H, m, CH_2CH_3); 3.88 (3H, s, OCH_3); 3.91–4.03 (1H, m, CHN); 6.71 (1H, dd, J_1=6.9, J_2=7.9 Hz, =CH); 6.96 (1H, broad s, NH); 7.41 (1H, dd, J_1=1.3, J_2=6.9 Hz, =CH); 7.82 (1H, dd, J_1=1.3, J_2=7.9 Hz, =CH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 10.24 (CH_2CH_3); 20.74 ($CHCH_3$); 30.69 (CH_2CH_3); 51.81 (OCH_3); 52.67 (CHN); 118.22 (=CH); 121.13 (=CCO_2CH_3); 124.13 (=CCl); 130.09 (=CH); 135.72 (=CH); 148.77 (=CNH); 168.25 (C=O). IR (NaCl, ν, cm^{-1}): 3318 (NH); 1692 (CO); 1580; 1510; 1440 (Arom.). MS *m/z* (%): 241/43 (M^+, 15); 212/14 (64); 194 (12); 180/82 (100); 153 (10); 90 (11). R_f=0.64 (EtOAc/hex.:20/80). Anal. Calcd for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.51; H, 6.55; N, 5.90.

3.3.7. Methyl 3-chloro-2-cyclopentylaminoanthranilate (4h). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.47–1.92 (8H, m, $(CH_2)_4$); 3.86 (3H, s, OCH_3); 4.42–4.46 (1H, m, NCH); 6.68 (1H, dd, J_1=1.6, J_2=7.9 Hz, =CH); 7.39 (1H, dd, J_1=1.6, J_2=7.9 Hz, =CH); 7.81 (1H, dd, J_1=1.6, J_2= 7.3 Hz, =CH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 23.43 (2×CH_2); 33.93 (2×CH_2); 51.95 (OCH_3); 57.61 (NCH); 118.09 (=CH); 121.15 (=CCO_2CH_3); 123.74 (=CCl); 130.15 (=CH); 135.87 (=CH); 148.75 (=CN); 168.37 (C=O). IR (NaCl, ν, cm^{-1}): 3320 (NH); 1688 (CO); 1580; 1510; 1450. MS *m/z* (%): 254/56 (M^++1, 7); 253/55 (M^+, 51); 238/40 (53); 224/26 (69); 220/22 (41); 211 (15); 192/94 (100); 179/81 (13); 164/66 (20); 153/55 (42); 130 (12); 111 (10); 90 (14); 84 (36); 75 (14); 67 (12); 63 (11); 55 (14); 51 (10); 41 (38). R_f=0.2 (Hex./CH_2Cl_2: 80/20). Anal. Calcd for $C_{13}H_{16}ClNO_2$: C, 61.54; H, 6.36; N, 5.52. Found: C, 61.70; H, 6.25; N, 5.60.

3.3.8. Ethyl 3-chloro-2-cyclopentylaminoanthranilate (4i). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.89 (3H, t, J= 7.2 Hz, CH_2CH_3); 1.51–1.91 (8H, m, $(CH_2)_4$); 4.34 (2H, q, J=7.1 Hz, CH_2CH_3); 4.44–4.48 (1H, m, CHN); 6.70 (1H, t, J=7.8 Hz, =CH); 7.41 (1H, dd, J_1=1.3, J_2= 7.8 Hz, =CH); 7.85 (1H, dd, J_1=1.3, J_2=7.8 Hz, =CH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 14.07 (CH_2CH_3); 23.49 (2×CH_2); 33.59 (2×CH_2); 57.67 (NCH); 60.94 (OCH_3); 118.15 (=CH); 118.42 (=CCO_2Et); 123.88 (=CCl); 130.15 (=CH); 135.78 (=CH); 148.81 (=CN); 167.98 (C=O). IR (NaCl, ν, cm^{-1}): 3318 (NH); 1685(CO) 1590; 1515; 1450 (Arom.). MS *m/z* (%): 267/69 (M^+, 34); 238/40 (100); 220/22 (54); 204 (10); 192/94 (73); 164/66 (16); 153/55 (27); 90 (14); 84 (19); 75 (12); 55 (15); 41 (31). R_f=0.26 (hex./CH_2Cl_2: 80/20); This anthranilate could not be obtained pure despite all chromatographic efforts, this compound was only obtained with a purity of about 85%.

3.3.9. Ethyl 3-chloro-2-(*sec*-butylamino)anthranilate (4j). ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.88 (3H, t, J= 7.8 Hz, Me); 0.92 (3H, t, J=7.4 Hz, CH_2CH_3); 1.13 (3H, d, J=6.3 Hz, $CHCH_3$); 1.35–1.51 (2H, m, CH_2CH_3); 3.89–3.98 (1H, m, NCH); 4.33 (2H, q, J=6.9 Hz, OCH_2); 6.72 (1H, t, J=7.9 Hz, =CH); 6.94 (1H, broad s, NH); 7.40 (1H, dd, J_1=1.6, J_2=7.9 Hz, =CH); 7.84 (1H, dd, J_1=1.64, J_2=7.9 Hz, =CH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 10.39 (CH_2CH_3); 20.83 ($CHCH_3$); 30.78 (CH_2CH_3); 52.85 (CHN); 60.97 (OCH_2); 118.44 (=CH); 119.07 (=CCO_2Et); 124.46 (=CCl); 130.17 (=CH); 135.69 (=CH); 148.81 (=CN); 167.98 (C=O). IR (NaCl, ν, cm^{-1}): 3314 (NH); 1687 (CO); 1580; 1510; 1450 (Arom.). MS *m/z* (%): 255/57 (M^+, 11); 226/28 (47); 208/10 (19); 194/96 (11); 180/82 (100); 84/86 (10); 67/69 (25); 53 (14); 49 (12); 41 (25).). R_f=0.19 (hex./CH_2Cl_2: 80/20). Anal. Calcd for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.09; N, 5.48. Found: C, 61.18; H, 7.23; N, 5.41.

3.4. General procedure for the synthesis of 1,3,3-trichloro-2-oxocyclohexane-1-carboxylates 5

To a flask containing 1 mmol of α,γ,γ-trichloro-β-iminoester **3** in 2.5 ml of dichloromethane was added a solution of 1 mmol of oxalic acid ($(COOH)_2{\cdot}2H_2O$) in 2.5 ml of water. The two phase system was refluxed during 20 h and the aqueous layer was extracted afterwards three times with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo. The alkyl 1,3,3-trichloro-2-oxocyclohexane-1-carboxylates 5 were recrystallised from an ether/pentane mixture.

3.4.1. Methyl 1,3,3-trichloro-2-oxocyclohexane-1-carboxylate (5a). (R^1=Me, R^3=H) ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.87–2.26 (3H, m, CH_2); 2.50–2.62 (1H, m); 2.83–2.90 (1H, m); 3.01–3.07 (1H, m); 3.81 (3H, s, OMe). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 20.38 (CH_2); 39.41 (CH_2CCl); 47.30 (CH_2CCl_2); 53.82 (OCH_3); 71.55 (CCl); 87.51 (CCl_2); 165.80 (COOMe); 185.48 (C=O). IR (KBr, ν, cm^{-1}): 1735 (CO); 1245 (COOMe). MS *m/z* (%): 258/60/62 (12); 223 (3); 191 (3); 179/81 (9); 136/38 (85); 124 (37); 123 (48); 122 (57); 121 (100); 108 (15); 89 (28); 75 (29); 59 (36); 40 (23); 39 (30). Mp: 80.1°C, Yield: 76%. Anal. Calcd for $C_8H_9Cl_3O_3$: C, 37.03; H, 3.50. Found: C, 37.19; H, 3.62.

3.4.2. Ethyl 1,3,3-trichloro-2-oxocyclohexane-1-carboxylate (5c). (R^1=Et, R^3=H) ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.30 (3H, t, J=7 Hz, Me); 1.86–2.26 (3H, m, CH_2); 2.51–2.62 (1H, m); 2.83–2.90 (1H, m); 2.88–3.07 (1H, m); 4.26 (2H, m, OCH_2Me). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 13.66 (Me); 20.36 (CH_2); 39.32 (CH_2CCl); 47.30 (CH_2CCl_2); 63.47 (OCH_2CH_3); 71.77 (CCl); 87.53 (CCl_2); 165.24 (COOMe); 185.55 (C=O). IR (KBr, ν, cm^{-1}): 1700–1770 (CO). MS *m/z* (%): 272/74/76 (M^+, 12); 227/29 (5); 200/02 (13); 165/67/69 (86); 150/52/54 (100); 135/37 (62); 122/24/26 (44); 107/09/11 (97); 89 (34); 75 (39); 65 (31); 39 (44). Mp: 39.5–39.6°C, yield: 82%. Anal. Calcd for $C_9H_{11}Cl_3O_3$: C, 39.52; H, 4.05. Found: C, 39.71; H, 3.93.

3.4.3. Methyl 5-*tert*-butyl-1,3,3-trichloro-2-oxocyclohexane-1-carboxylate (5e). (R^1=Me, R^3=$C(CH_3)_3$) ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.99 (9H, s, $C(CH_3)_3$); 2.26–2.55 (4H, m, CH_2); 2.95–3.02 (1H, m); 3.88 (3H, s, OMe).

^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 27.28 ($C(CH_3)_3$); 32.02 ($C(CH_3)_3$); 39.17 (CH); 39.53 (CH_2CCl); 48.75 (CH_2CCl_2); 54.27 (OCH_3); 69.68 (CCl); 84.35 (CCl_2); 167.24 (COOMe); 188.80 (C=O). IR (KBr, ν, cm^{-1}): 1730–1775 (CO). MS *m/z* (%): 314/16/18/20 (M^+, 2); 258/60/62/64 (3); 223/25/27 (4); 188/90 (2); 164/66/68 (2); 136 (5); 121 (5); 57 (100); 41 (11). Mp: 98.6°C, yield: 81% (purity: 87%).

Acknowledgements

The authors are indebted to the Fund for Scientific Research-Flanders (Fonds voor Wetenschappelijk Onderzoek-Vlaanderen) and Ghent University for financial support. E. R. A. is indebted to the Mexican National Council for Science and Technology (CONACyT).

References

1. Cai, S. X.; Zhou, Z.-L.; Huang, J.-C.; Whittemore, E. R.; Egbuwoku, Z. O.; Lü, Y.; Hawkinson, J. E.; Woodward, R. M.; Weber, E.; Keana, J. F. W. *J. Med. Chem.* **1996**, *39*, 3248–3255.
2. Corral, C.; Madroñero, R.; Vega, S. *J. Heterocycl. Chem.* **1977**, *14*, 99–102.
3. Lehmann, J.; Kraft, G. *Arch. Pharm.* **1984**, *317*, 595–606.
4. Hörlein, U. *Arch. Pharm.* **1971**, *104*, 81–98.
5. Schneller, S. W.; Ibay, A. C.; Christ, W. J.; Bruns, R. F. *J. Med. Chem.* **1989**, *32*, 2247–2254.
6. Hays, S. J.; Caprathe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R.; Michael, W.; Nadimpalli, R.; Nath, R.; Raser, K. J.; Stafford, D.; Watson, D.; Wang, K.; Jaen, J. C. *J. Med. Chem.* **1998**, *41*, 1060–1067.
7. Stewart, G. M.; Rewcastle, G. W.; Denny, W. A. *Aust. J. Chem.* **1984**, *37*, 1939–1950.
8. Unsubstituted 2-alkoxycarbonylcyclohexanones are commercially available from Acros, Aldrich or Fluka. 4-*t*-Butyl-2-alkoxycarbonylcyclohexanones can be prepared according to: Kayser, R. H.; Brault, M.; Pollack, R. M.; Bantia, S.; Sadoff, S. F. *J. Org. Chem.* **1983**, *48*, 4497–4502.
9. Parr, R. W.; Reiss, J. A. *Aust. J. Chem.* **1984**, *37*, 389–394.
10. Merck and Co. Jpn. Kokai Tokkyo JP 62 33,140 [87 33,140] 13 Feb 1987, US Appl. 760,423, 30 Jul 1985; *Chem. Abstr.* **1988**, *108*, 185853v.
11. Hodgson, A.; Marshall, J.; Hallet, P.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2169–2174.
12. Labelle, M.; Gravel, D. *Can. J. Chem.* **1985**, *63*, 1884–1890.
13. De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Tetrahedron Lett.* **1985**, *26*, 2709–2712.
14. De Kimpe, N.; Schamp, N. *Org. Prep. Proced. Int.* **1981**, *13*, 245–313.
15. De Kimpe, N.; Schamp, N. *Org. Prep. Proced. Int.* **1983**, *15*, 71–135.
16. De Kimpe, N.; Verhé, R. In *The Chemistry of* α*-Haloketones,* α*-Haloaldehydes and* α*-Haloimines*, Patai, P., Rappoport, Z., Eds.; Wiley: Chichester, 1988.
17. Saeki, T.; Ishikawa, H.; Oki, T. Eur. Pat. Appl. EP 313,740, 3 Aug. 1988; *Chem. Abstr.* **1989**, *111*, 173731c.
18. Leblond, B. PhD Thesis, University of Rouen, France, 1991.
19. De Kimpe, N.; Keppens, M. *Tetrahedron* **1996**, *52*, 3705–3718.
20. Duerbeck, H. W.; Duttka, L. L. *Tetrahedron* **1973**, *29*, 4285–4290.