REACTION MECHANISM AND STRUCTURE OF NEW HETEROCYCLES VIA 1,4-DIPOLAR CYCLOADDITION OF IMIDAZO[2,1-b]THIAZOLIUM-BETAINE

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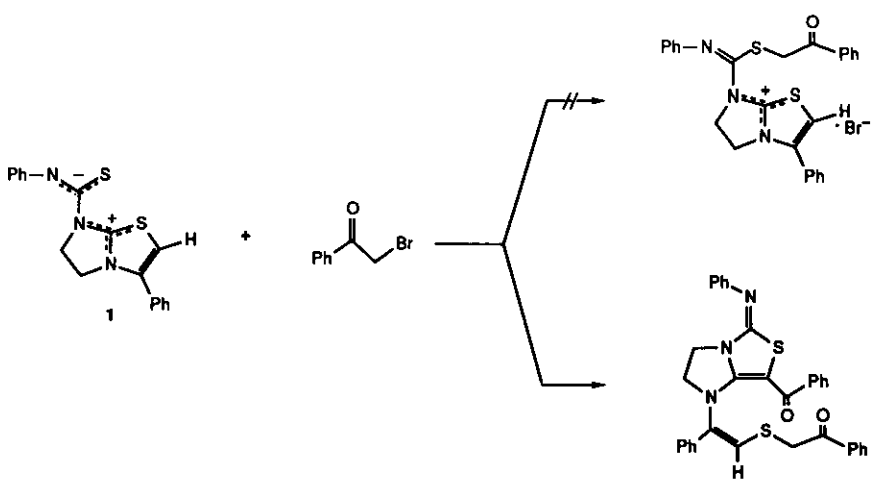
Abstracts - New heterocycles, (12RS,13SR)- and (12SR,13SR)-12-benzoyl-2,4-dioxo-1,3,9-triphenyl-6,7-dihydro-12H-thiazino[3',4'; 2,3]imidazo[1,2-a][1,3,5]triazines (4a and 4b), were synthesized via 1,4-dipolar cycloaddition from 5,6-dihydro-3-phenyl-7-[N-phenyl(carbamoyl)]imidazo[2,1-b]thiazolium-betaine (2) by the treatment of phenacyl bromide.

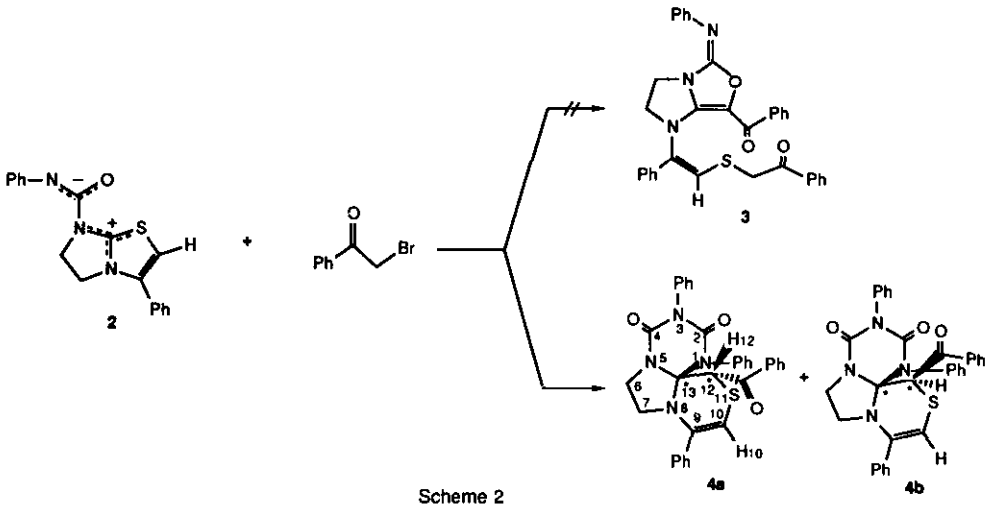
The ring transformation reaction of 3-substituted 5,6-dihydro-7-[N-phenyl(thiocarbamoyl)]imidazo[2,1-b]thiazolium-betaine (1) with phenacyl bromide was reported in the previous publication (Scheme 1).[1] Interestingly the negative charge of 5,6-dihydro-3-phenyl-7-[N-phenyl(thiocarbamoyl)]imidazo[2,1-b]thiazolium-betaine (1), herein, has nucleophilicity.



Scheme 1

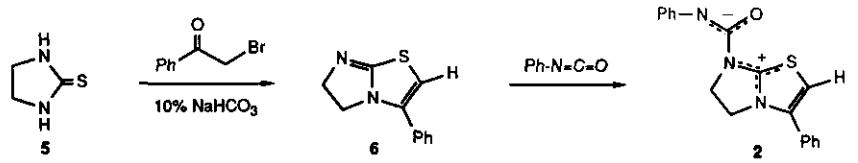
We have performed the reaction of 5,6-dihydro-3-phenyl-7-[N-phenyl(carbamoyl)]imidazo-[2,1-b]thiazolium-betaine (2) with phenacyl bromide (Scheme 2), providing new diastereomeric heterocycles, (12RS,13SR)- and (12SR,13SR)-12-benzoyl-2,4-dioxo-1,3,9-triphenyl-6,7-dihydro-12H-thiazino[3',4'; 2,3]imidazo[1,2-a][1,3,5]triazines (4a and 4b), in place of the ring transformation compound (3). The difference of nucleophilicity between the

N-phenyl carbamoyl and N-phenyl thiocarbamoyl moieties of N-bridged thiazolium-betaines (1) and (2), respectively, caused the quite different results. Here N-alkylation instead of S-alkylation occurred exclusively. In this paper, we describe the reaction mechanism and structure elucidation of cycloadducts (4a) and (4b).



Scheme 2

Ethylene thiourea (5) as starting material was prepared by the methods described in the literature.[2-4] The N-bridged imidazothiazole, 5,6-dihydro-3-phenylimidazo[2,1-b]thiazole (6) was prepared by condensing 5 with phenacyl bromide.[5-8] Then, the betaine (2) was synthesized from imidazothiazole (6) by the treatment with phenyl isocyanate at room temperature (Scheme 3).[1,9] This reaction was carried out in aprotic solvents such as acetone and acetonitrile, due to occurring the decomposition of betaine in protic solvents. As most betaine compounds are insoluble in common organic solvents, the formation of 2 was detected from white precipitate.



Scheme 3

Structure Elucidation of 4a and 4b

Structures of 4a and 4b were characterized by the spectroscopic methods including 2D correlated nmr spectroscopies and ^{13}C multiplicity analyses. ^{1}H Nmr spectrum of 4a showed the existence of W-coupling[10] via hetero atom between H-10 (vinylic, δ 4.78) and H-12

(methine, δ 5.60) (doublets, coupling constant $\underline{J}$=1.6 Hz). It means that both H-10 and H-12 protons are placed nearly on the same plane in ring system, though they do not have coplanarity completely. Owing to this W-coupling a methine proton was remarkably shifted to the down field. The 2D correlated spectrum of 4a in Figure 1 showed that the peaks of

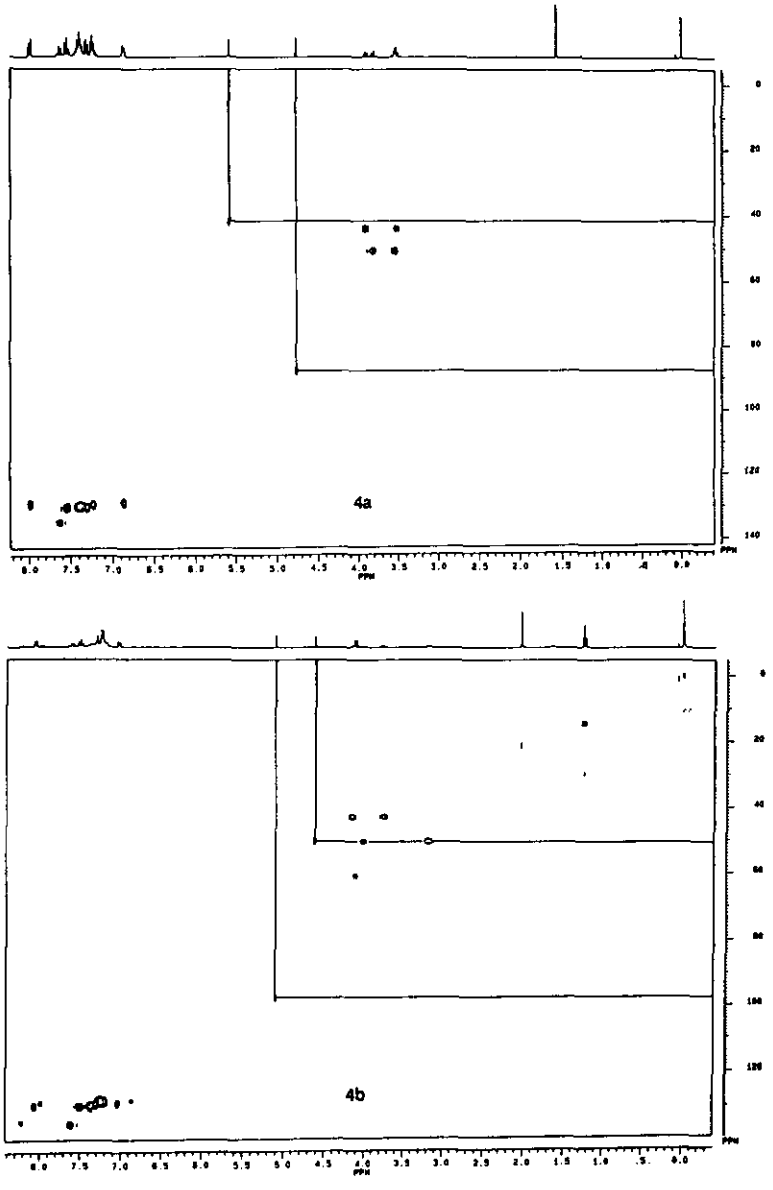
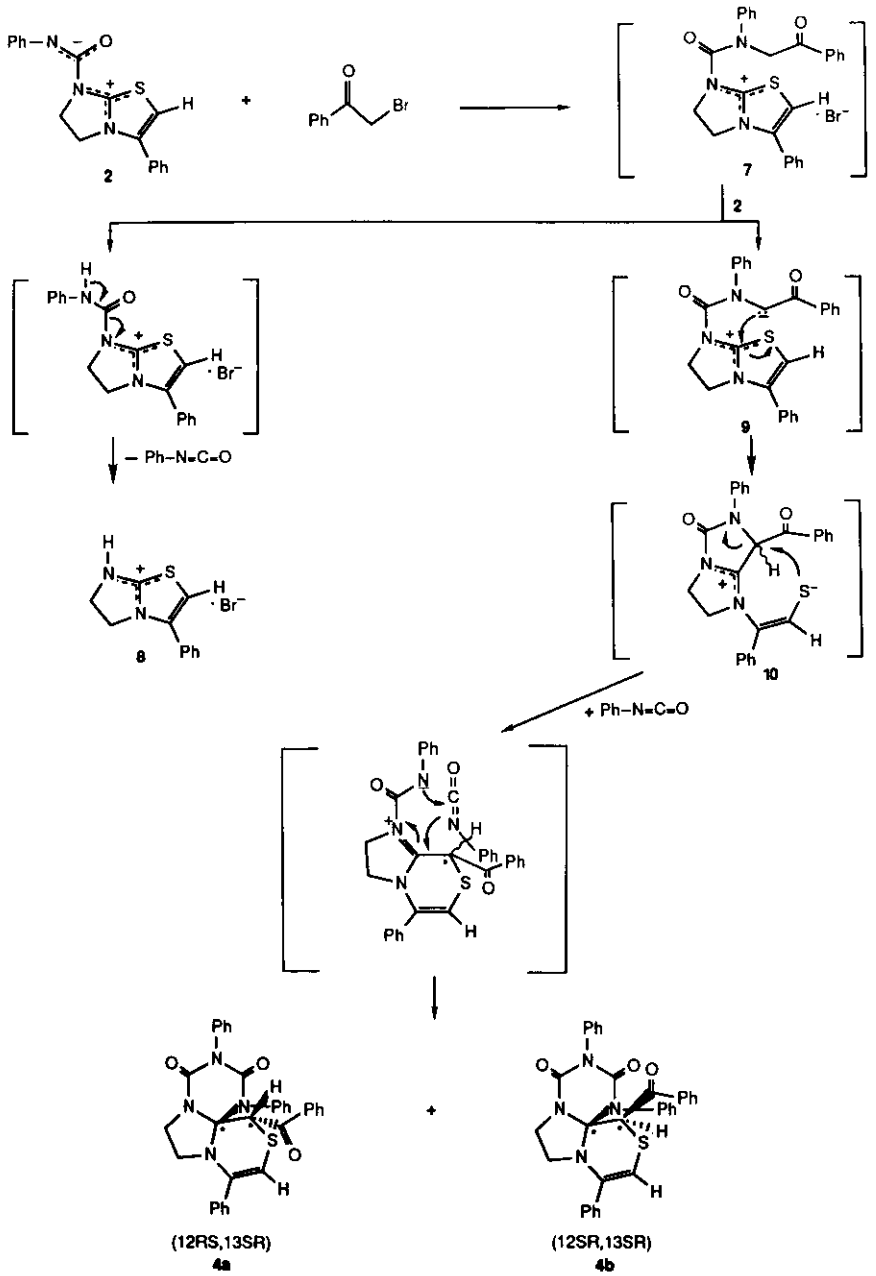


Figure 1. 2D correlated spectra of **4a** and **4b**

C-10 and C-12 were δ 87.4 and δ 41.4. The peaks of δ 87.4 and δ 41.4 were conformed as =CH and -CH groups by the ^{13}C multiplicity analysis. In addition, methylene groups of C-6 and C-7 were assigned by ^{13}C multiplicity analysis (δ 43.7 and δ 50.4) and ^{1}H nmr

spectrum (δ 3.46-3.59 and δ 3.75-3.98). The intense peaks of 1720, 1680 cm^{-1} on the ir spectrum manifested the presence of carbonyl groups. And the principal fragmentations of ms spectrum were as follows : m/z 559 (M^+), 119 (Ph-N=C=O), 105 (Ph-C$\equiv$O$^+$). On the other



Scheme 4

band, ir spectrum, ms spectrum and elemental analysis of **4b** were very similar with those of **4a**. As we judged from 2D correlated spectrum (Figure 1), ^{13}C multiplicity analysis, and ^{1}H nmr spectrum of **4b**, **4b** was diastereomer of **4a**. The ^{1}H nmr peaks of H-10 (vinylic) and H-12 (methine) of compound (**4b**) appeared as singlets at δ 5.11 and δ 4.22. This fact proved that H-10 and H-12 of **4b** did not exist on the same plane because of the non-existence of W-coupling.

Proposed Mechanism

We propose the reaction mechanism for the formation of new heterocycles (**4a**) and (**4b**) as shown in Scheme 4. The key step of this reaction is 1,4-dipolar cycloaddition. First, the reaction of **2** with phenacyl bromide undergoes N-alkylation giving an intermediate (**7**). Then the intermediate (**7**) is disproportionated to give the intermediate (**9**) together with the unreacted starting material (**2**), forming quarternary ammonium salt (**8**) by loss of phenyl isocyanate. The carbanion of **9** attacks the bridgehead carbon of imidazothiazole, providing **10** which was converted into the 1,4-dipole by the attack of sulfide anion on the methine carbon. Subsequently the 1,4-dipolar cycloaddition reaction with phenyl isocyanate formed triazine ring. The C=N double bond of phenyl isocyanate can participate in polar cycloaddition reaction as the dienophile. Other reports has mentioned about similar type of this 1,4-dipolar cycloaddition.[11-15] The cycloadducts (**4a**) and (**4b**) were separated by column chromatography (silica gel, hexane/ethyl acetate=3:2).

EXPERIMENTALS

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. Ir spectra were recorded on a Analect FX-6160 FT-IR spectrophotometer using potassium bromide pellet. The following descriptive abbreviations were used; s=strong, m=medium and w=weak. ^{13}C Multiplicity and 2D correlated spectroscopies including ^{1}H nmr and ^{13}C nmr spectra were carried out with 200 MHz AM-200-SY and 300 MHz FT-NMR AC300P Brucker nmr spectrometer. Chemical shift values from tetramethylsilane were reported on the δ scale. Ms spectra were determined on a GC-MASS 5985B spectrometer. Elemental analyses were determined with a Perkin-Elmer Model 240C elemental analyzer.
Phenacyl bromide was purified by recrystallization from ethanol. Kieselgel 60 (70-230 mesh ASTM, MERCK) was used for column chromatography.

5,6-Dihydro-3-phenylimidazo[2,1-*b*]thiazole (**6**)[5-8]

A mixture of 2-mercaptoimidazoline (**5**, 10.21 g, 100.0 mmol) and phenacyl bromide (19.91 g, 100.0 mmol) in ethanol (100 ml) was refluxed for 5 h. Upon cooling, the hydrobromide salt was precipitated and the precipitate was collected by filtration, washed with ethanol. Then the hydrobromide salt was dissolved in hot water (50 ml) and neutralized with 10% sodium bicarbonate, providing white solid **6**. Filtration, washing with hot water and recrystallization with ethanol gave **6**. Yield 15.75 g (77.9%); mp 110.0-112.0 °C.

5,6-Dihydro-3-phenyl-7-[N-phenyl(carbamoyl)]imidazo[2,1-b]thiazolium-betaine (2)[1,9]

To a solution of 5,6-dihydro-3-phenylimidazo[2,1-b]thiazole (6, 2.02 g, 10.0 mmol) in acetone (50 ml) was added phenyl isocyanate (1.19 g, 10.0 mmol) dropwise at room temperature. While phenyl isocyanate was dropped, the white solid was formed. The mixture was stirred for 30 min. Then the precipitate was collected by filtration and dried to give the betaine 2 as white solid. Yield 2.62 g (81.5%); mp 196.0-197.0 °C; ir (KBr) 1640 (vs C=O), 1580 (s ArC=C) cm^{-1}; ^1H nmr (CF_3CO_2D) δ 7.68 (s, 5H, ArH), 7.47 (s, 5H, ArH), 7.18 (s, 1H, =CH), 5.01 (s, 4H, NCH_2CH_2N).

(12RS,13SR)- and (12SR,13SR)-12-Benzoyl-2,4-dioxo-1,3,9-triphenyl-6,7-dihydro-12H-thiazino[3',4';2,3]imidazo[1,2-a][1,3,5]triazines (4a and 4b)

To a refluxed solution of 5,6-dihydro-3-phenyl-7-[N-phenyl(carbamoyl)]imidazo[2,1-b]-thiazolium-betaine (2, 1.01 g, 3.15 mmol) in acetone (300 ml) was slowly added phenacyl bromide (0.30 g, 1.50 mmol). This was refluxed for 1 h and cooled to room temperature. Then the white salt (8) (mp > 250 °C) was removed by filtration. Removal of solvent of the filtrate and column chromatography (silica gel, hexane/ethyl acetate=3:2) gave 1,4-dipolar cycloadducts (4a) and (4b).

Isomer 4a

Yellow powder, yield 0.25 g (29.8%); mp 166.0-166.5 °C (decomp.); ir (KBr) 1720, 1680 (vs C=O), 1590 (s ArC=C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.46-3.59, 3.75-3.98 (m, 4H, NCH_2CH_2N), 4.78 (d, $J_{10,12}$=1.6 Hz, 1H, =CH), 5.60 (d, $J_{12,10}$=1.6 Hz, 1H, CH), 6.86-8.02 (m, 20H, ArH); ^{13}C nmr ($CDCl_3$) δ 189.2 (COPh), 151.7 (C-4), 149.7 (C-2), 87.4 (C-10), 83.9 (C-13), 50.4 (C-7), 43.7 (C-6), 41.4 (C-12); ms m/z 559 (M^+), 119 (C_6H_5-N=C=O), 105 (C_6H_5-C$\equiv$O$^+$); Anal. Calcd for $C_{33}H_{25}N_4O_3S$: C, 70.95; H, 4.69; N, 10.03. Found: C, 70.91; H, 4.67; N, 9.92.

Isomer 4b

Yellow powder, yield 0.22 g (26.2%); mp 156.5-157.5 °C (decomp.); ir (KBr) 1720, 1680 (vs C=O), 1590 (s ArC=C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.16-3.25, 3.65-3.71, 3.98-4.08, 4.13-4.22 (m, 4H, NCH_2CH_2N), 4.62 (s, 1H, CH), 5.11 (s, 1H, =CH), 7.02-8.25 (m, 20H, ArH); ^{13}C-nmr ($CDCl_3$) δ 195.6 (COPh), 151.6 (C-4), 149.2 (C-2), 97.3 (C-10), 84.1 (C-13), 50.4 (C-12), 49.9 (C-7), 42.7 (C-6); ms m/z 559 (M^+), 119 (C_6H_5-N=C=O), 105 (C_6H_5-C$\equiv$O$^+$); Anal. Calcd for $C_{33}H_{25}N_4O_3S$: C, 70.95; H, 4.69; N, 10.03. Found:C, 71.03; H, 4.73; N, 10.00.

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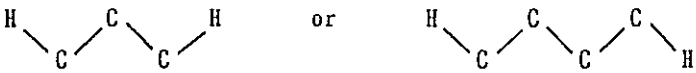
10. ^4J and ^5J couplings are observed in saturated compounds, in particular when the C-H and C-C bonds exist in the zig-zag arrangement of the form as follows:



^4J coupling occurs through an arrangement of atoms in the form of the M or W. If the coplanar arrangement of the bonds is destroyed, the magnitude of ^4J and ^5J rapidly decreases. See: H. Günter, 'NMR Spectroscopy,' Wiley-Interscience, New York, 1980, pp. 115-116.

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