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APPLICATION OF THE HECK REACTION FOR THE SYNTHESIS OF 1-ALKOXYISOQUINOLINE-3-CARBOXYLIC ACIDS ESTERS

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It has been shown that the cyclization of the methyl 2-(2,2,2-trifluoroacetylamino)acrylate arylation product using methyl 4,6-dichloro-2-iodobenzoate gives the corresponding 1-methoxyisoquinoline-3-carboxylic acid ester through loss of water rather than methanol. This feature of the condensation has been used for the synthesis of methyl 1-(tert-butoxycarbonylmethoxy)isoquinoline-3-carboxylate.

Keywords: 2-iodobenzoic acids, methyl 2-(2,2,2-trifluoroacetylamino)acrylate, 1-oxo-1,2-dihydroquinoline-3-carboxylic acid, condensation, Heck reaction.

The isoquinoline-3-carboxylic acid structure has attracted the attention of chemists to this time due to the many variants of its modification at different isoquinoline positions and also the possibility of converting the carboxyl group into esters, amides, and heterocycles. For instance, esters of 2,4,6-substituted isoquinoline-3-carboxylic acids have been used in the development of novel protein kinase inhibitors [1]. Selective inhibition of phosphodiesterase type 5 has been found in a series of 1,4,6,7-substituted isoquinoline-3-carboxylic acids [2]. 1-Arylisoquinoline-3-carboxylic acid dialkylamide PK11195 (ligand of peripheral benzodiazepine receptors) is a known chemical biomarker of neurodegeneration [3]. A recent synthesis of 1-aryl-substituted isoquinolines involves the use of the Suzuki reaction [4] and is now used for the preparation of PK11195 [5] and its analogs [6]. The most suitable starting materials for the Suzuki reaction are 1-halo-substituted isoquinoline-3-carboxylic acid esters which are readily prepared from the corresponding 1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid esters. The main methods for the synthesis of such compounds are condensation of 1-isochromenones with ammonia or with amines [7, 8] or the reaction of *o*-formylbenzoic acids with derivatives of glycine or its cyclic analogs [9–11] or with nitrogen-containing Horner-Wadsworth-Emmons reagents [12, 13].

A more attractive method for the synthesis of 1-oxo-1,2-dihydroisoquinolines has recently appeared, i.e. the tandem Heck reaction [14] of 2-(acetylamino)acrylates with *o*-iodobenzoic acid esters and their subsequent cyclization [15]. This route has already been used in the preparation of compound PK11195 [5] and also for development of solid-phase synthetic methods [16]. The indicated method allows the preparation of 1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid esters unsubstituted in the benzene ring in 60–65% yields.

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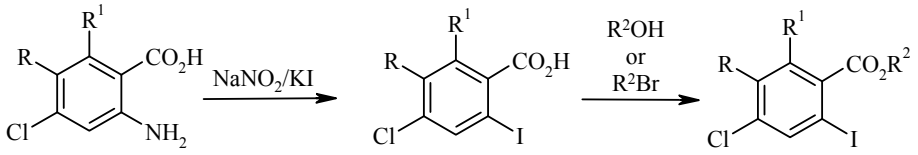
Within a medicinal chemistry project, we were interested in a convenient synthetic method for isoquinoline-3-carboxylic acid esters containing a halogen atom (preferable in positions 6, 7, and 8) as well as intermediate products suitable for subsequent functionalization at the C-1 atom. For the preparation of halo-substituted 1-oxo-1,2-dihydroisoquinoline-3-carboxylic acid esters of interest, we selected the Heck reaction [15] since the halo-substituted *o*-formylbenzoic acids needed for traditional preparative methods were mostly difficult to obtain and only through multistage syntheses.

The starting iodide **3** was prepared from the corresponding anthranilic acid **1a** [17] by the standard Sandmeyer reaction and subsequent esterification of the iodobenzoic acid **2a**.

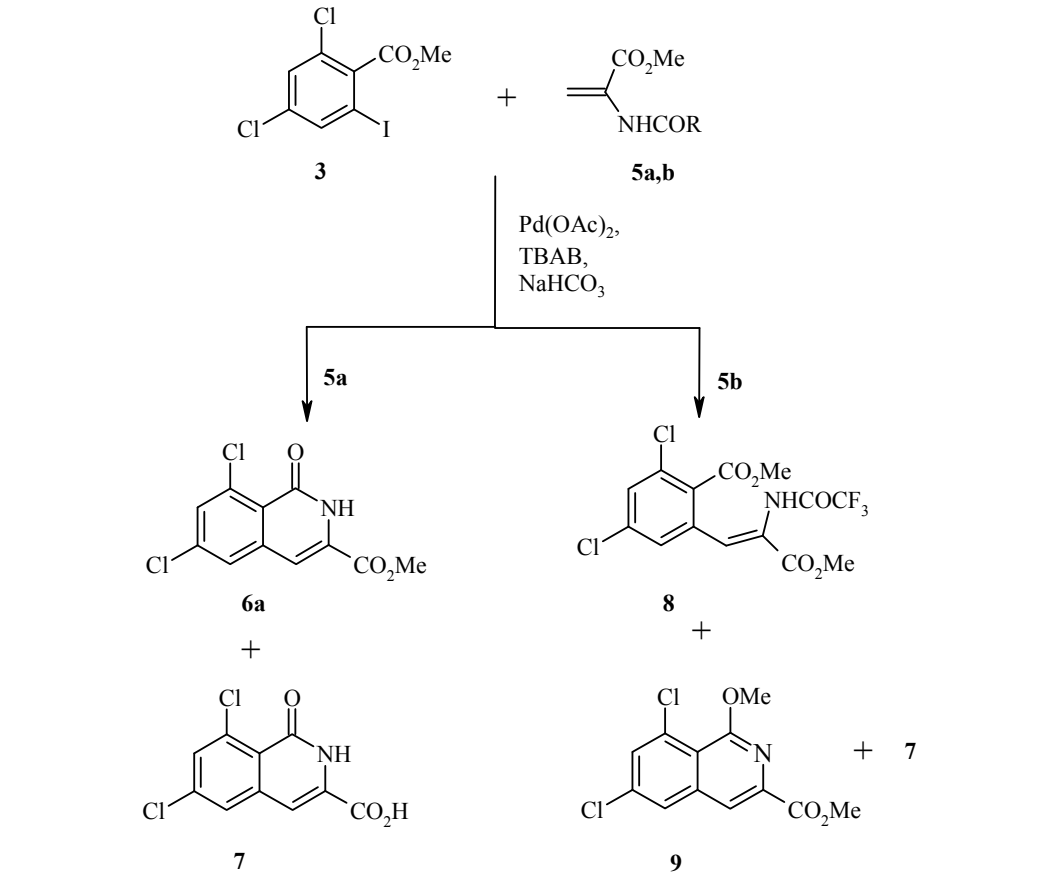


1a,b **2a,b** **3, 4a,b**

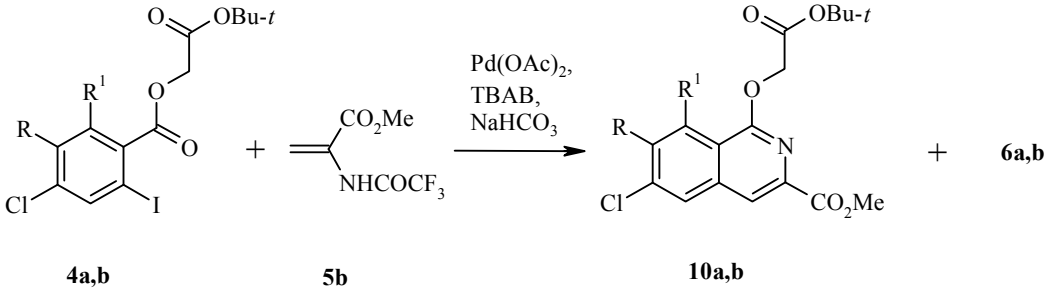
1, **2**, **4 a** R = H, R^1 = Cl; **1**, **2**, **4 b** R = Cl, R^1 = H; **4a**,**b** R^2 = CH_2COOBu-*t*; **3** R = H, R^1 = Cl, R^2 = Me

Arylation of acrylate **5a** by iodide **3** was carried out by the method given in [15] with optimized conditions reported by T. Jeffery [18]. Liquid chromatography–mass spectrometry pointed to the formation of several products but some of them could not be determined unambiguously because of low solubility and weak ionization. The target ester **6a** was obtained in only 23% yield together with its hydrolysis product **7** (1%). The use of bases other than sodium bicarbonate (potassium or cesium carbonate, triethylamine, diisopropylethylamine) led to a lower yield of the isoquinolone **6a** in all cases. We proposed that the yield of the target product **6a** would increase by changing the acetyl group in the acrylate **5a** for trifluoroacetyl since a better leaving group could assist the cyclization. Separation of the mixture of products of the reaction of iodide **3** with acrylate **5b** [19] showed that the main reaction product is the acyclic diester **8** (52% yield). The yield of the isoquinolone carboxylic acid **7** was 5%, the ester **6a** could not be separated. To our surprise, the main product of the cyclization step proved to be 1-methoxyisoquinoline **9** in 25% yield. The overall yield of compounds **7**, **8**, and **9** was 82% hence the Heck reaction under the Jeffery conditions [18] proved very efficient.

The proposal that the Heck reaction product **8** can exist as a mixture of (*Z*)- and (*E*)-isomers, the latter of which cannot cyclize to isoquinolone **6a**, could not be confirmed. The structure of the (*Z*)-isomer of the diester **8** was proved by the presence of an interaction between the proton at atom C-1' with atom C-3' (HMBC method, $^3J_{(H–C)}$ ~4 Hz, corresponding to a *cis* configuration) and with the ester methyl group at atom C-2' (the Overhauser effect). Refluxing diester **8** in ethanol in the presence of sodium ethylate gives isoquinolone **6a** (35%) but complete conversion of diester **8** could not be achieved. The mechanism of formation of the 1-methoxyisoquinoline **9** with cyclization of the intermediate diester **8** has remained unclear and needs additional study. However, the actual retention of the methoxy group during cyclization suggested that the exchange of the methyl group of the ester in iodide **3** for another alkyl group (including one functionally substituted) leads to a novel method for synthesizing 1-alkoxyisoquinolines. The importance of this finding is underlined by the fact that all of the reported examples of the alkylation of isoquinolines occur unselectively to give a mixture of *O*-and *N*-alkyl derivatives with the latter predominating. Only in a single patent a selective alkylation of an isoquinolone with the use of benzyl bromide to give a 94% yield of 1-benzyloxyisoquinoline has been reported [20]. Our attempts to *O*-alkylate isoquinolone **6a** using *tert*-butyl bromoacetate gave hardly separable mixture of products with a low conversion of the starting compound **6a**. The *O*-alkylation product **10a** is a very attractive intermediate for the preparation of novel 1-substituted isoquinoline-3-carboxylic acids and their derivatives.



5 a R = Me, **b** R = CF_3



a R = H, R^1 = Cl; **b** R = Cl; R^1 = H

Next, we undertook to study the possible preparation of compounds **10a,b** under the conditions for formation of isoquinoline **9**. The necessary starting iodides **4a,b**, containing a *tert*-butoxycarbonylmethyl ester group, were prepared from the corresponding iodobenzoic acids **2a,b**. In turn, the acid **2b** was synthesized from anthranilic acid **1b** according to [21]. Use of iodides **4a,b** in the Heck reaction with acrylate **5b** gave the diesters **10a,b** although in low yields (24 and 13% respectively). However, the isoquinolones **6a** (12%) and **6b** (47%) were also separated and these can be used as valuable starting materials in the synthesis of 1-substituted isoquinoline-3-carboxylic acids.

In conclusion, we have developed an original, single stage method for the synthesis of 1-alkoxyisoquinoline-3-carboxylic acids esters *via* a Heck reaction of the corresponding alkyl *o*-iodobenzoates and methyl 2-(2,2,2-trifluoroacetylamino)acrylate with simultaneous ring closure of the intermediate product.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-400 instrument (400 and 100 MHz respectively) for compounds **2a,b**, **3**, and **4a,b** and on a Varian Unity-600 instrument (600 and 150 MHz respectively) for compounds **6a,b**, **7–9**, and **10a,b** with HMDS as internal standard at δ = 0.05 ppm. In recording HMBC, HSQC, and NOESY 2D spectra, a 4096×1024 matrix was used which provided for ^{1}H τ_{2max} = 250 ms recorded along the *F*2 axis and τ_{1max} = 100 ms along the *F*1 axis. In order to improve the relative signal to noise, the matrix of Fourier transformed data was carried out to zero twice and expanded in a cosine function. The mixing time in the 2D-NOESY was 1 s. ESI–MS mass spectra (inductively coupled mass spectrometry) were performed on a Micromass Quatro Micro™ API instrument in MeCN or MeOH with HCOOH. Monitoring of the reaction course was carried out by TLC on Merck Kieselgel plates and revealed in UV light. Analysis of the reaction mixtures was performed by liquid chromatography–mass spectrometer (liquid chromatograph Shimadzu CBM-20A, mass spectrometer Applied Biosystems API 2000). Preparative column chromatography used Merck Kieselgel grade silica gel (0.060–0.200 mm). Reagents and materials used in the experiments were obtained from the companies Acros, Aldrich, and Alfa Aesar.

4,6-Dichloro-2-iodobenzoic Acid (2a). A solution of $NaNO_2$ (1.7 g, 24.6 mmol) in water (5 ml) was added dropwise at -2 ºC with stirring to a suspension of 2-amino-4,6-dichlorobenzoic acid (5 g, 24.3 mmol) in 3.5 M HCl (1000 ml). The mixture was stirred for 1 h at -2 to 0 ºC, cooling removed, and a solution of KI (4.1 g, 24.7 mmol) in water (5 ml) was added dropwise. The reaction mixture was heated to 80 ºC and heating was then removed. The product was stirred for 18 h and the precipitate formed was filtered off, washed with water and dried in air to give compound **2a** (3 g, 39%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.78 (1H, d, *J* = 2.0, H Ar); 7.98 (1H, d, *J* = 2.0, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 93.6 (C-2); 128.6 (C-1), 129.4 (C-3); 134.5 (C-6), 136.6 (C-5); 139.4 (C-4); 167.1 (C=O).

4,5-Dichloro-2-iodobenzoic Acid (2b). Obtained similarly to compound **2a** from 2-amino-4,5-dichlorobenzoic acid (2.21 g, 10.7 mmol), $NaNO_2$ (0.55 g, 8 mmol), and KI (1.32 g, 8 mmol) to give compound **2b** as a white powder with mp 142–145ºC (2.15 g, 69%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.91 (1H, s, H Ar); 8.26 (1H, s, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 93.1 (C-2); 130.9 (C-1); 131.2 (C-6); 134.2 (C-3); 137.1 (C-5); 141.2 (C-4); 166.1 (C=O). Found, %: C 26.79; H 1.15. $C_7H_3Cl_2IO_2$. Calculated, %: C 26.53; H 0.95.

Methyl 4,6-Dichloro-2-iodobenzoate (3). A mixture of compound **2a** (4 g, 12.6 mmol) and thionyl chloride (20 ml) was refluxed for 2 h and then evaporated to dryness. The residue was dissolved in dichloromethane (30 ml), absolute MeOH (1.5 ml) and triethylamine (5.33 ml) were added dropwise, and the mixture was stirred at room temperature for 3 h. The reaction product was washed with water and the organic phase was separated, dried over anhydrous sodium sulfate, and then evaporated. The residue was purified by column chromatography on silica gel eluting with a 4:1 mixture of hexane and ethyl acetate to give compound **3a** (2.6 g, 63%) as a light-yellow powder with mp 152–155 ºC. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.97 (3H, s, OCH_3); 7.40 (1H, d, *J* = 2.0, H Ar); 7.73 (1H, d, *J* = 2.0, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 53.2 (CH_3); 91.9 (C-2); 127.99 (C-1); 129.1 (C-3); 131.5 (C-6); 136.2 (C-5); 138.2 (C-4); 166.4 (C=O). Found, %: C 29.92; H 1.55. $C_8H_5Cl_2IO_2 \cdot 0.2EtOAc$. Calculated, %: C 31.32; H 1.91.

***tert*-Butoxycarbonylmethyl 4,6-Dichloro-2-iodobenzoate (4a)**. A mixture of compound **2a** (9.25 g, 29.2 mmol), K_2CO_3 (4.03 g, 29.2 mmol), and *tert*-butyl bromoacetate (4.28 ml, 29.2 mmol) in dry acetone (150 ml) was refluxed for 3 h, cooled to room temperature, filtered, and the filtrate evaporated *in vacuo*. The raw product was purified by column chromatography on silica gel eluting with a 10:1 mixture of hexane and ethyl acetate to give compound **4a** (7.4 g, 59%) as an oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.51 (9H, s,

$(CH_3)_3C$); 4.75 (2H, s, CH_2); 7.42 (1H, d, J = 2.0, H Ar); 7.75 (1H, d, J = 2.0, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 28.1 (($\underline{C}H_3)_3C$); 62.6 (OCH_2); 82.8 (($CH_3)_3\underline{C}$); 92.2 (C-2); 129.3 (C-1); 131.9 (C-3); 136.5 (C-6); 137.1 (C-5); 137.2 (C-4); 165.2 (C=O); 165.6 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 431 $[M+H]^+$ (100).

***tert*-Butoxycarbonylmethyl 4,5-dichloro-2-iodobenzoate (4b)** was prepared similarly to compound **4a** from compound **2b** (1.35 g, 4.27 mmol), K_2CO_3 (0.43 g, 3.1 mmol), and *tert*-butyl bromoacetate (0.63 ml, 4.27 mmol) as an oil (1.1 g, 60%). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.49 (9H, s, $(CH_3)_3C$); 4.73 (2H, s, CH_2); 8.05 (1H, s, H Ar); 7.75 (1H, s, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 28.4 (($\underline{C}H_3)_3C$); 61.2 (OCH_2); 81.8 (($CH_3)_3\underline{C}$); 90.69 (C-2); 131.9 (C-1); 132.0 (C-6); 132.9 (C-3); 136.1 (C-5); 141.6 (C-4); 162.9 (C=O); 165.4 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 431 $[M+H]^+$ (100).

Methyl 6,8-Dichloro-1-oxo-1,2-dihydroisoquinoline-3-carboxylate (6a). The acrylate **5a** (0.389 g, 2.72 mmol), tetrabutylammonium bromide (0.584 g, 1.81 mmol), $NaHCO_3$ (0.381 g, 4.53 mmol), and $Pd(OAc)_2$ (0.061 g, 0.27 mmol) were added with stirring under an argon atmosphere to a solution of compound **3** (0.6 g, 1.81 mmol) in DMF (5 ml). The mixture was stirred at 90 ºC for 24 h and cooled to room temperature. The obtained heterogeneous mixture was filtered and the precipitate on the filter was washed with acetone to give compound **6a** (1.15 g, 23%) as a light-yellow powder with mp > 240ºC (decomp.). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.85 (3H, s, OCH_3); 7.33 (1H, s, H-4); 7.73 (1H, d, J = 1.9, H-7); 8.00 (1H, d, J = 1.9, H-5); 11.30 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 53.5 (CH_3); 109.1 (C-3); 123.2 (C-8a); 127.5 (C-5); 131.3 (C-4a); 131.4 (C-7); 135.9 (C-8); 137.5 (C-6); 140.7 (C-4); 159.7 (N–C=O); 161.5 (O–C=O). Found, *m/z*: 271.9857 $[M+H]^+$. $C_{11}H_8O_3NCl_2$. Calculated: 271.9881.

Reaction of Methyl 4,6-Dichloro-2-iodobenzoate (3) with Methyl 2-(2,2,2-Trifluoroacetylamino)-acrylate (General Method). The acrylate **5b** (0.106 g, 0.54 mmol), tetrabutylammonium bromide (0.116 g, 0.36 mmol), sodium bicarbonate (0.076 g, 0.9 mmol), and palladium diacetate (0.02 g, 0.09 mmol) were added with stirring under an argon atmosphere to a solution of compound **3** (0.116 g, 0.36 mmol) in DMF (5 ml). The mixture was stirred for 20 h at 90 ºC, cooled to room temperature, and diluted with water (30 ml). The heterogeneous mixture obtained was extracted with ethyl acetate (2×20 ml) and the organic phase was washed with saturated sodium chloride solution (4×20 ml), dried over sodium sulfate, and the solvent evaporated to dryness *in vacuo*. The reaction products **7–9** were separated by column chromatography on silica gel eluting with a 1:5 mixture of ethyl acetate and hexane or with dichloromethane.

6,8-Dichloro-1-oxo-1,2-dihydroisoquinoline-3-carboxylic Acid (7). White powder (0.008 g, 5%); mp > 240 ºC (decomp.). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.26 (1H, s, H-4); 7.69 (1H, d, J = 1.8, H-7); 7.97 (1H, d, J = 1.8, H-5); 10.89 (1H, br. s, NH); 14.00 (1H, br. s, OH). ^{13}C NMR spectrum (DMSO-d_6), δ , ppm: 109.3 (C-4); 122.9 (C-8a); 127.3 (C-5); 131.0 (C-7); 132.9 (C-4a); 135.9 (C-8); 137.4 (C-6); 141.1 (C-3); 159.7 (C=O); 162.7 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 256 $[M-H]^+$ (100).

Methyl 4,6-Dichloro-2-[(*Z*)-2-methoxycarbonyl-2-(2,2,2-trifluoroacetylamino)vinyl]benzoate (8). Oil, yield 0.075 g (53%). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.89 (3H, s, OCH_3); 3.91 (3H, s, $OC\underline{H}_3$); 7.18 (1H, d, J = 1.8, H-3); 7.41 (1H, d, J = 1.8, H-5); 7.48 (1H, s, H vinyl). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 53.2 (CH_3); 53.5 (CH_3); 115.3 (CF_3, $^1J_{C\text{-}F}$ = 289.0); 125.2 (C-1'); 126.0 (C-3); 128.4 (C-2'); 130.1 (C-5); 130.8 (C-1); 133.1 (C-6); 134.5 (C-2); 136.4 (C-4); 154.4 ($\underline{C}OCF_3$); 163.3 (C=O); 166.4 (C=O). Found, *m/z:* 421.9764 $[M+Na]^+$. $C_{14}H_{10}O_5NCl_2F_3$. Calculated: 421.9786.

Methyl 6,8-Dichloro-1-methoxyisoquinoline-3-carboxylate (9). Oil, yield 0.036 g (25%). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.97 (3H, s, OCH_3); 4.17 (3H, s, OCH_3); 7.62 (1H, d, J = 2.1, H-7); 7.71 (1H, d, J = 2.1, H-5); 7.97 (1H, s, H-4). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 52.8 ($CO_2\underline{C}H_3$); 54.2 (OCH_3); 117.5 (C-8a); 117.7 (C-4); 125.9 (C-5); 132.0 (C-7); 133.2 (C-8); 136.3 (C-6); 140.1 (C-4a); 140.7 (C-3); 160.32 (C-1); 165.55 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 286 $[M+H]^+$ (100).

Reaction of *tert*-Butoxycarbonylmethyl 4,6-Dichloro-2-iodobenzoate (4a) with Methyl 2-(2,2,2-Trifluoroacetylamino)acrylate (5b). Acrylate **5b** (0.686 g, 3.48 mmol), tetrabutylammonium bromide (0.748 g, 2.32 mmol), sodium bicarbonate (0.487 g, 5.8 mmol), and palladium diacetate (0.13 g, 0.58 mmol) were added with stirring under an argon atmosphere to a solution of compound **4a** (1.0 g, 2.32 mmol) in DMF (5 ml). The

mixture was stirred for 18 h at 90 ºC, cooled to room temperature, and diluted with water (300 ml). The obtained heterogeneous mixture was extracted with ethyl acetate (2×20 ml) and the organic phase was washed with saturated sodium chloride solution (4×20 ml), dried over sodium sulfate, and solvent removed *in vacuo*. The reaction products **6a** and **10a** were separated by column chromatography on silica gel eluting with a 1:5 mixture of ethyl acetate and hexane.

Methyl 1-(1-*tert*-Butoxycarbonylmethoxy)-6,8-dichloroisoquinoline-3-carboxylate (10a). White powder (0.2 g, 24%); mp > 130 ºC (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.38 (9H, s, $(CH_3)_3C$); 3.86 (3H, s, OCH_3); 4.96 (2H, s, CH_2); 7.99 (1H, d, *J* = 2.0, H-7); 8.25 (1H, s, H-4); 8.31 (1H, d, *J* = 2.0, H-5). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 28.2 ($(\underline{C}H_3)_3C$); 53.0 (OCH_3); 64.1 (OCH_2); 81.7 ($(CH_3)_3\underline{C}$); 116.9 (C-8a); 119.0 (C-4); 127.4 (C-5); 132.1(C-4a); 132.5 (C-7); 136.2 (C-6); 139.5 (C-8); 141.3 (C-3); 158.4 (C-1); 164.8($\underline{C}O_2CH_3$); 167.4 ($\underline{C}O_2CH_2$). Mass spectrum, *m/z* (I_{rel}, %): 386 $[M+H]^+$ (100). Found, %: C 52.05; H 4.29; N 3.50. $C_{17}H_{17}Cl_2NO_5 \cdot 0.5H_2O$. Calculated, %: C 51.66; H 4.59; N 3.54.

Reaction of *tert*-Butoxycarbonylmethyl 4,5-Dichloro-2-iodobenzoate (4b) with Methyl 2-(2,2,2-Trifluoroacetylamino)acrylate (5b). Methyl 2-(2,2,2-trifluoroacetylamino)acrylate (0.089 g, 0.45 mmol), tetrabutylammonium bromide (0.097 g, 0.3 mmol), sodium bicarbonate (0.063 g, 0.75 mmol), and palladium diacetate (0.01 g, 0.045 mmol) were added with stirring under an argon atmosphere to a solution of compound **4b** (0.13 g, 0.3 mmol) in DMF (5 ml). The mixture was stirred for 19 h at 90 ºC, cooled to room temperature, and diluted with water (30 ml). The obtained heterogeneous mixture was filtered and the precipitate on the filter was washed with water and then ethyl acetate and dried in air to give compound **6b**. The filtrate was extracted with ethyl acetate (3×40 ml) and the organic phase was washed with saturated sodium chloride solution (2×30 ml) and water (2×20 ml), dried over sodium sulfate, and solvent removed *in vacuo*. The oily, dry product of compound **10b** was separated by column chromatography on silica gel eluting with dichloromethane.

Methyl 6,7-Dichloro-1-oxo-1,2-dihydroisoquinoline-3-carboxylate (6b). White powder (0.039 g, 47%) with mp>230 ºC (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.86 (3H, s, OCH_3); 7.41 (1H, s, H-4); 8.27 (1H, s, H-7); 8.29 (1H, s, H-5); 11.55 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 53.5 (OCH_3); 108.9 (C-4); 128.1 (C-8a); 129.0 (C-8); 130.5 (C-5); 131.0 (C-4a); 132.2 (C-7); 136.2 (C-3); 136.4 (C-6); 160.5 (N–C=O); 161.9 (O–C=O). Mass spectrum, *m/z* (I_{rel}, %): 272 $[M+H]^+$ (100). Found, %: C 45.28; H 2.59; N 5.19. $C_{11}H_7Cl_2NO_3 \cdot H_2O$. Calculated, %: C 45.54; H 3.13; N 4.83.

Methyl 1-(*tert*-Butoxycarbonylmethoxy)-6,7-dichloroisoquinoline-3-carboxylate (10b). Oil, yield 0.015 g (13%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.48 (9H, s, $(CH_3)_3C$); 3.96 (3H, s, OCH_3); 5.04 (2H, s, CH_2); 7.98 (1H, s, H-5); 8.06 (1H, s, H-4); 8.48 (1H, s, H-8). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 28.0 ($(\underline{C}H_3)_3C$); 52.7 (OCH_3); 63.6 (OCH_2); 82.3 ($(CH_3)_3\underline{C}$); 117.8 (C-4); 119.9 (C-8a); 126.1 (C-8); 128.7 (C-5); 133.7 (C-7); 136.3 (C-4a); 136.6 (C-6); 139.7 (C-3); 158.3 (C-1); 165.5 ($\underline{C}O_2CH_3$); 167.5 ($\underline{C}O_2CH_2$). Mass spectrum, *m/z* (I_{rel}, %): 386 $[M+H]^+$ (100).

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