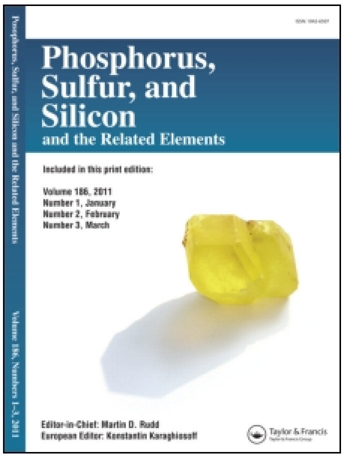

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Synthesis and Characterization of N-benzoyl-N'-carboxyalkyl Substituted Thiourea Derivatives

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SYNTHESIS AND CHARACTERIZATION OF N-BENZOYL-N′-CARBOXYALKYL SUBSTITUTED THIOUREA DERIVATIVES

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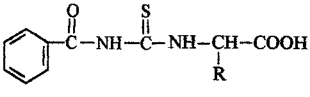
N-Benzoyl-N′-carboxyl substituted thiourea derivatives (I-X) have been synthesized by the reaction of benzoyl isothiocyanate with amino acids. Their structures are confirmed by IR, ^{1}HNMR, and elemental analysis. The reaction conditions are experimentally investigated, and the preliminary biological tests show that some of the compounds have excellent plant growth promotion activities.

Keywords: Amino acid; N-benzoyl-N′-carboxyl substituted thiourea; synthesis

Acyl substituted thiourea derivatives are not only important intermediates in organic synthesis, but they also possess various biological activities. It has been reported that phenylureas and thioureas form the basis of many molecules possessing biological activity, some of them are successfully used as insecticides,[1] bactericides,[2] and plant growth regulators.[3] In order to search for new compounds with excellent plant growth regulation, ten N-benzoyl-N′-carboxyl substituted thioureas derivatives (I-X) were synthesized by the reaction



(I—X)

I. $R = H$, II. $R = CH_3$, III. $R = C_2H_5$, IV. $R = CH(CH_3)_2$,
V. $R = n\text{-}C_4H_9$, VI. $R = CH_2CH(CH_3)_2$, VII. $R = CH_2CH_2SCH_3$,
VIII. $R = CH(OH)CH_3$, IX. $R = C_6H_5$, X. $R = CH_2C_6H_5$.

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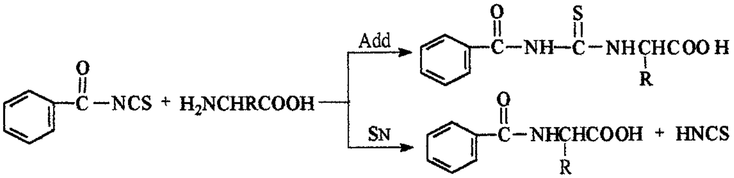
of benzoyl isothiocyanate with amino acids. Their structures are confirmed by ^{1}HNMR, IR, MS, and elemental analyses. The preliminary biological tests show that the compounds have excellent plant growth promotion activities for plant root and stalk growing.

RESULT AND DISCUSSIONS

Acylthiourea derivatives usually are synthesized from the appropriate substituted anilines and acyl isothiocyanates, the reaction being executed easily because aniline plays a role as both a nucleophile and a base catalyst.[4] The reaction with amino acids as nucleophiles, however, might seem hard to conduct. The reason might be due mainly to characteristics of amino acids. Since amino acids are amphoteric compounds, in solution a dipolar ion ($^+NH_3CH(R)$-COO^-) is formed by a proton transformation from the carboxyl group to the nitrogen atom of amino group.[5] It is the amphoteric nature of amino acids that largely reduces the electron density on nitrogen. Thus the zwitterions amino acids possess lower nucleophility than amines and are difficult to react with acyl isothiocyanates. In order to facilitate the reaction, adding an organic base such as pyridine might enhance the reaction rate.

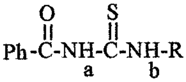
Because addition and substitution always happened simultaneously in the reaction course, besides the expected addition products, N-benzoyl-N′-carboxyl substituted thioureas and some substituted benzoyl amide derivatives usually occurred.[6] The competed reactions could be indicated as the following.



It was found that the undesired by-product could be reduced to a certain extent if the reaction was carried out in anhydrous non-protonic solvent such as acetone or acetonitrile. The amino acids did not immediately dissolve in the solvent, but they did dissolve in acyl isothiocyanates. Thus a little excessive acyl isothiocyanate is needed actually.

In their IR spectra, N-benzoyl-N′-carboxyl-substituted thiourea derivatives displayed a broad peak for N—H and O—H absorption between 3000–3300 cm^{-1}. The frequencies of the two bonds were close and overlapped with each other. The C=O group (benzoyl) occurred at 1650 cm^{-1} which was lower than the usual carbonyl group, owning to the conjugation of it with benzene ring and the hydrogen bond formation of it with NH,[7] Another C═O group (carboxyl) was at 1715 cm^{-1}. It was similar to that of the normal carboxylic acids. With a small force constant, the C═S bond appeared at 1250 cm^{-1} with moderate intensity.

The ^{1}HNMR characteristic of N-benzoyl-N′-carboxyl substituted thiourea derivatives was the two imine protons labeled a and b. Proton a was affected by the deshielding effect of C═O and C═S groups, and the chemical shift was 5.5–7.0 ppm, which was downfield compared to that of normal amides. Proton b was around 10 ppm. This was quite downfield and a little affected by the R groups, because of the intramolecular hydrogen bond interaction. A weak signal at 11.0 ppm for the proton of the O—H group appeared. It disappeared immediately when treated with D_2O.



$$\mathrm{Ph{-}\overset{\overset{O}{\|}}{C}{-}\underset{a}{NH}{-}\overset{\overset{S}{\|}}{C}{-}\underset{b}{NH}{-}R}$$

The preliminary plant growth promotion activities of the title compounds for the root and stalk growth of monocotyledon and dicotyledonous plant were tested, the results showed that some of the compounds have excellent growth promoting propensities. At the concentration of 10 ppm, for example, the promotive percentage of compound I, V, VI, and VII for the root growth of rape was 39, 65, 48, and 51 respectively, Compounds I and V promoted the root growth of wheat by 55% and 38%, and for barnyard grass 40% and 39%.

EXPERIMENTAL

All reagents were desiccated or redistilled. IR spectra were recorded on a Perkin-Elmer Model 983 spectrophotometer (KBr pellets). ^{1}HNMR spectra were obtained using a Varian Associates XL-200 spectrophotometer using deuterated acetone as solvent and tetramethylsilane as an internal standard (abbreviations used: b, broad; d, doublet; m, multiplet; s, singlet; t, triplet). MS were measured on a Hewlett Packard 5988 instrument. Elemental analyses were performed on a PE-2100 automatic meter. A X-4 numerical display meter determined melting points, and the thermometer was uncorrected.

The general synthesis procedure of N-benzoyl-N′-carboxyalkyl-substituted thioureas (I-X) is described as follows: A solution of 7.3 g (75 mmol) of potassium isothiocyanate dissolved in 15 ml of anhydrous acetone was treated slowly with 50 mmol of benzoyl chloride. The mixture was stirred at 55–60°C for 1 h, and then 50 mmol of amino acid and a few drops of pyridine were added. The mixture was refluxed for 6 h. The solution was treated with cooled ice-water. When standing, a precipitate appeared which was filtrated, washed with water, and recrystallized (ethanol) to provide the product.

N-Benzoyl-N′-carboxyl methylene thiourea (I): Yellow solid, m.p. 199–200°C, yield 73%. IR (cm^{-1}): 3000–3300 (N—H, O—H), 1655, 1700 (C=O), 1245 (C=S): ^{1}HNMR (δ ppm): 5.86–6.75 (b, 1H, NH), 7.35–8.10 (m, 5H, ArH), 10.28 (s, 1H, NH), 11.10 (s, 1H, COOH): m/e: 238 (M^+): Anal. calcd. for $C_{10}H_{10}N_2O_3S$: C, 50.42; H, 4.20; N, 11.77: Found: C, 51. 10; H, 3.77; N, 12.01.

N-Benzoyl-N′-carboxyl ethylidene thiourea (II): Yellow solid, m.p. 187–189°C, yield 69%. IR (cm^{-1}): 3100–3400 (N—H, O—H), 1670, 1720 (C=O), 1265 (C=S); ^{1}HNMR (δ ppm): 5.75–6.85 (b, 1H, NH), 7.53–8.25 (m, 5H, ArH), 10.25 (s, 1H, NH), 11.25 (s, 1H, COOH); Anal. calcd. for $C_{11}H_{12}N_2O_3S$: C, 52.38; H, 4.76; N, 11.11; Found: C, 52.01: H, 4.93; N, 10.95.

N-Benzoyl-N′-carboxyl propylidene thiourea (III): White solid, m.p. 189–190°C, yield 63%. IR (cm^{-1}): 3015–3200 (N—H, O—H), 1670, 1725 (C=O), 1265 (C=S); ^{1}HNMR (δ ppm): 5.70–6.80 (b, 1H, NH), 7.45–8.20 (m, 5H, ArH), 10.15 (s, 1H, NH), 11.15 (s, 1H, COOH): Anal. calcd. for $C_{12}H_{14}N_2O_3S$: C, 54. 14; H, 5.26; N, 10.53; Found: C, 53.96: H, 5.02: N, 10.11.

N-Benzoyl-N′-carboxyl butylidene thiourea (IV): White solid, m.p. 185–186°C, yield 65%. IR (cm^{-1}): 3025–3150 (N—H, O—H), 1675, 1725 (C=O), 1260 (C=S); ^{1}HNMR (δ ppm): 5.72–6.85 (b, 1H, NH), 7.40–8.25 (m, 5H, ArH), 10.30 (s, 1H, NH), 11.20 (s, 1H, COOH).

N-Benzoyl-N′-carboxyl isobutylidene thiourea (V): Yellow solid, m.p. 131–132°C, yield 58%. IR (cm^{-1}): 3100–3250 (N—H, O—H), 1670, 1700 (C=O), 1250 (C=S); ^{1}HNMR (δ ppm): 5.90–6.80 (b, 1H, NH), 7.40–8.15 (m, 5H, ArH), 10.25 (s, 1H, NH), 10.15 (s, 1H, COOH): m/e: 294 (M^+): Anal. calcd. for $C_{14}H_{18}N_2O_3S$: C, 57.14; H, 6.12; N, 9.52; Found: C, 57.32; H, 5.87; N, 9.13.

N-Benzoyl-N′-carboxyl isopentylidene thiourea (VI): Yellow solid, m.p. 149–151°C, yield 53%. IR (cm^{-1}): 3005–3200 (N—H, O—H), 1660, 1720 (C=O), 1240 (C=S); ^{1}HNMR (δ ppm): 5.86–6.90 (b, 1H, NH), 7.25–8.20 (m, 5H, ArH), 10.20 (s, 1H, NH), 11.20 (s, 1H, COOH); Anal. calcd. for $C_{14}H_{13}N_2O_3S$: C, 57.14: H, 6.12; N, 9.52; Found: C, 57.32; H, 5.87; N, 9.13.

N-Benzoyl-N′-carboxyl methylthiopropylidene thiourea (VII): White solid, m.p. 150–152°C, yield 48%. IR (cm^{-1}): 3100–3250 (N—H, O—H), 1670, 1700 (C=O), 1250 (C=S); ^{1}HNMR (δ ppm): 5.90–6.80 (b, 1H, NH), 7.40–8.15 (m, 5H, ArH), 10.25 (s, 1H, NH), 10.15 (s, 1H, COOH).

N-Benzoyl-N′-carboxyl 2-hydrovyl propylidene thiourea (VIII): White solid, m.p. 131–132°C, yield 58%. IR (cm^{-1}): 3100–3250 (N—H, O—H), 1670, 1700 (C=O), 1250 (C=S); ^{1}HNMR (δ ppm): 5.90–6.80 (b, 1H, NH), 7.40–8.15 (m, 5H, ArH), 10.25 (s, 1H, NH), 10.15 (s, 1H, COOH).

N-Benzoyl-N′-carboxyl phenylmethylidene thiourea (IX): White solid, m.p. 161–162°C, yield 60%. IR (cm^{-1}): 3125–3250 (N—H, O—H), 1670, 1720 (C=O), 1245 (C=S); ^{1}HNMR (δ ppm): 5.85–6.75 (b, 1H, NH), 7.40–8.15 (m, 5H, ArH), 10.25 (s, 1H, NH), 10.15 (s, 1H, COOH).

N-Benzoyl-N′-carboxyl phenylethylidene thiourea (X): White solid, m.p. 172–173°C, yield 58%. IR (cm^{-1}): 3100–3250 (N—H, O—H), 1670, 1700 (C=O), 1250 (C=S); ^{1}HNMR (δ ppm): 5.90–6.80 (b, 1H, NH), 7.40–8.15 (m, 5H, ArH). 10.25 (s, 1H, NH), 10.15 (s, 1H, COOH).

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