ELSEVIER

www.elsevier.com/locate/farmac

Il Farmaco 56 (2001) 715–718

IL FARMACO

Short Communication

A new alternative synthesis of 5-cyanophthalide, a versatile intermediate in the preparation of the antidepressant drug citalopram

Fabrizio Micheli *, Luca Crippa, Daniele Donati, Romano Di Fabio, Colin Leslie

GlaxoSmithKline Group, GlaxoWellcome SpA, Medicines Research Centre, Via Fleming 4, 37135 Verona, Italy

Received 15 March 2001; accepted 30 March 2001

Abstract

An alternative versatile synthesis of 5-cyanophthalide, a key synthetic intermediate in the preparation of the antidepressant drug Citalopram, is presented. The synthesis reported here allows the preparation of this important intermediate in three steps, avoiding the manipulation of environmentally detrimental cyanides. © 2001 Elsevier Science S.A. All rights reserved.

Keywords: Antidepressant; Citalopram; Synthesis

1. Introduction

5-Cyanophthalide (**1**, Fig. 1) (1-oxo-1,3-dihydro-isobenzofuran-5-carbonitrile) is a key intermediate in the synthesis of the antidepressant drug Citalopram (**2**, Fig. 1), a well known Serotonin reuptake inhibitor. The original approach in preparation of this drug required the reaction of intermediate **1** with the appropriate Grignard reagents to introduce the requisite side chains; surprisingly, during these reactions, almost no nucleophilic attack on the cyano moiety is observed and only modest amounts of by-products are reported. It is not surprising that, considering the high commercial value of Citalopram, a number of patent applications covering alternative methodologies for its synthesis have been filed subsequently [1–9].

Apparently, less attention was being paid to intermediate **1**. Its first preparation was reported in 1931 by Levy [10]. This procedure involves the reaction of the corresponding diazonium salt with copper cyanide as depicted in Scheme 1 (route a).

Cyanides are commonly employed reagents in many industrial fields, but clearly their highly toxic nature makes them environmentally unfriendly and their use is best avoided where possible. Copper cyanide is much less toxic than the corresponding sodium or potassium salt, but it is also much less water soluble if not

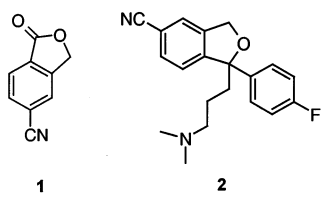
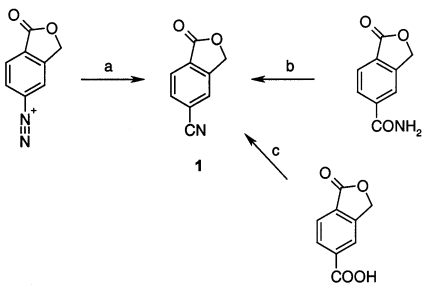


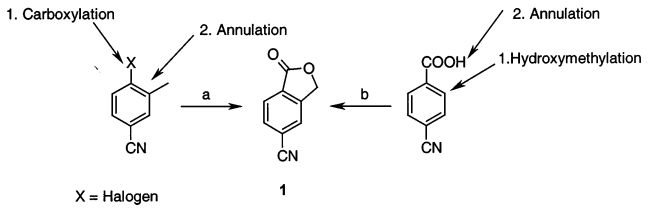
Fig. 1.



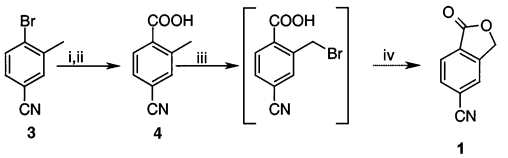
Scheme 1.

* Corresponding author.
E-mail address: fm20244@glaxowellcome.co.uk (F. Micheli).

PII: S0014-827X(01)01108-9

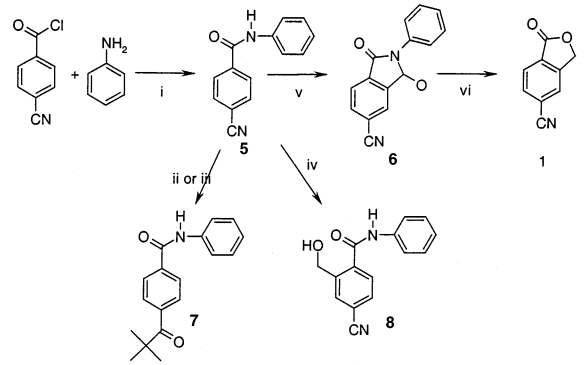


Scheme 2.



i) *t*-BuLi, THF, -78 °C; ii) CO_2; iii) NBS, $(PhCOO)_2$, CCl_4, 90 °C; iv) Base

Scheme 3.



i) CH_2Cl_2, Py. r.t.;; ii) 1) *t*-BuLi, THF, -78 °C 2) DMF, -78 °C; iii) 1) *t*-BuLi, THF, -78 °C 2) DMF, from -78 °C to 0°C ; iv) 1) LiTMP, THF, -78 °C 2) gaseous CH_2O, -78 °C v) 1) LiTMP, THF, -78 °C 2) DMF, -78 °C; vi) 1) $NaBH_4$, MeOH, 2) HCl

Scheme 4.

prepared freshly in situ or complexed using a large excess of the water-soluble sodium or potassium cyanides. Another preparation of intermediate **1** involving cyanides was reported in 1951 by Tirouflet [11].

Two recent patents [12,13] report the preparation of intermediate **1** avoiding the need of cyanides and starting from 5-carboxyphtalide. The first methodology (Scheme 1, route b) involves the preparation of an amide which is dehydrated to the corresponding cyano derivative, while the second method (Scheme 1, route c) involves the reaction of the acid itself with a dehydrating agent in the presence of an appropriate sulphonamide.

In our continuing effort to develop new synthetic methodologies, we were interested in finding alternative methods for the preparation of 5-cyanophthalide via a simple method, free of the need of using cyanides, and starting from readily available commercial intermediates.

After having evaluated the commercially available starting materials in which the cyano moiety was already present and analysing the target from a retro-synthetic point of view, two possible alternatives for the generation of the lactone ring were identified, which are illustrated in Scheme 2:

1. Start from a halogenated benzonitrile, introduce the carboxylic moiety, generate an appropriate leaving group and build the lactone.
2. Start from 4-cyanobenzoic acid, introduce a hydroxymethyl equivalent and build the lactone.

2. Results and discussion

According to the hypothesised path a in Scheme 2, we decided to start from commercially available 4-bromo-3-methyl benzonitrile (**3**) as depicted in Scheme 3.

Metal–halogen exchange was performed using *t*-BuLi at low temperature and the resulting anion was trapped with solid carbon dioxide. The resulting benzoic acid (**4**) was reacted under radical conditions to introduce a leaving group on the methyl group and a number of cyclisation reactions were attempted on this transient intermediate.

Various bases such as NaOH, K_2CO_3 and $NaHCO_3$ were used to promote the bromo-lactonisation, unfortunately the desired product was never identified. Probably, the cyano moiety was so sensitive to the radical conditions to originate a number of side reactions which, in the end, led to complex reaction mixtures and extensive degradation.

Due to the poor results obtained following path a, we moved to the proposed path b starting from 4-cyanobenzoyl chloride as depicted in Scheme 4.

The benzoyl chloride was transformed into the *ortho*-directing phenyl amide ($y = 92\%$) using equimolar quantities of the reactants and a slight excess of pyridine in dichloromethane at r.t. The use of *t*-BuLi to generate the *ortho*-anion was not possible because of the reactivity of the cyano group; in all of the conditions used the undesired *t*-butyl ketone derivative (**7**) was isolated. To limit this side reaction we decided to use a more hindered base. Lithium tetramethylpiperidine (LiTMP), freshly prepared in THF at -20°C, was therefore used to *ortho*-metalate the intermediate cyano phenyl amide (**5**) (-78°C, 30 min). The hydroxymethyl group was introduced in its masked form as a formyl moiety (DMF, -78°C, 1.5 h followed by overnight stirring at r.t.). Acid quenching of the reaction mixture (1 N HCl was added dropwise until pH 1) followed by phase extraction with AcOEt and chromatographic purification (cyclohexane/AcOEt 70:30) consequently allowed the isolation of the desired hemiaminal (**6**) in 68% yield.

The reduction of this intermediate was performed with sodium borohydride ($NaBH_4$, 14 equiv. in MeOH, 24 h, r.t.), the solvent was evaporated and the crude was submitted to acid cyclisation (1 N HCl, 48 h, r.t.). After extraction (CH_2Cl_2) and chromatographic purification (cycloexane/AcOEt 9:1) the desired product (**1**) was obtained in acceptable yield.

Direct introduction of the hydroxymethyl moiety (**8**) was also attempted (step iv, Scheme 4), unfortunately the use of gaseous formaldehyde proved unsuccessful.

To conclude, we have described a novel three-step synthesis of 5-cyanophthalide (**1**) starting form commercially available intermediates, which does not involve the manipulation of toxic cyanides.

3. Experimental

Infrared spectra were recorded on a Bruker IFS 48 spectrometer. ^{1}H NMR spectra were recorded on a Varian Unity 400 (400 MHz); the data are reported as follows: chemical shift (in ppm) from the Me_4Si line as external standard, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

Chromatography was carried out by use of Merck silica gel 60 (230–400 mesh). Elemental analyses were determined by an EA 1108 Carlo Erba elemental analyser and the analyses of the reported compounds are in agreement with the calculated values. All the reactions were carried out under a controlled atmosphere in flame dried glassware. Anhydrous solvents were purchased from Aldrich. Reactions were monitored by analytical thin-layer chromatography (TLC) using Merck silica gel 60 F-254 glass plates (0.25 mm).

3.1. 4-Cyano-N-phenylbenzamide (*5*)

4-Cyanobenzoylchloride (4.0 g, 24.2 mmol), aniline (2.2 g, 24.2 mmol) and pyridine (2.64 ml, 26.6 mmol) were dissolved carefully in methylene chloride (20 ml) in a round bottom flask. The reaction was stirred overnight at r.t. The mixture was then washed with 0.1 N HCl and with a saturated solution of K_2CO_3. The organic layer was then dried over sodium sulphate and evaporated at reduced pressure to give 5.0 g of intermediate **5** as a white solid ($y = 92\%$).

IR (nujol, cm^{-1}): ν(NH) 3354, ν(C≡N) 2232, ν(C=O) 1656. ^{1}H NMR (DMSO-d_6): δ 10.47 (bs, 1H), 8.10 (m, 2H), 8.03 (m, 2H), 7.77 (m, 2H), 7.37 (m, 2H), 7.13 (m, 1H).

3.2. 1-Oxo-3-hydroxy-1,3-dihydro-N-phenyl-isoindole-5-carbonitrile (*6*)

HTMP (0.250 ml, 1.48 mmol) was dissolved in dry THF (5 ml) and cooled to −20°C in a round bottom flask and 1.6 M BuLi (0.925 ml, 1.48 mmol) was carefully added dropwise. The reaction was stirred for 10 min at −20°C, warmed to r.t. and additionally stirred for 30 min.

This solution was added dropwise to a solution of intermediate **5** (150 mg, 0.67 mmol) in dry THF (5 ml) at −78°C. The resulting mixture was stirred at −78°C for 30 min and subsequently DMF (0.115 ml, 1.48 mmol) was added. The reaction was then stirred for 1.5 h at −78°C and overnight at r.t.

The mixture was quenched by adding water (20 ml) and 1 N HCl was added dropwise until pH 1. The mixture was extracted with AcOEt (20 ml × 3). The organic phase was dried over sodium sulphate and evaporated under reduced pressure. The crude was purified by chromatography (cyclohexane/AcOEt 7:3) to give 115 mg of intermediate **6** as a yellow oil ($y = 68\%$).

IR (nujol, cm^{-1}): ν(NH) 3340, ν(C≡N) 2231, ν(C=O) 1674. ^{1}H NMR (DMSO-d_6): δ 8.16 (dd, 1H), 8.05 (dd, 1H), 7.96 (d, 1H), 7.86 (dd, 2H), 7.46 (td, 2H), 7.25 (t, 1H), 6.70 (d, 1H), 6.02 (d, 1H).

3.3. 1-Oxo-1,3-dihydro-isobenzofuran-5-carbonitrile (*1*)

Intermediate **6** (10 mg, 0.04 mmol) was dissolved in MeOH (20 ml) and $NaBH_4$ (21.16 mg, 0.56 mmol) was added. The mixture was stirred for 24 h at r.t., the solvent was evaporated and water (20 ml) was added. The solution was treated with 1 N HCl until pH 1 and the resulting mixture was stirred for 48 h at r.t. The aqueous phase was extracted with CH_2Cl_2 (20 ml × 5). The organic phase was dried over sodium sulphate and evaporated under reduced pressure. The crude was purified by chromatography (cycloexane/AcOEt 9:1) to give 2.5 mg of the desired product (**1**) ($y = 35\%$). IR and NMR spectra in accordance to those reported in the literature.

Acknowledgements

We would like to thank Dr. Carla Marchioro and the Analytical Dept. for their precious collaboration.

References

[1] K.P Bøgesø, A.S. Toft, Anti-depressive substituted 1-dimethylaminopropyl-1-phenyl phtalans. U.S. Patent 4,136,193, 1979.
[2] K.P. Bøgesø, Intermediate in the preparation of 1-(3-dimethylaminopropyl)-1-(4′-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. EP 171943, 1986.
[3] K.P. Bøgesø, J. Perregaard, Preparation and isolation of antidepressant drug citalopram enantiomers and their pharmaceutical compositions. EP 347066, 1989.
[4] H. Petersen, K.P. Bøgesø, M. Bech Sommer, Method for the preparation of citalopram. WO 9819511, 1998.
[5] H. Petersen, P. Bregnedal, K.P. Bøgesø, Method for the preparation of citalopram. WO 9819512, 1998.

[6] H. Petersen, Bregnedal, K.P. Bøgesø, Method for the preparation of citalopram. WO 9819513, 1998.
[7] H. Petersen, Method for the preparation of citalopram. WO 9930548, 1999.
[8] M.H. Rock, H. Petersen, P. Ellegaard, Method for the preparation of citalopram. WO 0012044, 2000.
[9] H. Petersen, M.H. Rock, H. Svane, Method for the preparation of citalopram. WO 0013648, 2000.
[10] S. Levy, J. Chem. Soc. (1931) 867–870.
[11] J. Tirouflet, Bull. Soc. Sci. Bretagne (1951) volume 26, Sonderheft S.39.
[12] H. Petersen, P. Dahlberg Nielsen, Esterification, amidation and dehydration method for the preparation of 5-cyanophthalide. WO 0039112, 2000.
[13] B. Weber, Manufacture of 5-cyanophthalide by dehydration of 5-carboxyphthalide. WO 0044738, 2000.