A synthesis of 4H-1, 4-benzothiazines

Lizhi Fu, Jinyi Xu*, Hequan Yao and Xiaoming Wu

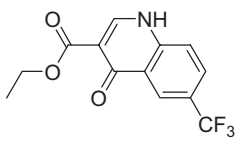
Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, P. R. China

A convenient synthesis of 4H-1, 4-benzothiazines is described. The key step is the coupling between 2-amino-5-chlorophenyl disulfide (**3**) and ethyl acetylenecarboxylate (**4**) in the presence of CuI as a catalyst or by microwave irradiation in moderate yield.

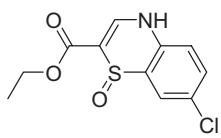
Keywords: 4H-1, 4-benzothiazines, synthesis, CuI catalysis

The 3-ethoxycarbonyl-4-quinolone **1** has been identified as an interesting lead compound for ligand binding at the benzodiazepine site of $GABA_A$ receptors.[1] As a receptor agonist, **1** exhibited sedative and anti-anxiety activities. A number of high-affinity ligands for the benzodiazepine site have been obtained through pharmacophore-guided optimisation of this lead compound.[2] Recently we modified this lead compound to obtain bio-isosteric 4H-1, 4-benzothiazines **2**.

It has been reported[3,4] that 4H-1, 4-benzothiazines can be synthesised by reaction of 2, 2'-dithiodianiline with ethyl acetylenecarboxylate in a sealed tube or autoclave. However, both methods need a high reaction temperature, high pressure and long reaction time, which limit the preparation of the relatively large scale amounts for clinical tests. We now report a convenient synthesis of 4H-1, 4-benzothiazines.



1



2

Results and discussion

Recently, a large number of heterocyclic compounds have been synthesised via cyclisation of alkene, alkyne and enyne, catalysed by transition metal such as palladium, rhodium, cobalt or nickel. Copper(1) iodide is the most used metal catalyst due to its cheap and high efficiency, exemplified by the efficient cyclisation reaction of an alkynyl and amino group.[5] Encouraged by this result, we tried CuI as a catalyst (Scheme 1) for the coupling reaction between 2-amino-5-chlorophenyl disulfide (**3**) and ethyl acetylenecarboxylate (**4**). After optimisation of the reaction conditions, we found that the coupling reaction could be catalysed by 5% of CuI in over 62% yield to give compound **5.**

An alternative method for the coupling between **3** and **4** uses microwave irradiation to promote this coupling reaction (Scheme 1). When the coupling reaction was performed in sealed tube, irradiated by microwaves for only 25 min at 100 °C, compound **5** was obtained in over 75% yield. Finally, cyclisation of compound **5** in DMSO, followed by the oxidation using *m*-CPBA afforded the 4H-1, 4-benzothiazines **2**.

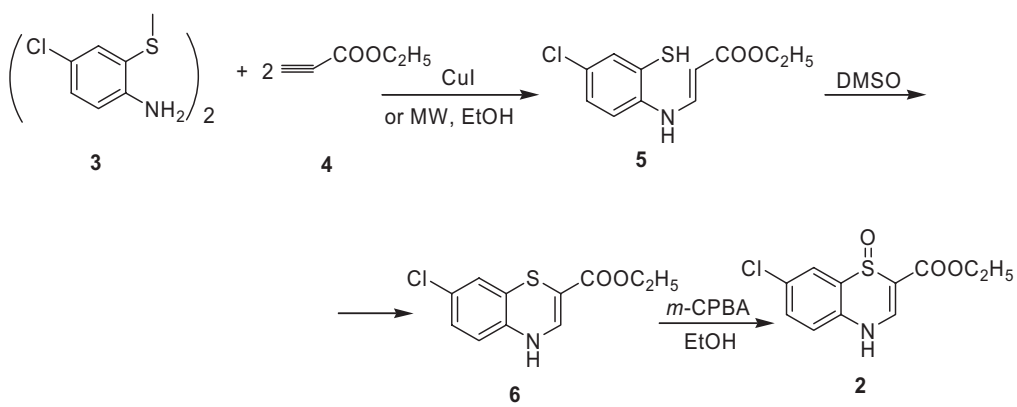
Similar examples were observed by treatment of 2-aminophenyl disulfide and 2-amino-5-bromophenyl disulfide with ethyl acetylenecarboxylate in the presence of CuI as a catalyst to give the corresponding products in yields 60% and 57%, respectively. These products were also obtained by microwave irradiation in yields 70% and 73%, respectively.

Conclusions

We describe here a convenient synthesis of 4H-1, 4-benzothiazines. The key step is the efficient coupling between 2-amino-5-chlorophenyl disulfide and ethyl acetylenecarboxylate catalysed by CuI or promoted by microwave irradiation. Microwave irradiation can more efficiently shorten the coupling reaction time from a few hours to half an hour, dramatically reduce the side products and improve the preparative efficiency. The methods reported here can be applied for the preparation of 4H-1, 4-benzothiazines and their derivatives. This facilitate the synthesis of a series of derivatives of compound **2** for further biological experiments.[7]

Experimental

All melting points were determined on a XT-4 melting point apparatus and were uncorrected. Mass spectra were performed on a Finnigan FTMS-2000 mass instrument. ^{1}H NMR spectra were performed on a AM-300 Bruker NMR spectrometer with TMS as internal standard. IR spectra were performed on a Nicolet Impact 410 instrument and recorded as KBr discs. TLC was carried out using silica GF_{254}. Column chromatography was carried out using silica gel (100-200 mesh). Elemental analysis was performed on a Elementar Vario EL III instrument. All reagents and solvents are commercially available.



3 **4** **5** **6** **2**

Scheme 1

* Correspondent. E-mail: jinyixu@china.com

(E)-ethyl 3- (4-chloro-2-mercaptophenylamino) acrylate (**5**)
Method 1: A solution of 2-amino-5-chlorophenyl disulfide **3** (316 mg, 1 mmol) and ethyl acetylenecarboxylate **4** (196 mg, 2 mmol) in ethanol (10 ml) was refluxed with a catalytic amount of CuI (5%) for 8 hours. After cooling to room temperature, the reaction mixture was filtered, concentrated and the residue was purified by chromatography (petroleum ether: EtOAc = 15:1) on silica gel to give the title ester **5** (320 mg, 62.3%) as a yellow solid. M.p. 102–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38 (d, *J* = 2.4 Hz, 1 H), 7.15 (dd, *J* = 8.6 Hz, *J* = 2.4 Hz, 1 H), 6.92 (d, *J* = 10.0 Hz, 1 H), 6.71 (d, *J* = 8.6 Hz, 1 H), 5.95 (d, *J* = 10.0 Hz, 1 H), 4.30 (s, 1 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H); EIMS (75eV), *m/z* (%): 257 (M^+, 100). Elemental anal. Calcd for $C_{11}H_{12}ClNO_2S$: C, 51.26; H, 4.69; N, 5.43; found: C, 51.52; H, 4.54; N, 5.62%.

Method 2: Microwave irradiation
2-Amino-5-chlorophenyl disulfide **3** (100 mg, 0.3 mmol), ethyl acetylenecarboxylate **4** (60 mg, 0.6 mmol) was dissolved in ethanol (2 ml) in a sealed tube (CEM designed 10-ml pressurerated reaction vial). The reaction mixture was exposed to microwave irradiation at 100 °C for 25 min. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by chromatography (petroleum ether: EtOAc = 15:1) on silica gel to yield ester **5** (120 mg, 75.5%) as a yellow solid. M.p. 102–104 °C.

Ethyl 7-chloro-4H-1, 4-benzothiazine-2-carboxylate (**6**):[6] A solution of **5** (1.3 g, 5 mmol) in dimethyl sulfoxide (20 ml) was heated to 140 °C for 1.5 h. The reaction mixture was cooled to room temperature, poured in water and extracted with chloroform. The organic layer was washed with water, dried over anhydrous Na_2SO_4. After filtration and concentration, the result residue was purified by chromatography (petroleum ether: EtOAc = 10:1) on silica gel to afford **6** (0.91 g, 70.6%) as a pale red solid. M.p. 180–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.76 (d, *J* = 6.6 Hz, 1 H), 7.01(d, *J* = 6.5 Hz, 1 H), 6.89 (dd, *J* = 6.5 Hz, *J* = 2.3 Hz, 1 H), 6.79 (d, *J* = 2.3 Hz, 1 H), 6.43 (d, *J* = 8.4 Hz, 1 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 1.18 (t, *J* = 7.1 Hz, 3 H); EIMS (75eV), *m/z* (%): 255 (M^+, 100). Elemental anal. Calcd for $C_{11}H_{10}ClNO_2S$: C, 51.66; H, 3.94; N, 5.48; found: C, 51.38; H, 4.12; N, 5.23%.

Ethyl 7-chloro-4H-1, 4-benzothiazine-2-carboxylate-1-oxide (**2**):[4] To a solution of **6** (1.2 g, 4.7 mmol) in absolute ethanol (60 ml), a solution of *m*-CPBA (1.64 g, 5.2 mmol) in absolute ethanol (15 ml) was added dropwise at room temperature. After stirring for 1 h, the reation mixture was diluted with H_2O (80 ml), extracted with EtOAc. The organic layer was washed with saturated $NaHSO_3$, saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4. After filtration and concentration, the result residue was crystallised in ethanol to get the title compound **2** (0.76 g, 60%) as a yellow solid. M.p. 157–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.84 (s, 1 H), 8.10 (d, *J* = 6.5 Hz, 1 H), 7.91(d, *J* = 2.3 Hz, 1 H), 7.72 (dd, *J* = 6.5 Hz, *J* = 2.3 Hz, 1 H), 7.46 (d, *J* = 8.9 Hz, 1 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 1.27 (t, *J* = 7.1 Hz, 3 H); IR (KBr), ν/cm^{-1}: 3453, 3264, 2990, 1678, 1619, 1529, 1478, 1248, 829; EIMS (75eV), *m/z* (%): 271 (M^+, 100). Elemental anal. Calcd for $C_{11}H_{10}ClNO_3S$: C, 48. 62; H, 3.71; N, 5.15; found: C, 48. 85; H, 3.56; N, 4.91%.

Received 8 June 2008; accepted 11 August 2008
Paper 08/5317 doi: 10.3184/030823408X356323
Published online: 8 October 2008

References

1 P. Kahnberg, M.H. Howard, T. Liljefors, M. Nielsen, E.O. Nielsen, O. Sterner and I. Pettersson, *J. Mol. Graphics. Modell.,* 2004, **23**, 253.
2 E. Lager, P. Andersson, J. Nilsson, I. Pettersson, E.O. Nielsen, M. Nielsen, O. Sterner and T. Liljefors, *J. Med. Chem.,* 2006, **49**, 2526.
3 G. Liso, G. Trapani, V. Berardi and P. Marchini, *J. Heterocyclic. Chem.*, 1980, **17**, 377.
4 V. Cecchetti, A. Fravolini, F. Schiaffella, O. Tabarrini, W. Zhou and P.G. Pagella, *J. Heterocyclic. Chem.*, 1992, **29**, 375.
5 A.V. Kel'in, A.W. Sromek and V. Gevorgyan, *J. Am. Chem. Soc*., 2001, **123**, 2074.
6 G. Liso, G. Trapani, V. Berardi and P. Marchini, *J. Heterocyclic. Chem.*, 1980, **17**, 793.
7 J.Y. Xu, L.Z. Fu, B. Jiang, H.Q. Yao, X.M. Wu, Y.F. Chen, H. Ji and C. Zhang, *Chinese Patent Application*: CN 10123243.9, 2008.