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An Unexpected Reaction in the Synthesis of 3-Substituted Thienoazetidinones

J. SARAVANAN*, VANITA SOMASEKHAR† and S. MOHAN‡

M.S. Ramaiah College of Pharamacy, M.S.R.I.T. Post, Bangalore-560 064, India

The compounds 2-amino-3-(N-tolylcarboxamido)-4,5,6,7-tetrahydrobenzo(b)thiophenes (**I, II** and **III**) were treated with various substituted aryl aldehydes to yield the corresponding Schiff bases (**Ia–j** to **IIIa–j**). Later these new Schiff bases were subjected to treatment with chloro acetyl chloride to obtain the title compounds. However, all the Schiff bases underwent cleavage at the enamine group yielding the corresponding chloro acetylated derivatives.

Key Words: Synthesis, Characterization, Substituted thienoazetidinones.

INTRODUCTION

In our earlier[1-3] communications, we reported the synthesis, characterization and antibacterial activity of some new Schiff bases of thiophenes. In continuation we attempted the synthesis of thienoazetidinones using Schiff bases of 2-amino-3-(N-tolylcarboxamido)-4,5,6,7-tetrahydrobenzo(b)thiophenes (**Ia–j** to **IIIa–j**). However, during the attempted synthesis of the title compounds using chloroacetyl chloride, instead of the expected thienoazetidinones, we obtained new compounds 3-N-tolylcarboxamido-2-(ω-chloroacetamido)-4,5,6,7-tetrahydro benzo(b)thiophenes, which were characterized by their analytical and spectroscopic data.

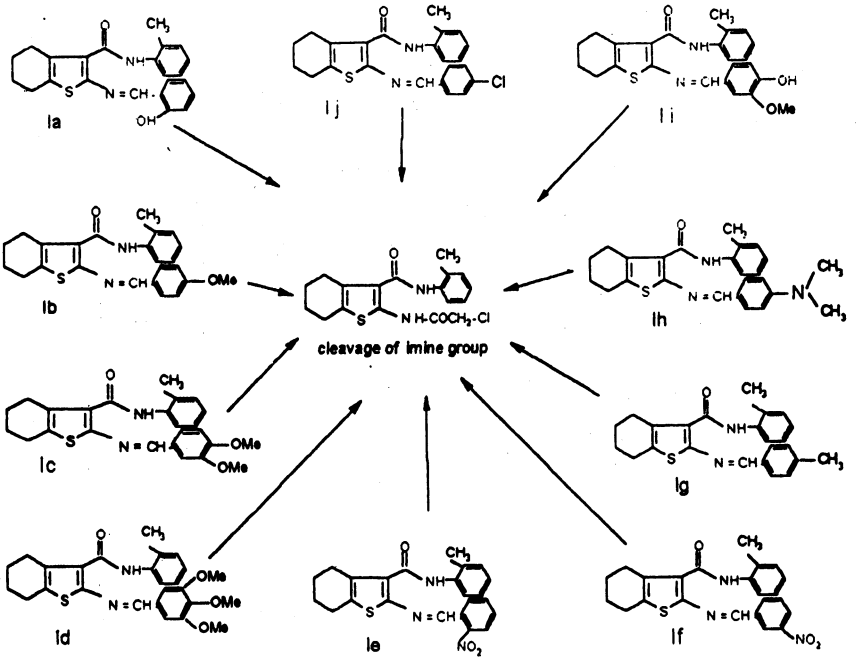
EXPERIMENTAL

All the compounds were colourless solids. Melting points are uncorrected. The UV spectra were recorded on Shimadzu 1601 spectrometer, IR (KBr) were recorded on FT-IR 8201. ^{1}H NMR spectra were recorded on Brucker DPX 200, the chemical shift values are in δ ppm. The mass spectra were recorded on Shimadzu GCMS QP 500 at an ionization potential of 70 eV. Elemental analyses were within ±0.4% of their calculated values.

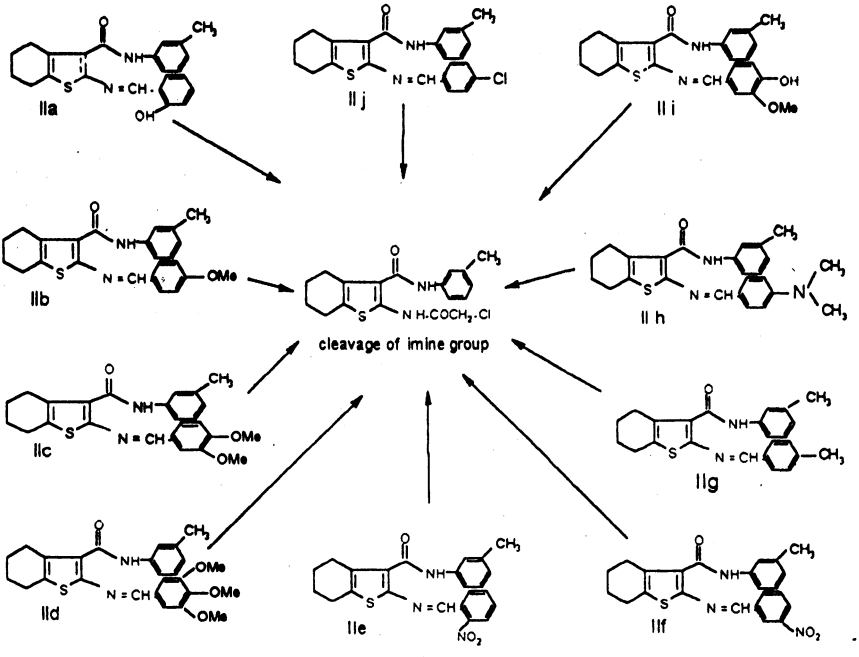
†P.E.S. College of Pharmacy, Hanumanthanagar, Bangalore-560 050, India.

‡Al-Ameen college of Pharmacy, Bangalore-560 027, India.

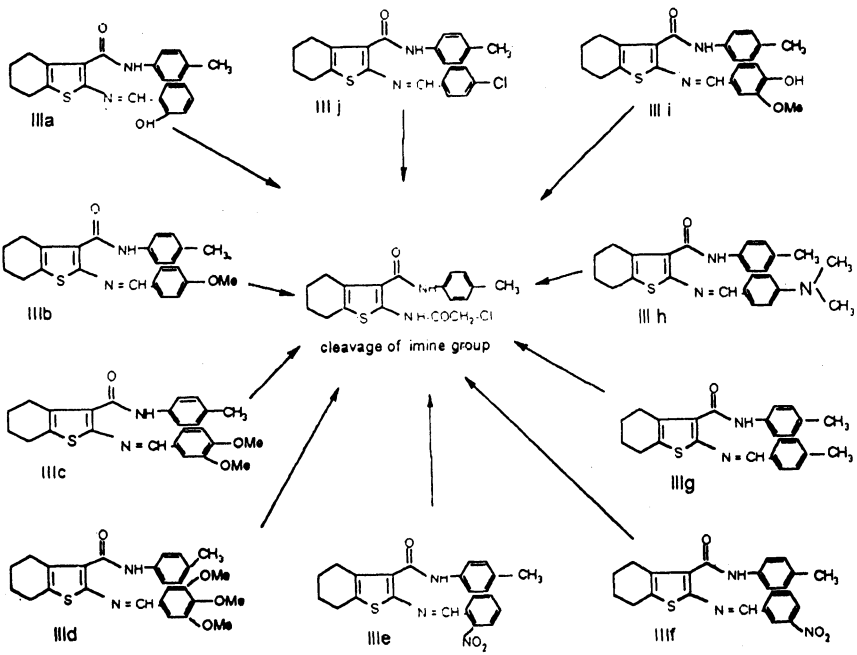
*Author for correspondence: S. Mohan, Principal, Prof. & H.O.D. Department of Pharmaceutical Chemistry, P.E.S. College of Pharmacy, Hanumanthanagar, Bangalore-560 050, India.



Scheme 1



Scheme 2



Scheme 3

The Schiff bases (**Ia–j** to **IIIa–j**) were subjected to treatment with chloro acetyl chloride to obtain the title compounds by adopting standard procedures[4–11]. The final compounds obtained were found to be different from their starting materials by difference in m.p. and R_f values. Hence we subjected a few of these newly formed compounds to NMR and mass spectral studies.

The comparison of the analytical and spectroscopic data of Schiff bases and the newly formed compounds showed a cleavage of the enamine group from Schiff bases and addition of chloroacetyl group to the corresponding thiophene at its amino group in second position (**Schemes 1, 2** and **3**) without any change in the thiophene system and also in the tolyl carboxamido group at position **3**.

The obtension of the final compounds from different Schiff bases was an unexpected reaction for us. It required 3 moles of chloro acetyl chloride per mole of the Schiff bases.

In order to elucidate the possible mechanism of this reaction we carried out some additional experiments with different Schiff bases and chloro acetyl chloride molar ratios. A mixture of Schiff base and chloro acetyl chloride in different solvents like dioxane/benzene was treated under different conditions like difference in contact period and reaction temperature. However, all the reactions yielded the same open chain chloro acetyl derivative.

RESULTS AND DISCUSSION

The unexpected reaction was understood by the following facts:

(a) All the final compounds obtained from one series had melted at a very narrow range, *i.e.*, the final compounds obtained from the different Schiff bases **(Ia–j)** were melted between 182–184°C. Similarly, the final compounds obtained from the different Schiff bases **(IIa–j)** were melted between 158–162°C and the Schiff bases **(IIIa–j)** were melted between 202–206°C. Mixed melting points were also taken for confirming the final products by mixing two final products of the same series. The melting points were sharp. Hence it was concluded that the final product obtained from one series is the same as shown in the **Schemes 1, 2** and **3.**

(b) The conspicuous absence of aryl protons of the Schiff bases in all the NMR spectra was observed.

(c) Finally, the mass spectra of the final products obtained from three different schiff bases of three different series **(Ia, IIf** and **IIIg)** confirmed the open chain N-acyl chloride derivative of the corresponding thiophenes. Hence, the method of synthesis was modified and the same was carried out under different reaction conditions such as different solvent systems, temperature and duration of reaction. The cleavage was found to occur even at temperatures as low as 0°C and at reaction times as short as 20 min.

M/S: m/e Ia: 362 (M^+, 208%), 256 (25.47), 206 (6.72), 192 (5.44), 180 (15.3), 151 (7.8), 107 (100).

^{1}H NMR Ia: 7.8 (s, 1H, —CO—NH— proton), 7.5 (s, 1H, —NH—CO— proton), 7.2 (m, 4H, Arom), 4.2 (s, 2H, —CO—CH_2— proton), 2.8 (d, 4H, dimethylenic protons of cyclohexane ring), 2.4 (s, 3H, —CH_3 Arom), 2.0 (s, 4H, dimethylenic protons of cyclohexane ring).

M/S: m/e IIf: 362 (M^+, 2.94%), 256 (4.59), 206 (1.18), 192 (1.61), 180 (3.87), 151 (3.97), 107 (100).

^{1}H NMR IIf: 7.6 (s, 1H, —NH—CO— proton), 7.4 (d, 1H, Arom and 1H —CO—NH— proton), 7.2 (m, 3H, Arom), 4.2 (s, 2H, —CO—CH_2— proton), 2.8 (d, 4H, dimethylenic protons of cyclohexane ring), 2.4 (s, 3H, —CH_3 Arom), 2.0 (s, 4H, dimethylenic protons of cyclohexane ring).

M/S: m/e IIIg: 362 (M^+, 21.88%), 256 (18.59), 206 (5.55), 192 (3.60), 180 (8.89), 151 (6.69), 107 (100).

^{1}H NMR IIIg: 7.8 (s, 1H, —NH—CO— proton), 7.2–7.4 (m, 4H, Arom), 6.9 (d, 1H —CO—NH— proton), 4.2 (s, 2H, —CO—CH_2— proton), 2.8 (d, 4H, dimethylenic protons of cyclohexane ring), 2.4 (s, 3H, —CH_3 Arom), 2.0 (s, 4H, dimethylenic protons of cyclohexane ring).

With the information summarized above, the mechanism of the reaction becomes obvious that to our knowledge it is the first time that an open chain chloro acetyl derivative was obtained through the cleavage of enamine group from the starting compounds **Ia–j** to **IIa–j.** The new unexpected products may be due to steric hindrance by the presence of bulky substituent at position 3 on the thiophene nucleus and also may be due to the non-stability of the Schiff bases with highly reactive chloro acetyl chloride.

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Contact:
Prof. Max Malacria
E-mail: gis-facs@ccr.jussieu