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A green process for the preparation of 11-{4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl}dibenzo[*b*,*f*][1,4]thiazepine

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Abstract: A green process for the synthesis of 11-{4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl}dibenzo[*b*,*f*][1,4]thiazepine by the reaction of 11-(1-piperazinyl)dibenzo[*b*,*f*][1,4]thiazepine or its dihydrochloride salt with 2-(2-chloroethoxy)ethanol in the presence of an inorganic base and water is reported (conversion 99.9 % in a short time and without any impurities). The metal halides and phase transfer catalyst increase the rate of reaction, especially in water as the solvent.

Keywords: quetiapine; KI; tetrabutylammonium bromide (TBAB); 2-(2-chloroethoxy)ethanol; *N*,*N*-dimethylformamide; sodium carbonate.

INTRODUCTION

Water is a major constituent of life. It is not only inexpensive and environmentally benign but also gives completely new reactivity. Enzymatic processes in nature must occur by necessity in an aqueous environment. However, water as a solvent is uncommon for many organic reactions. Nevertheless, due to the hydrophobic effect, small size and large cohesive energy density, water not only accelerates reaction rates but also enhances reaction selectivity even when the reactants are sparingly soluble or insoluble and for water sensitive compounds.[1,2] Since the pioneering studies of the Diels–Alder reaction by Breslow, there has been increasing search for organic reactions which can proceed well in aqueous media. These offer advantages over those occurring in organic solvents. Diels–Alder,[3] pericylic,[4] carbanion[5] reactions have been reported in water with good yields and selectivity. On considering the broad applications and bright future for water as a solvent, in this study this application has been expanded to include the synthesis of pharmaceutical drugs. There has been an explosion of research acti-

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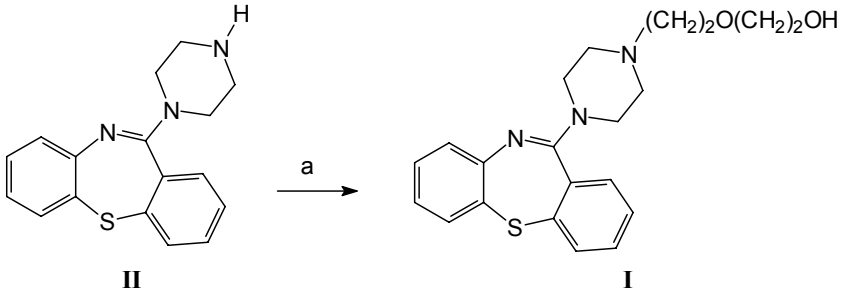
vities in this field, which has been partially attributed to the development of the field of green chemistry.

Dibenzo[*b*,*f*][1,4]thiazepine is a class of compound used as antipsychotic drug. 11-{4-[2-(2-Hydroxyethoxy)ethyl]-1-piperazinyl}dibenzo[*b*,*f*][1,4]thiazepine (compound **I**) (trade name Quetiapine) is a typical antipsychotic drug.[6] It has been successfully employed for the treatment of schizophrenia and bipolar disorders for many years.[7] Recently, it has also been used to treat delirium and agitation.[8]

The process reported in the literature for the synthesis of **I** by the reaction of 11-(1-piperazinyl)dibenzo[*b*,*f*][1,4]thiazepine (compound **II**) or its dihydrochloride salt with 2-(2-chloroethoxy)ethanol in the presence of an inorganic base, such as sodium carbonate or potassium carbonate, in various organic solvents is well known.[9,10] The solvents used for this reaction are mainly polar aprotic and protic, such as DMF (*N*,*N*-dimethylformamide), *N*-methylpyrrolidone and methanol, ethanol, 2-propanol and *n*-hexanol or its isomers. Compound **II** may be employed in the reaction as its free base or its dihydrochloride salt (Scheme 1). The reactions were carried out in the presence of a promoter or catalyst, such as sodium iodide and tetrabutylammonium bromide (TBAB). The reaction was reportted for 24 h or more.[8,10] In another method, the reaction of 11-chlorodibenzo[*b*,*f*][1,4]thiazepine with 1-[2-(2-hydroxyethoxy)ethyl]piperazine, haloethoxypiperazine/ethyleneglycol is described.[11–13] The reaction did not precede to completion even when an excess of 2-(2-chloroethoxy)ethanol is used.



II **I**

Scheme 1. A typical reaction in water; a – 2-(2-chloroethoxy)ethanol, K_2CO_3, TBAB, KI, water.

As per pharmacopeias and drug master file requirements, the impurity level limit is very stringent.[14] This incomplete reaction gave a challenging task to attain 100 % conversion. Further purification, incurring heavy losses of the product is difficult due to the similar properties of the product and the starting material.[9,13]

A modification of the above process was reported, which deals with an attempt to reduce the reaction time and the purification procedure. According to this process, 9.7 % of unreacted **II** was found after 4 h of reaction. However, even after 17 h, only 95.5 % conversion was observed, accompanied with **II** and

some other unidentified impurities. In this paper, for the first time, this reaction in aqueous medium in a shorter reaction time is described. A systematic study of the reaction parameters, such as the reaction temperature and time, the nature of the solvents and solvent to water wt. ratios (DMF:water) and the use of bases was undertaken. The typical reaction is shown in Scheme 1.

EXPERIMENTAL

The progress of the reaction was monitored by HPLC (Waters Alliance) equipped with an inertsil ODS-3, C18 (150×4.6×5 μm^3) column. The mobile phase was buffer:ACN (78:22 gradient), λ_{max} = 254 nm. ^{1}H-NMR spectroscopy of the sample was performed on a Brucker 400 MHz instrument. The ^{1}H- and ^{13}C-NMR chemical shift values are reported in ppm using TMS as the internal standard. The IR spectrum of the sample was recorded using a Perkin Elmer Spectrum 1 FTIR spectrophotometer. The mass analysis was performed on a Thermo Finnigan LCQ Advantage instrument.

General procedure for synthesis of compound ***I***

Compound **II** was prepared using the process reported by Warawa and Migler.[15,16] Then in a 100 ml four-necked round bottom flask equipped with overhead stirring, thermometer pocket and a heating oil bath, a mixture of **II** (33.30 mmol), 2-(2-chloroethoxy)ethanol (50.84 mmol), sodium carbonate (203.30 mmol) and sodium iodide (2.0 mol % w.r.t. **II**) was taken in 30 ml water and heated to about 100±2 °C. After checking the HPLC analysis, the reaction mixture was cooled to 30 °C and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain compound **I** as an oil (98 %).

Anal. Calcd. for $C_{21}H_{25}N_3O_2S$: C, 65.79; H, 6.52; N, 10.96 Found: C, 65.29; H, 6.60; N, 10.82. IR (KBr, cm^{-1}): 3390, 3054, 2856, 1943, 1574, 1306, 1147, 953, 761, 699. ^{1}H-NMR (400 MHz, DMSO, δ, ppm): 2.19–2.58 (*m*, 6H, −CH_2−N(CH_2)−CH_2), 3.52–4.10 (*m*, 11H, −CH_2−N(C=)−CH_2 + −CH_2−O−CH_2−CH_2−OH), 6.79–7.44 (*m*, 8H, Ar). ^{13}C-NMR (400 MHz, $CDCl_3$, δ, ppm): 160.5 (C−Ar), 148.7 (C−Ar), 139.7 (C−Ar), 133.9 (C−Ar), 132.0 (C=N), 132.0 (C−Ar), 130.7 (CH−Ar), 129.0 (CH−Ar), 128.8 (CH−Ar), 128.2 (CH−Ar), 127.8 (CH−Ar), 125.2 (CH−Ar), 122.7 (CH−Ar), 72.3 (CH_2), 67.3 (CH_2), 61.6 (CH_2), 57.8 (CH_2), 52.9 (CH_2), 52.9 (CH_2), 45.6 (CH_2), 45.6 (CH_2); MS (*m*/*z*): 384 (M+1), 279, 253.

RESULTS AND DISCUSSION

The reaction reported by Warawa and Migler[9,13] in organic polar aprotic and protic solvents required 17 h under the employed reaction conditions and the yields were low (Table I, entries 1–8). Moreover, in practice, about 7 to 8 % of **II** remained unreacted even after 35 h. The reaction in water was found to be faster as compared to those in polar aprotic and protic organic solvents. The results show that water is a good solvent in combination with NaI and TBAB. The addition of TBAB slightly improved the reaction rates (Table I, entries 11 and 12). The reaction was almost completed within 30 min but trace amounts of unreacted **II** were observed up to 7 h (Table I, entry 9). However, there was no change in the concentration of **II** even after 20 h (Table I, entries 13 and 14), which depicts

that after 7 h the reaction had become steady. The use of KI also gives comparable results to those obtained with NaI (Table I, entry 15).

TABLE I. A comparison of the catalytic activity of different employed catalysts and solvents. Reaction conditions: compound **II**, 33.30 mmol; 2-(2-chloroethoxy)ethanol, 50.24 mmol; K_2CO_3, 203.30 mmol; NaI or equivalent, 2 mol % to **II**; TBAB, 5 mol % to **II**; water, 30 ml

Entry	Solvents	Catalyst	Time, h	*t* / °C	Conversion, %
1	NMP	NaI	24	Reflux	98.7[9]
2	*n*-Propanol, NMP	NaI	24	Reflux	98.9[9]
3	Toluene	NaI	17	115–120	92.9[9]
4	Toluene	NaI/TBAB	17	115–120	99.5[9,13]
5	*n*-Butanol	NaI	17	112–115	95.7[13]
6	*n*-Butanol	NaI/TBAB	17	112–115	99.2[13]
7	DMF	NaI	4	103	90.3[13]
8	DMF	NaI/TBAB	18	103	99.3[13]
9	Water	NaI	7	98–102	99.7
10	Water	NaI	9	98–102	99.9
11	Water	NaI/TBAB	5	98–102	99.7
12	Water	NaI/TBAB	0.5	98–102	99.2
13	Water	NaI/TBAB	7	98–102	98.9
14	Water	NaI/TBAB	20	98–102	99.9
15	Water	KI	9	98–102	99.8
16	Water	NaI	7	98–102	99.8[a]
17	Water	NaI	7	98–102	99.7[b]
18	Water	KI/TBAB	7	98–102	99.9

Base: [a]triethylamine; [b]sodium bicarbonate

Different bases were employed other than sodium carbonate. The conversion of **II** in sodium bicarbonate was corroborated with the use of potassium carbonate. However, with triethylamine, the reaction mass became dark in colour and was accompanied by the formation of unidentified impurities (Table I, entry 16 and 17).

The stabilities of the compounds **I** and **II** were found to be very good under aqueous conditions. According to literature reports, the reactions were performed under inert and dry conditions.[9,13]

The influence of temperature on the reaction rate was also studied. The reactions were performed at different temperatures ranging from 30 to 102±2 °C. At lower temperatures, the conversion of **II** was very low (Table II, entry 1). However, at 50–55 °C, the conversion initially increased significantly (Table II, entry 2) but not much change was observed thereafter. At higher temperatures (100±2 °C), almost 100 % conversion was observed (Table II, entry 4).

Furthermore, the reaction was studied using different solvents and the results are summarized in Table III. In a typical reaction, water, DMF and a mixture of water and DMF were used as the solvent, in the presence of different alkali halides and TBAB. In DMF, 96.0 % conversion of **II** was observed (Table III, entry

1). The reaction mass in DMF solvent went a blackish colour. The different solvents (either DMF or water or a combination of water and DMF) at different substrate to solvent ratios were studied in order to achieve maximum conversion. The conversion increases with the water to DMF wt. ratios. At a water:DMF wt. ratio of 3:0, the maximum conversion of 99.92 % was achieved (Table III, entry 5). The reaction mass in water was of a pale yellow colour.

TABLE II. The effect of temperature on the conversion of compound **II** in water. Reaction conditions: compound **II**, 33.30 mmol; 2-(2-chloroethoxy)ethanol, 50.24 mmol; K_2CO_3, 203.30 mmol; NaI, 2 mol % to **II**; TBAB, 5 mol % to **II**; water, 30 ml

Entry	Temperature, °C (precision: ±2 °C)	Conversion, %
1	30–35	5.80
2	50–55	93.88
3	75–80	96.77
4	98–102	99.92

TABLE III. The effect of the ratio of water to DMF on the conversion of compound **II**. Reaction conditions: compound **II**, 33.30 mmol; 2-(2-chloroethoxy)ethanol, 50.24 mmol; K_2CO_3, 203.30 mmol; NaI, 2 mol % to **II**; TBAB, 5 mol % to **II**; temperature, 100±2 °C

Entry	Sub:water:DMF wt. ratio	Conversion of compound **II**, %
1	1:0:3	96.00
2	1:1:2	98.80
3	1:2:1	99.70
4	1:2.5:0.5	99.90
5	1:3:0	99.92

The quantity of water was optimized by performing the reaction at different dilution levels with respect to the **II**. The results are shown in Table IV. The reaction mass was very viscous without water and was difficult to analyze (Table IV, entry 1). As the dilution increased, the conversion decreased (Table IV). The maximum conversion was observed at a water:substrate wt. ratio 3:1 without DMF in the reaction medium (Table IV, entry 2).

TABLE IV. The effect of the concentration of water on the conversion of compound **II**. Reaction conditions: compound **II**, 33.30 mmol; 2-(2-chloroethoxy)ethanol, 50.24 mmol; base, 203.30 mmol; NaI, 2 mol % to **II**; TBAB, 5 mol % to **II**; temperature, 100±2 °C; time, 7 h

Entry	Water dilution, wt. % to **II**	Conversion, %
1	No water	RM is not uniform for analysis
2	3	99.92
3	4	99.20
4	6	98.90

A comparison of the reaction rates with and without TBAB is shown in Fig. 1. The reaction using TBAB showed a faster rate as compared to that of the reaction without TBAB. After achieving the maximum conversion in 7 h, with and without TBAB, no significant change was observed in the conversion of **II**.

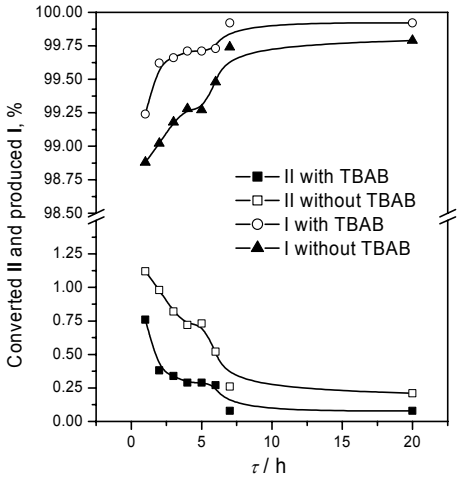


Fig. 1. The conversion to **I** and the unreacted **II**, in %, with time. Reaction conditions: Compound **II**, 33.30 mmol; 2-(2-chloroethoxy)ethanol, 50.24 mmol; base, 203.30 mmol; NaI, 2 mol % to **II**; TBAB, 5 mol % to **II**; water, 30 ml; temperature, 100±2 °C.

CONCLUSIONS

From above results, it can be concluded that the reaction in water is better than in polar aprotic and protic organic solvents. The mixture of water and DMF is also not suitable. The maximum conversion without DMF was ≈ 99.9 %. The reaction time in water was also considerably reduced, from 24 to 7 h. Phase transfer catalysts and metal halides, such as KI or NaI, were found to be important for enhancing the reaction rate.

ИЗВОД

ЕКОЛОШКИ ЧИСТО ДОБИЈАЊЕ 11-{4-[2-(2-ХИДРОКСИЕТОКСИ)ЕТИЛ]-1-ПИПЕРАЗИНИЛ}ДИБЕНЗО[*b*,*f*][1,4]ТИАЗЕПИНА

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Описан је еколошки чист и брз поступак синтезе 11-{4-[2-(2-хидроксиетокси)етил]-1-пиперазинил}дибензо[*b*,*f*][1,4]тиазепина, без нечистоћа, из 11-(1-пиперазинил)дибензо[*b*,*f*]-[1,4]тиазепина или његове дихидрохлоридне соли и 2-(2-хлоретокси)етанола у присуству неорганске базе и воде (конверзија 99,9 %). Метални халогениди и фазни трансфер катализатор убрзавају реакцију посебно у води као растварачу.

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