J. prakt. Chem. 339 (1997) 750–753

Journal für praktische Chemie
Chemiker-Zeitung

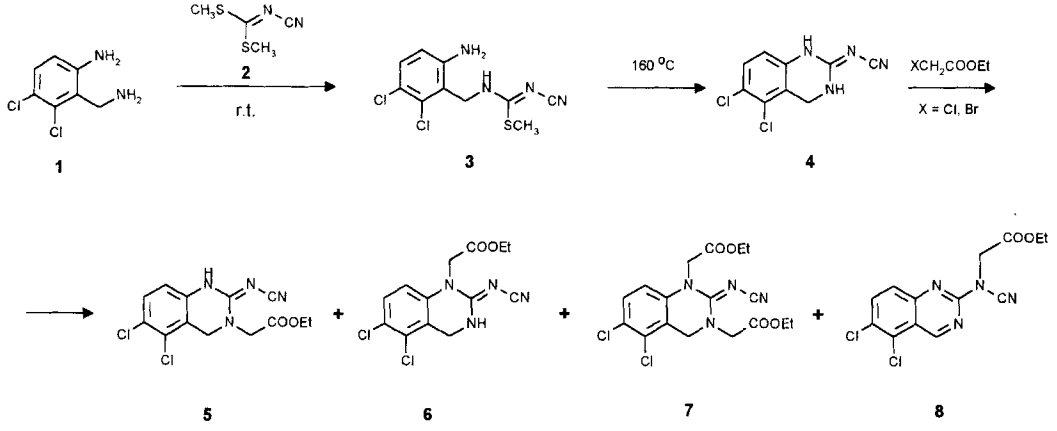
A Convenient Large-Scale Synthesis of Ethyl (2-cyanoimino-5,6-dichloro-1,2,3,4-tetrahydroquinazoline-3-yl)acetate

P. Trinka and J. Reiter

Budapest (Hungary), EGIS Pharmaceuticals Ltd.

Received May 21st, 1997, respectively August 1st, 1997

Ethyl (2-cyanoimino-5,6-dichloro-1,2,3,4-tetrahydroquinazoline-3-yl) acetate (**5**) is a key intermediate of a novel synthesis [1] of anagrelide (Agrylin^R) that was launched recently by Roberts Pharmaceuticals Corporation as the first drug approved for the oral treatment of essential thrombocythemia, a life-threatening blood disorder characterised by high platelet counts [2].

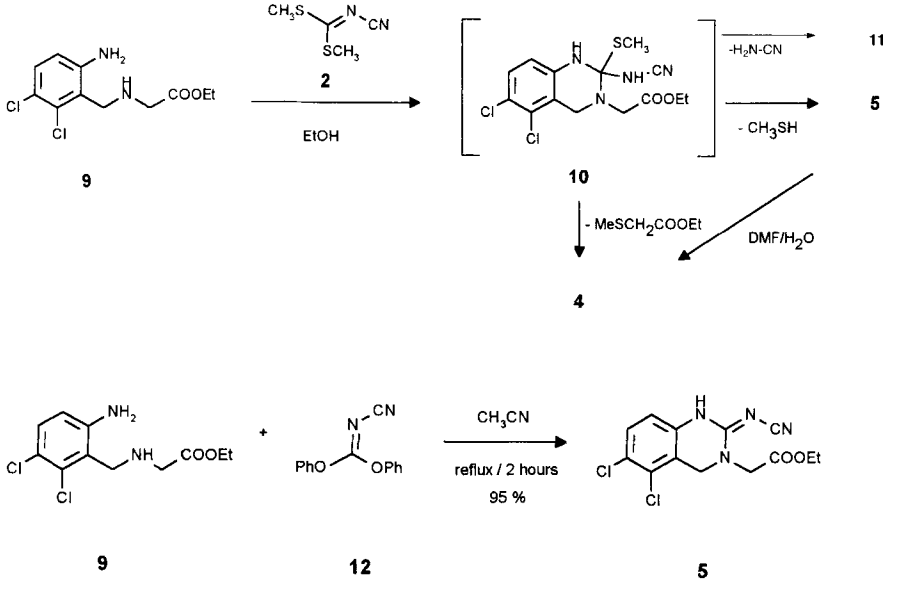


We will report about our efforts to elaborate a practical synthetical route applicable in industrial scale for the synthesis of **5** starting either from 2-amino-5,6-dichloro-benzylamine (**1**) or ethyl (2-amino-5,6-dichlorobenzyl)glycinate (**9**).

2-Amino-5,6-dichlorobenzylamine (**1**) was converted with dimethyl (*N*-cyanoimidodithiocarbonate) (**2**) to the isothiourea derivative **3** that was ring closed by heating in *N*-methylpyrrolidone at 160 °C to yield 2-cyanoimino-5,6-dichloro-1,2,3,4-tetrahydroquinazoline (**4**) in excellent yield. However, the alkylation of **4** with ethyl chloro- or bromoacetate under different reaction conditions did not produce the required ethyl (2-cyanoimino-5,6-dichloro-1,2,3,4-tetrahydroquinazoline-3-yl)acetate (**5**) as a sole product, but different mixtures of **5** and derivatives **6**–**8** were obtained. Compound **8** was probably formed by *in situ* oxidation of the corresponding dihydro derivative. The reaction mixtures were analysed by HPLC using pure products as standards for calibration. Compounds **5**–**8** could not be separated by crystallisation, thus this route proved to be of little value for industrial purposes.

The ring closure of the glycinate **9** with dimethyl *N*-cyanimidodithiocarbonate (**2**) proceeded smoothly in the presence of 1 mole equivalent of mercuric oxide to form the acetate **5** in good yield [4]. However, industrial synthesis of drugs using heavy metals is highly disadvantageous as the heavy metals may appear as impurities of the end products. Thus this method, too, proved to be unsuitable for an industrial synthesis of **5**. Without using the mercuric oxide catalyst the reaction mixture obtained contained besides **5** an equal amount of **11** and a considerable amount of **4** from which **5** was isolated in 30% yield.

Compounds **4**, **5** and **11** may be formed *via* intermediate **10**. Loss of methylthio from **10** yields **5**, while loss of cyan-



amide [5] leads to **11**. The formation of **4** may proceed *via* an intramolecular nucleophilic attack of the methylthio sulphur atom of **10** to the positively charged methylene carbon atom of the acetic ester moiety leading to splitting of ethyl methylthioacetate observed by GC MS (CI) in the reaction mixture.

In principal, derivative **4** could also be formed by ethanolysis of **5**. This possibility was excluded because no decomposition was observed when **5** was heated in ethanolic solution (*i.e.* at conditions analogues to those used in the reaction of **9** and **2**) for a week. However, prolonged heating of **5** in a water containing dimethylformamide led to large amounts of not isolated **4**.

Unfortunately the by-product **11** could not be transformed to **5** with cyanoamine. In consequence this method was again useless from the point of view of an industrial synthesis of **5**. The above problems were overcome with a more reactive **2**-type derivative. Such a compound is diphenyl *N*-cyanoimidocarbonate (**12**) that reacted with **9** in acetonitrile smoothly to yield **5** in excellent yield even in an industrial scale. Recently the method was patented [6].

Authors thank is due to Mrs. Dr. Éva Szabó for recording the MS spectra, to Mr. Péter Slégel for the LC MS determinations and to Mr. Tibor Merczel and Mr. Ádám Sárosi for technical help.

Experimental

Melting points were determined on a Kofler–Boëtius apparatus and are not corrected. The infrared spectra were obtained using potassium bromide pellets using Bruker IFS-113 spectrophotometer. The ^1H NMR and ^{13}C NMR measurements were performed using Bruker WM-250 instrument at 250 MHz (^1H) and 62.89 MHz (^{13}C), respectively, in DMSO-d_6 solution using TMS and DDS, respectively, as internal standards. The MS spectra were taken with a KRATOS MS 25 RFA double focusing instrument, ionisation energy 70 eV, speeding voltage 4 kV in EI and CI (isobutane) mode. The GC determinations were performed with a Shimadzu GC-9A apparatus using a Chrompack, CP-SIL-PCB, 25 m long half capillary column. The peaks were determined by GC MS with the above GC instrument attached to a Carlo Erba/HRGC/MS apparatus. The HPLC determinations were performed using a KNAUER apparatus (KNAUER HPLC PUMP 64, KNAUER MODEL detector UV-1 used at 254 nm, EURO-SPHER column 100-C18, 25×4 mm ID, 5 μm; EURO- CHROM-2000 software, loop 20 μl), as eluent a 4 : 6 mixture of acetonitrile and 0.1M ammonium acetate buffer (pH = 4.4) was used. The LC-MS determinations were performed with a VQ QUATRO apparatus (electronspray) connected to a HPLC (Spectra Physics P-200 pump, UV-100 detector, HPMOS 2,1×100 mm (C-8) column, eluent a 1:1 mixture of formic acid and water, software MASSLYNX). The reactions were followed by GC, TLC and HPLC respectively. All TLC determinations were performed on DC-Alufolien Kieselgel 60 F_{254} (Merck 5562). The spots were detected by UV at 254 and 366 nm, iodine vapours, 0.1 $KMnO_4$ and 0.1% ethanolic Bromocresol Green solution. The dry column flash chromatography [7] as performed using Kieselgel 60H (Merck 7736) absorbent. As eluents different mixtures of cyclohexane and ethyl acetate and ethyl acetate and methanol of increasing polarities were used.

S-Methyl-N-cyano-N'-(2-amino-5,6-dichlorobenzyl)isothiourea (**3**)

To a solution of 2-amino-5,6-dichlorobenzylamine hydrochloride (**1**· HCl) (46.8 g, 0.2 mol, purity 97%) [3] in 2-propanol (100 ml) triethylamine (29.3 ml, 0.21 mol) was added by dropping it to the stirred reaction mixture at room temperature. To the mixture thus obtained dimethyl *N*-cyanoimidodithiocarbonate (**2**) (29.4 g, 0.2 mol) was added and stirred for 2 hours at room temperature. The crystals that precipitated were filtered off, washed with water (20 ml), 2-propanol (20 ml) and dried. Yield 49.1 g (84.9%), *m.p.* 174–

176 °C (dec.). – IR: ν_{max}/cm^{-1} = 2167 (CN). – ^1H NMR: δ/ppm = 2.58 (s, SCH_3), 4.51 (bs, CH_2), 5.6 (b, NH_2), 6.68 (d, J = 8.7 Hz, Ph-5), 7.24 (d, J = 8.7 Hz, Ph-4), 8.5 (b, NH).– ^{13}C NMR: δ/ppm = 14.5 (SCH_3), 42.0 (CH_2), 115.2* (PhC-5), 115.4* (CN), 118.3 (PhC-1 and 3), 129.8 (PhC-4), 132.8 (PhC-2), 147.8 (PhC-6), 170.3 ($\underline{C}SCH_3$). – MS (EI): $M^{+\cdot}$ = 288, (CI) : $(M+2H)^{+\cdot}$ = 290.

2-Cyanoimino-5,6-dichloro-1,2,3,4-tetrahydroquinazoline (**4**)

A stirred solution of **3** (29.0 g, 0.1 mol) in *N*-methylpyrrolidone (20 ml) was kept at 160 °C for 1 hour. After cooling the precipitate was collected by filtration and washed with DMF (5 ml), MeCN (2 ml). Yield 22.1 g (92%), *m.p.* 315–320 °C. – IR: ν_{max}/cm^{-1} 2196 (CN). – ^1H NMR: δ/ppm = 4.47 (s, CH_2), 6.91 (d, J = 8.7 Hz, H-8), 7.45 (d, J = 8.7 Hz, H-7), 8.3 (b, H-3), 10.4 (b, H-1). – ^{13}C NMR: δ/ppm = 41.4 (C-4), 114.4 (C-8), 116.3* (CN), 117.8* (C-6), 124.7 (C-4a), 128.4 (C-5), 129.2 (C-7), 135.2 (C-8a), 155.5 (C-2). – MS (EI): 240 $M^{+\cdot}$ (CI): 242 $(M+2H)^{+\cdot}$.

Ethyl (2-cyanoimino-5,6-dichloro-1,2,3,4-tetrahydroquinazoline-3-yl)acetate (**5**), *Ethyl (2-cyanoimino-5,6-dichloro-1,2,3,4-tetrahydroquinazoline-1-yl)acetate* (**6**), *Diethyl (2-cyanoimino-5,6-dichloro-1,2,3,4-tetrahydroquinazoline-1,3-diyl)diacetate* (**7**) *and Ethyl N-cyano-N-(5,6-dichloroquinazoline-2-yl)glycinate* (**8**)

To a mixture of **4** (4.80 g, 20 mmol) and NaH (0.96 g, 20 mmol, 50% in paraffin oil) in DMF (40 ml) ethyl bromoacetate (6.68 g, 40 mmol) was added in two equal portions at the begin of the reaction and after 1 hour. After stirring at 25 °C for further 2 hours the solution was evaporated to dryness and the residue (10 g) consisting of **4, 5, 6, 7, 8** in a ratio of 5: 21: 18: 49: 3 was dry column flash chromatographed to yield successively:

a) Compound **8** (0.05 g, 0.8%), *m.p.* 132–135 °C (ethyl acetate: cyclohexane = 4 : 1), HPLC retention time in a 4.5 : 5.5 mixture of acetonitrile and 0.1 M ammonium acetate buffer (pH = 4.4) 28 min. – IR: ν_{max}/cm^{-1} = 1743 cm^{-1} (CO), 2245 cm^{-1} (CN). – ^1H NMR: δ/ppm = 1.30 (t, J = 6.4 Hz, CH_3), 4.27 (qa, J = 6.4 Hz, OCH_2), 4.69 (s, NCH_2), 7.73 (d, J = 9.2 Hz, H-8), 7.88 (d, J = 9.2 Hz, H-7), 9.64 (s, H-4). Irradiated at 1.30 ppm DNOE at 4.27 ppm; irr. at 4.69 ppm **no** DNOE observed. – ^{13}C NMR: δ/ppm = 14.1 (CH_3), 49.9 (NCH_2), 62.2 ($O\underline{C}H_2$ COOEt), 110.7 (CN), 120.9 (C-6), 126.9 (C-8), 130.1* (C-5), 130.6* (C-8a), 136.6 (C-7), 150.6 (C-4a), 155.2 (C-4), 160.2 (C-2), 166.6 (CO). – MS (EI, %): 324 (50%, $M^{+\cdot}$), 251 (90%, $(M-COOEt)^{+\cdot}$), 224 (20%, $(M-HCN)^{+\cdot}$) 197 (100%, $(M-2HCN)^{+\cdot}$).

b) Compound **7** (0.73 g, 8.8%), *m.p.* 108–110 °C (ethanol), HPLC retention time in a 4.5 : 5.5 mixture of acetonitrile and 0.1 M ammonium acetate buffer (pH = 4.4) 17 min. – IR: ν_{max}/cm^{-1} = 1742 (CO, two splitted bands), 2183 (CN). – ^1H NMR: δ/ppm = 1.20 (t, J = 7.2 Hz, CH_3-1), 1.22 (t, J = 7.2 Hz, CH_3-3), 4.16 (qa, J = 7.2 Hz, OCH_2-1), 4.17 (qa, J = 7.2 Hz, OCH_2-3), 4.64 (s, NCH_2-3), 4.67 (s, C-4), 4.74 (s, NCH_2-1), 7.10 (d, J = 8.8 Hz, H-8), 7.60 (d, J = 8.8 Hz, H-7). – ^{13}C NMR: δ/ppm = 12.5 [CH_3 (1) and (3)], 46.8 [NCH_2 (1)], 47.3 (C-4), 51.1 [NCH_2 (3)], 59.8 [OCH_2 (1) and (3)], 114.5 (CN), 121.7 (C-6), 125.5 (C-4a), 126.2 (C-5), 128.3 (C-7), 136.1 (C-8a), 153.3 (C-2), 166.8* [CO (3)], 167.2* [CO (1)]. – MS (EI, %): 412 (100%, $M^{+\cdot}$), 325 (65%, $(M-CH_2COOEt)^{+\cdot}$); (CI): 413.$(M+H)^{+\cdot}$

c) Compound **5** (0.52 g, 8.0%), *m.p.* 279–281 °C dec. (DMF), HPLC retention time in a 4.5 : 5.5 mixture of acetonitrile and 0.1 M ammonium acetate buffer (pH = 4.4) 13.1 min. – IR: ν_{max}/cm^{-1} 1736 (CO), 2187 (CN). – ^1H NMR: δ/ppm = 1.22 (t , J = 7.1 Hz), 3H, CH_3), 4.17 (qa, J = 7.1 Hz, OCH_2), 4.29 (s, $C\underline{H}_2COOEt$), 4.65 (s, CH_2-4), 7.26 (d, J = 8.7 Hz, H-8), 7.54 (d, J = 8.7 Hz, H-7), 10.6 (b, NH). – assignment checked by DNOE. – ^{13}C NMR: δ/ppm = 13.9 (CH_3), 47.9 (C-4), 49.9 ($\underline{C}H_2COOEt$), 60.8 (OCH_2), 115.2 (C-8 and CN), 118.2 (C-6), 125.5 (C-4a), 128.0 (C-5), 129.7 (C-7), 134.3 (C-8a), 154.2 (C-2), 168.0 (CO). – MS (EI, %): 326 (17%, $M^{+\cdot}$), 239 (100%, $(M-CH_2COOEt)^{+\cdot}$), 199 (35%, $(M-NCN-CH_2COOEt)^{+\cdot}$); (CI): 327 $(M+H)^{+\cdot}$.

d) Compound **6** obtained as a 48 : 52 mixture with **4** that could not be separated even chromatography as repeated many times (0.51 g, 3.8% calculated for **6** present in the mixture), HPLC retention time in a 4.5 : 5.5 mixture of acetonitrile and 0.1 M ammonium acetate buffer (pH = 4.4) 10 min. Spectral data deduced from the mixture. – IR: ν_{max}/cm^{-1} 1749 (CO), 2184 (CN). – ^1H NMR: δ/ppm = 1.21 (t, J = 7.2 Hz, CH_3), 4.15 (qa, J = 7.2 Hz, $O-CH_2$), 4.48 (s, H-4), 4.67 (s, NCH_2), 7.03 (d, J = 8.8 Hz, H-8), 7.56 (d, J = 8.8 Hz, H-7), 8.6 (b, H-3). – ^{13}C NMR: δ/ppm = 14.2 (CH_3), 40.8 (C-4), 48.0 (NCH_2), 61.1 (OCH_2), 114.9 (C-8), 115.5 (CN), 118.5 (C-6), 125.6 (C-4a), 128.2 (C-5), 129.5 (C-7), 136.9 (C-8a), 154.5 (C-2), 168.1 (CO). – MS (EI, %): 326 (16%, $M^{+\cdot}$), 239 (50, $(M-CH_2COOEt)^{+\cdot}$), 240 (100% $M^{+\cdot}$, corresponding to **4** present); (CI): 327, $(M+H)^{+\cdot}$, 242 (100%, $(M+2H)^{+\cdot}$ corresponding to **4** present).

Ethyl (2-cyanoimino-5,6-dichloro-1,2,3,4-tetrahydroquinazoline-3-yl) acetate (**5**) (from **9** and **2** in the presence of mercuric oxide)

Ethyl *N*-(2-amino-5,6-dichlorobenzyl)glycinate (**9**) (27.7 g, 0.1 mol) [3] was dissolved at 50 °C in DMF (100 ml), and at this temperature mercuric oxide (21.7 g, 0.1 mol) and **2** (14.6 g, 0.1 mol) was added to the solution. The mixture was stirred at 70 °C for 3 hours. Water (30 ml) was added to the still warm suspension and the crystals precipitated were filtered off. The wet crystals were added to 18% hydrochloric acid (150 ml) and stirred at room temperature for 2 hours. The insoluble part was filtered off to yield raw **5** (23.9 g, 72.7%) that was recrystallised from 90 ml of dimethylformamide to yield pure **5** (20.8 g, 63.8%), *m.p.* 279–281 °C (dec). The product is identical (mixed *m.p.*, IR) with that of obtained above.

Ethyl (2-cyanoimino-5,6-dichloro-1,2,3,4-tetrahydroquinazoline-3-yl)acetate (**5**), *Ethyl (5,6-dichloro-2-methylthio-1,2,3,4-tetrahydroquinazoline-3-yl)acetate* (**11**), *and 5,6-Dichloro-2-cyanoimino-1,2,3,4-tetrahydroquinazoline* (**4**) (From **9** and **2**)

A suspension of ethyl *N*-(2-amino-5,6-dichlorobenzyl)glycinate (**9**) (27.7 g, 0.1 mol) [3], **2** (14.6 g, 0.1 mol) and ethanol (200 ml) was refluxed with stirring for 72 hours (HPLC analysis of the hot reaction mixture showed the presence of **5**:

12: 4 in a ratio of 38: 31:18). The still hot suspension was filtered and the crystals were washed with ethanol (50 ml) to yield **5** (10.0 g, 30.6%), *m.p.* 275–278 °C (DMF), that was identical (mixed *m.p.*, IR) with that of **5** obtained above.

The mother liquor was evaporated *in vacuo* to dryness and the residue was dry column flash chromatographed to yield
a) Compound **11** (8.2 g, 12.3%), *m.p.* 212–214 °C (DMF). – IR: ν_{max} 1746 cm^{-1} (CO). – ^1H NMR: δ/ppm = 1.32 (t, J = 7.2 Hz, CH_3), 2.49 (s, CH_2-4), 4.14 (s, $C\underline{H}_2COOEt$), 4.27 (qa, J = 7.2 Hz, OCH_2), 4.61 (s, CH_2-4), 6.89 (d, J = 8.5 Hz, H-8), 7.24 (d, J = 8.5 Hz, H-7). – ^{13}C NMR: δ/ppm = 13.9 (CH_3), 14.0 (SCH_3), 49.8 ($\underline{C}H_2COOEt$), 51.7 (C-4), 61.6 (OCH_2), 121.1 (C-6) 122.5 (C-8), 126.8 (C-4a), 128.4 (C-5), 129.3 (C-7), 141.9 (C-8a), 160.0 (C-2), 168.3 (CO). – MS (EI, %): 332 (25 %, $M^{+\cdot}$), 303 (6%, $(M–Et)^{+\cdot}$), 259 (15%, $(M–COOEt)^{+\cdot}$), 245 (100%, $(M–CH_2COOEt)^{+\cdot}$); (CI) : 333, $(M + H)^{+\cdot}$.
b) Compound **4** (4.7 g, 9.8%), *m.p.* 314–319 °C (dimethylformamide) that was identical (mixed *m.p.*, IR) with that of obtained above.

Ethyl (2-cyanoimino-5,6-dichloro-1,2,3,4-tetrahydroquinazoline-3-yl) acetate (**5**) (From **9** and **12**)

A suspension of ethyl *N*-(2-amino-5,6-dichlorobenzyl)glycinate (**9**) (442.6 g, 1.6 mol) [3] and compound **12** (400 g, 1.68 mol) in acetonitrile (2500 ml) was refluxed with stirring for 3 hours. After cooling the crystals that precipitated were filtered off and washed with acetonitrile (40 ml) to yield **5** (497.5 g, 95%), *m.p.* 281–284 °C (dec.), that was identical (mixed *m.p.*, HPLC) with that of **5** obtained above.

References

[1] J. Reiter, P. Trinka, P. Tömpe, M. Király Nee Ignácz, P. Slégel, É. Szabó, S. Benkõ Nee Márkus, M. Csögrõ, D. Dányi, P. Fekete, G. Gigler, F. Görgényi, P. Nee Zsarnóczay, J. Brlik, A. Halbauer Nee Nagy, K. Nee Kenyeres, I. Sztruhár, Hung. Pat. 209,633, US Pat. 5,391,737; Chem. Abstr. **122** (1995) P 265 395b
[2] SCRIP No 2217 (March 25th), 18 (1997)
[3] P. Trinka, P. Slégel, J. Reiter, J. Prakt. Chem. **338** (1996) 675
[4] P. Trinka, J. Reiter, L. Pongó, Hung. Pat. 213 619 (Appl. 92/9,201,223); Chem. Abstr. **120** (1994) P 270 448j
[5] J. Reiter, Org.Prep. Proced. Int. **20** (1988) 465
[6] J. Reiter, P. Trinka, P. Tömpe, É. Szabó, P. Slégel, J. Brlik, A. Halbauer Nee Nagy, I. Sztruhár, M. Kenyeres Nee Fehér, Hung. Pat. 207 713, US Pat. 5,391,737; Chem. Abstr. **122** (1995) P 265 395b
[7] L. M. Harwood, Aldrichimica Acta **18** (1985) 25

Address for correspondence:
Prof. József Reiter
EGIS Pharmaceuticals Ltd.
PO Box 100
H-1475 Budapest/Hungary