EFFICIENT METHOD FOR OBTAINING A PRECURSOR IN NON-STEREOSPECIFIC SYNTHESIS OF MIANSERIN AND EPINASTINE

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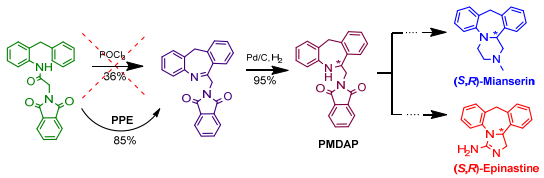
Abstract

A new method for obtaining one of the precursors in the non-stereospecific synthesis of the drugs mianserin and epinastine, namely, (*S,R*)-6-(phthalimidomethyl)-6,11-dihydro-5*H*-dibenzo[*b,e*]azepine is described, which consists in the cyclization of the intermediate amide in a polyphosphate ester medium (ethyl polyphosphate, PPE).



Key words: (*S,R*)-6-(phthalimidomethyl)-6,11-dihydro-5*H*-dibenzo[*b,e*]azepine (PMDAP), ethyl polyphosphate (PPE), cyclization, mianserin, epinastine.

Introduction

Mianserin **1** (Tolvon™, (±)-2-methyl-1,2,3,4,10,14*b*-hexahydrodibenzo[*c,f*]pyrazino[1,2-*a*]azepine Fig. 1) is a tetracyclic antidepressant that possesses a moderate sedative effect. Epinastine **2** (Alesion™, Elestat™, Purivist™, Relestat™, (±)-3-amino-9,13*b*-dihydro-1*H*-dibenzo[*c,f*]imidazo[1,5-*a*]azepine) is an analog of mianserin, which is used in a salt form as an antihistamine for the treatment of bronchial asthma, allergic rhinitis, and conjunctivitis.

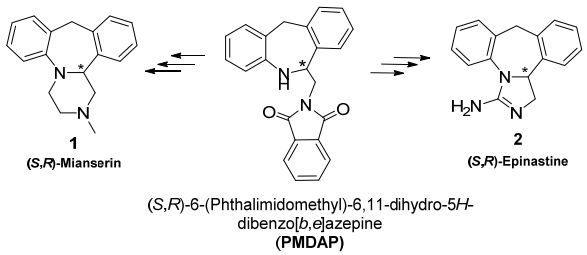


Figure 1. Chemical structures of mianserin (**1**), epinastine (**2**) and the intermediate compound PMDAP in their synthesis.

Mmianserin and epinastine are synthesized in several stages (see Fig. 2), where the common intermediate for both compounds is (*S,R)*-6-(phthalimidomethyl)-6,11-dihydro-5*H*-dibenzo[*b,e*]azepine (PMDAP) [1]. In this work, the non-stereospecific synthesis of PMDAP was accomplished, where one of the key intermediate stages was the cyclization of amidoimide **5** in ethyl polyphosphate, which proceeds with quantitative yield.

Results and discussion

Roszkowski *et al.* [1] used $POCl_3$ as a dehydrating coupling agent for the synthesis of intermediate **6**, which was obtained in 36% yield. This compound is a highly toxic, corrosive and unstable to moisture, and its use is accompanied by an increased risk of human poisoning and the occurrence of other irreversible consequences during the production.

Polyphosphate esters, in particular, ethyl polyphosphate (PPE) or trimethylsilyl polyphosphate (PPSE) are widely used in the synthesis of various heterocycles [2–5]. PPE can be readily synthesized, it is not volatile (a viscous liquid) and miscible with many organic solvents, and, presumably, has much lower toxicity than $POCl_3$. Therefore, it seemed interesting to study the possibility of using PPE as a coupling agent in the synthesis of PMDAP.

Herein it was revealed that the cyclization in PPE affords the precursor PMDAP, compound **6**, in almost quantitative yield. The structures of all the compounds obtained in this work were unambiguously confirmed by NMR spectroscopy. The optical isomerism of PMDAP has not been studied.

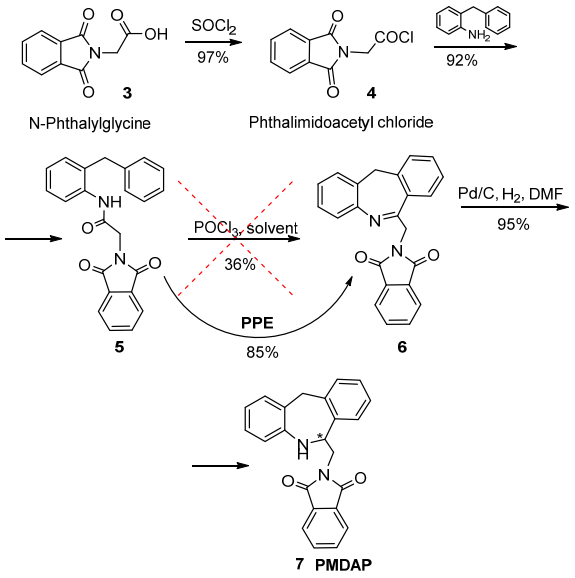


Figure 2. Scheme of reactions for obtaining PMDAP (**7**).

Experimental section

General remarks

The NMR spectra were recorded on an Agilent 400-MR spectrometer with operating frequencies of 400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C. The solvent was $CDCl_3$.

Syntheses

Phthalimidoacetyl chloride, 4 (yield 97%). The synthesis was carried out according to the published method [6]. Mp: 84.5 °C (cf. with 84–85 °C [6]). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.83 (s, 2H), 7.80 (dd, J = 5.4, 3.2 Hz, 2H), 7.93 (dd, J = 5.6, 3.0 Hz, 2H) ppm.

***N*-(2-Benzylphenyl)-2-(1,3-dioxo-1,3-dihydroisoindole-2-yl)acetamide, 5 (yield 92%)**. 2-Benzylaniline (1 equiv.) in a two-neck round-bottom flask equipped with a thermometer was dissolved in a mixture of dry DMAA (30 mL) and triethylamine (3 mL). A solution of compound **4** (1.2 equiv.) in DMAA (10 mL) was slowly added to the solution of 2-benzylaniline cooled to 5 °C (ice bath) under vigorous stirring, maintaining the temperature of the reaction mixture no higher than 10 °C. After the addition of the solution of compound **4**, the reaction mixture was heated to 30 °C for 1 h and poured into water upon vigorous stirring. The colorless precipitate was filtered off and washed several times with water containing a small amount of 10% aq. ammonia. The product was dried in air and then under vacuum. Mp: 233 °C (cf. with 234–235 °C [1]). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (br. s, 2H), 4.32 (s, 2H), 7.01–7.25 (m, 7H, Ar), 7.26–7.33 (m, 2H, Ar), 7.74–7.80 (m, 2H, Ar), 7.84–7.89 (m, 2H, Ar) ppm.

2-(11*H*-Dibenzo[*b*,*e*]azepin-6-ylmethyl)isoindole-1,3-dione, 6 (yield 85%). A two-neck 2 L flask equipped with a thermometer and reflux condenser was charged with compound **5** (50 g, 0.135 mol) and PPE (300 g), which was obtained according to the published procedure [7]. The reaction mixture was heated at 120 °C for 24 h, then at 130 °C for another 24 h (TLC control, eluent: chloroform–petroleum ether 1:1 (v/v)). Acetone (600 mL) was added to the resulting violet-black resin, which was dissolved upon heating to 40 °C under constant stirring. Then the resulting solution was poured into water (10 L), and the precipitate obtained was filtered off and dissolved in chloroform (500 mL). The organic fraction was washed twice with 10% aq. Na_2CO_3 (500 mL) and dried over Na_2SO_4. The solvent was removed under vacuum to give a red-orange solid, which was washed with petroleum ether and recrystallized twice from ethyl acetate to yield a light yellow solid. Mp: 208 °C (cf. with 208–209 °C [1]). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 2H), 5.14 (s, 2H), 7.11–7.17 (m, 4H, Ar), 7.27 (m, 2H, Ar), 7.38 (m, 1H, Ar), 7.58 (m, 1H, Ar), 7.69 (m, 2H, Pht), 7.86 (m, 2H, Pht) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 38.72, 44.56, 123.31, 125.29, 126.24, 126.37, 126.45, 126.80, 126.98, 127.01, 127.66, 130.50, 131.45, 132.40, 132.64, 133.82, 134.45, 143.35, 144.51, 145.16, 162.29, 168.10 ppm.

(±)-2-(6,11-Dihydro-5*H*-dibenzo[*b*,*e*]azepin-6-ylmethyl)-isoindole-1,3-dione, 7 (yield 95%). The synthesis was carried out according to the published method [1]. The compound was isolated as a dark green solid. Mp: 211 °C (cf. with 208–209 °C) ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (d, 1H, methylene bridge), 4.24–4.35 (m, 2H), 4.46–4.50 (d, 1H, methylene bridge), 5.22 (s, 1H, methine), 6.44–6.46 (d, 1H, Ar), 6.61 (m, 1H, Ar), 6.99 (d, 1H, Ar), 7.18–7.26 (m, 4H, Ar), 7.73–7.75 (m, 2H, Pht), 7.86–7.88 (m, 2H, Pht) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 39.90, 42.42, 55.01, 117.93, 118.68, 123.63, 123.88, 124.73, 127.13, 127.60, 128.32, 128.71, 130.29, 132.03, 134.33, 137.00, 139.76, 145.03, 168.86 ppm.

Conclusions

The efficient method for the heterocyclization of the intermediate amide in the synthesis of the non-stereospecific compound PMDAP (a common precursor of mianserin and epinastine) in ethyl polyphosphate with high yield was developed. The suggested approach allows for replacing highly toxic and less efficient $POCl_3$ as a coupling agent.

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