*Chemistry of Heterocyclic Compounds, Vol. 41, No. 10, 2005*

# LETTERS TO THE EDITOR

## UNUSUAL EFFECT OF A REMOTE SUBSTITUENT ON CHLORINATION OF MELATONIN

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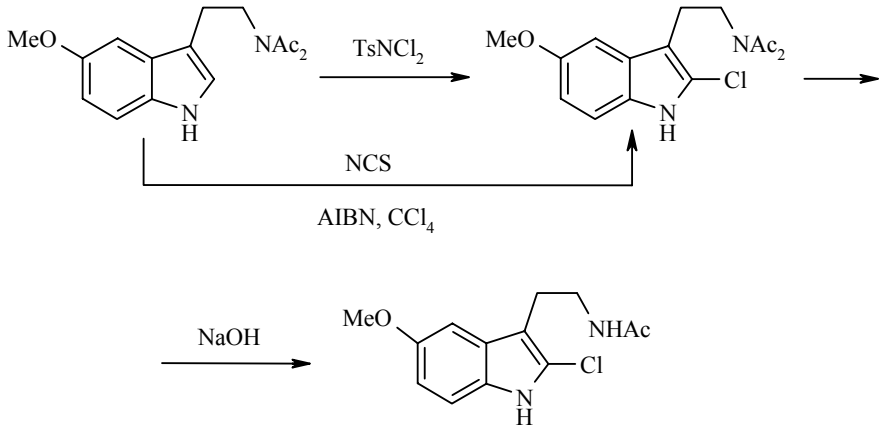
**Keywords:** N-acetylmelatonin, dichloroamine T, 2-chloromelatonin, N-chlorosuccinimide, radical chlorination, electrophilic chlorination.

No information is available in the literature on methods for obtaining N-acetyl-2-chlorotryptamines, although the existence of 2-chloromelatonin is mentioned in [1]. The need to develop methods for synthesis of 2-halotryptamine derivatives is dictated by their high activity with respect to melatonin receptors [2-4]. We have established that electrophilic chlorination of melatonin by N-chlorosuccinimide (NCS) in THF at low temperatures and also by dichloroamine T ($TsNCl_2$) (for different substrate:reagent ratios) in an AcOH–THF mixture at 20°C and -15°C does not lead to formation of the 2-chloro derivative, and the reaction mixtures mainly contain unreacted melatonin and tarry byproducts. We unexpectedly found that using N-acetylmelatonin (N,N-diacetyl-5-methoxytryptamine) as the substrate allows us to successfully carry out the process of electrophilic chlorination at the 2 position by dichloroamine T in THF at -50°C.




Introducing a second protective acetyl group allows us to carry out not only electrophilic chlorination but also radical chlorination of melatonin at the 2 position. In fact, we have shown that chlorination of N-acetylmelatonin by NCS under conditions favorable for the occurrence of free-radical processes (in $CCl_4$ in the presence of azobisisobutyronitrile (AIBN)) also leads to the 2-chloro derivative. Known attempts in the

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literature to carry out free-radical halogenation of N-acetyltryptamines (bromination of melatonin [2], chlorination and bromination of the methyl ester of N-acetyltryptophan [5]) were unsuccessful. We only know of a few examples of successful free-radical halogenation of tryptamine derivatives (bromination and chlorination of N-trifluoroacetyltryptophan) [5]. The reasons for this phenomenon are not yet known; but in this literature example, note the decrease in electron density at the nitrogen atom of the side chain as a result of introducing an electron-acceptor trifluoroacetyl group. We see that in our case, an analogous role is played by the second acetyl group on the nitrogen atom.

Thus the results obtained allow us to recommend a second acetyl group as a protective group enabling successful electrophilic and radical chlorination of N-acetyltryptamines, especially since this group is easily introduced into the molecule (boiling tryptamines and monoacetyl derivatives in acetic anhydride) and it is easily removed (by treatment of the reaction mixture with base). It is especially convenient that we can obtain the target N-acetyl-2-chlorotryptamines without separating the intermediate N,N-diacetyl-2-chloro derivatives.

**N-acetylmelatonin** was obtained by the procedure in [6].

**Free-radical chlorination of N-acetyl melatonin.** N-Acetylmelatonin (150 mg, 0.55 mmol) was dissolved with stirring in a minimal amount of boiling carbon tetrachloride (about 40 ml). A few drops of a solution of a few mg AIBN in 2 ml carbon tetrachloride was added, and NCS (80 mg, 0.60 mmol) was added immediately in small portions. The mixture was boiled for 5 min and then cooled down; the solvent was driven off under vacuum. A cooled 10% aqueous alcoholic (1:1) solution of NaOH (20 ml) was added to the residue (with cooling by ice) and the mixture was stirred for 30 min. The alcohol was driven off on a rotary evaporator, water (20 ml) was added to the solution and it was extracted with chloroform (2 × 40 ml). The solution was evaporated down to dryness and the residue was dissolved in a minimal amount of chloroform. After chromatography (Silica Gel 60 (0.0040-0.063 mm) from Merck, 50:1 $CHCl_3$-ethanol as the eluent), we isolated 2-chloromelatonin (30 mg), m.p. 124°C (30% based on the reacted melatonin) and 40 mg (27%) melatonin. $^1$H NMR spectrum (400 MHz, $CCl_4$-$CD_3CN$, 2:1, standard TMS), δ, ppm (*J*, Hz): 1.77 (3H, s, $CH_3CO$); 2.74 (2H, t, $J$ = 7.15, $\underline{CH_2}CH_2NH$); 3.45 (2H, q, $J$ = 7.15, $CH_2\underline{CH_2}NH$); 3.71 (3H, s, $OCH_3$); 6.51 (1H, broad s, NHCO); 6.64 (1H, dd, $J_{76}$ = 9.0, $J_{74}$ = 2.3, H-7); 6.88 (1H, d, $J_{47}$ = 2.3, H-4); 7.07 (1H, d, $J_{67}$ = 9.0, H-6); 9.24 (1H, broad s, N(1)H). Mass spectrum, *m*/*z* ($I_{rel}$, %): 266* [M]+* (21), 230 [M-HCl] (12), 207* [M-AcNH2] (100, 194* [M-$AcNHCH_2$] (95), 188 (4), 187 [M-HCl-$CH_2CO$] (7), 179* (20), 151* (17). Found, %: C 58.53; H 5.63; N 10.28. $C_{13}H_{15}ClN_2O_2$. Calculated, %: C 58.54; H 5.67; N 10.50.

**Electrophilic chlorination of N-acetylmelatonin.** A solution of N-acetylmelatonin (100 mg, 0.37 mmol) in absolute THF (3 ml) was cooled down to -50°C. Then dichloroamine T (40 mg, 0.17 mmol) [7] in absolute THF (4 ml) was added dropwise with rapid stirring. The reaction mixture was held for 20 min at -50°C and then was warmed up to -30°C over a 1 h period and then warmed up to room temperature over a 2 h period. After 30 min, the reaction mixture was poured into a 10% aqueous alcoholic (1:2) solution of sodium hydroxide (20 ml). The mixture was stirred for 30 min and then isolated as before. We obtained 2-chloromelatonin (30 mg, 0.11 mmol), identical to that obtained by the radical chlorination method (42% based on the reacted melatonin) and 30 mg melatonin (30%).

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