Michael Addition of *N*-Isobutylidene-*t*-butylamine to Dimethyl Methoxymethylenemalonate and a New Synthesis of Some Fused Pyrazole Derivatives from the Adduct

Kunio Ito, Shogo Ihara and Shingo Miyajima*

Department of Applied Chemistry,
Faculty of Engineering, Toyo University,
Kujirai, Kawagoe-shi, Saitama 350, Japan

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N-Isobutylidenemethylamine reacted with dimethyl methoxymethylenemalonate to afford the *N*-alkylation product **3a** exclusively. Exchanging the *N*-substituent of the Schiff's base from methyl to *t*-butyl altered the course of the reaction, allowing Michael addition to take place predominantly. The Michael adduct **4c** on reaction with hydrazinoalkanols **6a,b**, **6c,d** and **6e** gave tetrahydropyrazolo[5,1-*b*]oxazoles **9a,b**, tetrahydropyrazolo[5,1-*b*][1,3]oxazines **9c,d** and hexahydropyrazolo[5,1-*b*][1,3]oxazepine **9e**, respectively.

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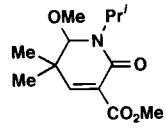
Previously we reported that *N*-alkylation of Schiff's bases with acetylenecarboxylic esters [1] was effectively hindered by the presence of the bulky *t*-butyl substituent on nitrogen and *C*-alkylation (Michael addtion) was allowed to take place predominantly [2]. In this paper we describe a similar effect of the *N*-substituent of the Schiff's base on the alkylation site in the reaction of isobutyraldehyde Schiff's bases with dimethyl methoxymethylenemalonate and the usefulness of the Michael adduct for the synthesis of some fused pyrazole derivatives.

When *N*-isobutylidenemethylamine (**1a**) was heated with dimethyl methoxymethylenemalonate (**2**) at 170°, a regioselective reaction took place; the sole material that could be isolated was the *N*-alkylation product, enamino ester **3a** (69%) (Scheme 1). This observation is in a marked contrast to a number of reports concerning *C*-alkylation of Schiff's bases with electrophilic olefins [3,4]. The alkylation site, however, depends on the size of the *N*-substituent of the Schiff's base. Thus, *N*-isobutylideneisopropylamine (**1b**) on heating with **2** at 170° gave a mixture of the *N*-alkylation product **3b**, Michael adduct **4b** and 2-oxopyridine-3-carboxylate **5**; these products were isolated by fractional distillation in 39, 14 and 12% yield, respectively. Compound **5** certainly arises from addition of methanol to the carbon-nitrogen double bond of **4b** followed by cyclization. *N*-Isobutylidene-*t*-butylamine (**1c**) when heated with **2** at 170° afforded, after fractional distillation, the Michael adduct **4c** in 66% yield, the *N*-alkylation product **3c** being obtained in only 5% yield.



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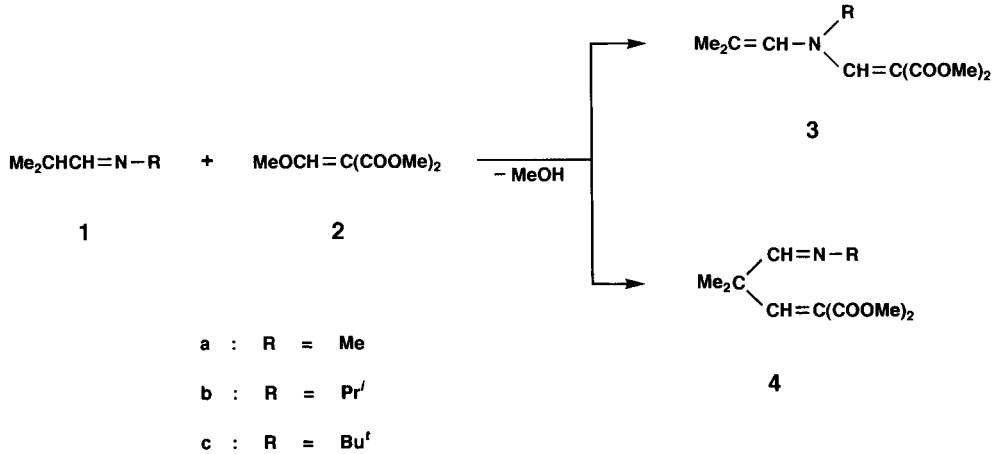
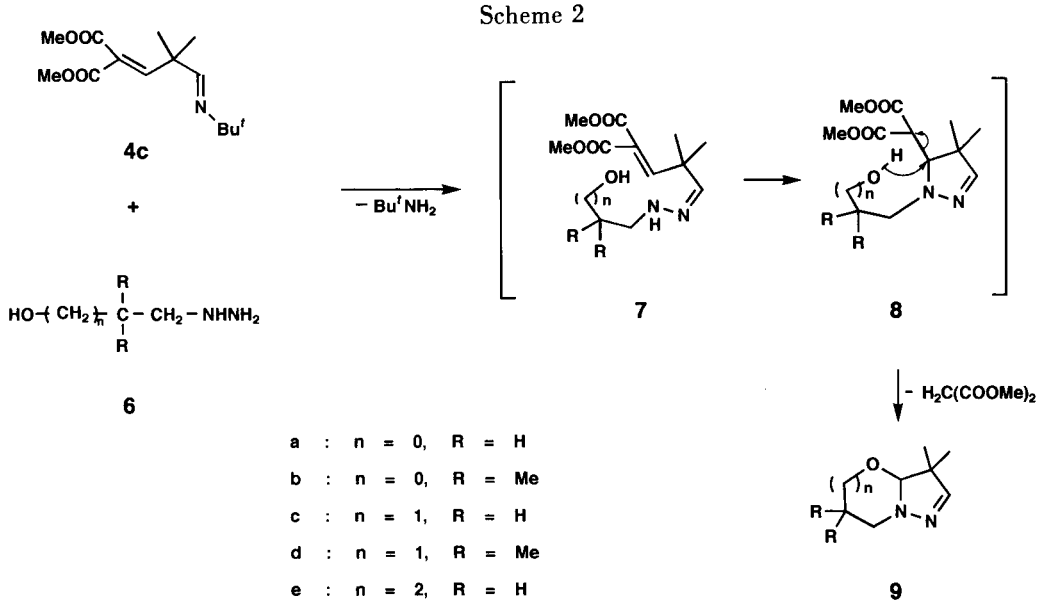
We have found that the Michale adduct **4c** reacts with hydrazinoalkanols to yield fused pyrazoles through a double cyclization process. Thus the adduct **4c**, when heated with 2-hydrazinoethanols **6a,b** in acetonitrile or methanol, produced tetrahydropyrazolo[5,1-*b*]oxazoles **9a,b** along with dimethyl malonate (Scheme 2). The adduct **4c** also yielded tetrahydropyrazolo[5,1-*b*][1,3]oxazines **9c,d** when allowed to react with 3-hydrazino-1-propanols **6c,d**. Furthermore, reaction of **4c** with 4-hydrazino-1-butanol (**6e**)

Scheme 1



Scheme 2



gave hexahydropyrazolo[5,1-*b*][1,3]oxazepine **9e**, a 5,7-ring system. The yields of **9** obtained were 67-75% when methanol was used as a solvent (Table 1). The structures of **9a-c** and **9e** were confirmed on the basis of their microanalyses and spectral data. Compound **9d** is described in the literature [5]; the ir and ^{1}H-nmr spectral characteristics recorded for this compound correspond to those of the material prepared in this study. The reaction

Table 1

Reaction of **4c** with **6**

Product	Method [a]	Yield %	
		9	Dimethyl malonate
9a	A	75	73
9a	B	55	54
9b	A	71	68
9c	A	74	70
9c	B	54	53
9d	A	67	63
9e	A	69	67
9e	B	60	58

[a] A: Solvent, methanol; temperature (time), reflux (8 hours).
B: Solvent, acetonitrile; temperature (time), reflux (15 hours).

pathway appears to involve initial cyclization of hydrazones **7** to pyrazoles **8** which subsequently cyclize to the bicyclic systems **9** with extrusion of dimethyl malonate.

Simple tetrahydropyrazolo[5,1-*b*]oxazoles and tetrahydropyrazolo[5,1-*b*][1,3]oxazines have rarely been reported; formation of **9d** with other products has been described in a reduction of 3,3,3′,3′-tetramethyl-1,1′-biazetidine-2,2′-dione [5]. Compound **9e** appears to be the first example of the pyrazolo[5,1-*b*][1,3]oxazepine ring system. The present method offers a facile synthetic route to these fused heterocyclic systems.

EXPERIMENTAL

The ir spectra were recorded on a Hitachi 260-50 spectrometer. The ^{1}H-nmr data were obtained with a JEOL JNM-FX90Q (90 MHz) or a JEOL JNM-EX400 (400 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured with a Shimadzu GCMS-QP1000 spectrometer at 70 eV of ionization energy. Microanalyses were performed at the Microanalysis Laboratory, Department of Chemistry, Faculty of Science, the University of Tokyo.

Schiff's bases **1a-c** were prepared according to the procedure of Tiollais [6]. Dimethyl methoxymethylenemalonate (**2**) was obtained by the method of Crombie *et al* [7]. 2-Hydrazinoethanol (**6a**) was commercially available and used without further purification. 3-Hydrazino-1-propanol (**6c**) and 4-hydrazino-1-butanol (**6e**) were obtained according to the procedure of Gever [8].

1-Hydrazino-2-methyl-2-propanol (**6b**).

To a stirred solution of sodium hydroxide (32.0 g, 0.80 mole) in hydrazine hydrate (200 g, 4.0 moles) heated at 95° was added 1-chloro-2-methyl-2-propanol (86.9 g, 0.80 mole) over a period of 30 minutes. Stirring and heating were continued for an additional 1 hour. The solution was concentrated *in vacuo* and the precipitated sodium chloride was removed by filtration. The precipitate was washed well with ethanol. The combined filtrates were distilled to give 56.7 g (68%) of **6b**, bp 72-74° (0.4 mm Hg); ir (liquid film): 3330 cm^{-1}; ^{1}H-nmr (90 MHz, deuteriochloroform): δ 1.23 (6H, s, CH_3), 2.75 (2H, s, CH_2), 3.66 (4H, br s, NH_2, NH and OH); ms: (CI) m/z 105 (MH^+).

Hydrogen oxalate, mp 147.5° dec.

Anal. Calcd. for $C_6H_{14}N_2O_5$: C, 37.11; H, 7.27; N, 14.43. Found: C, 37.14; H, 7.03; N, 14.65.

3-Hydrazino-2,2-dimethyl-1-propanol (**6d**).

To a stirred solution of potassium hydroxide (57.2 g, 1.02 moles) and 3-amino-2,2-dimethyl-1-propanol (206 g, 2.0 moles) in water (150 ml) heated at 95° was added a solution of hydroxylamine-*O*-sulfonic acid (56.6 g, 0.50 mole) in water (100 ml) over a period of 30 minutes. The solution was kept at 98° for 15 minutes, cooled and acidified with acetic acid (300 ml). The precipitated potassium sulfate was removed by filtration and the filtrate was warmed at 50° with benzaldehyde (53.1 g, 0.50 mole) for 15 minutes. The resulting emulsion was cooled and extracted with three 250-ml portions of ether. Oxalic acid dihydrate (63.0 g, 0.50 mole) and water (250 ml) were added to the combined ether solutions and the mixture was steam distilled. After the benzaldehyde had been removed, the residue was concentrated to dryness *in vacuo*. The residual solid was recrystallized from ethanol to give 45.7 g (44%) of the hydrogen oxalate of **6d**, mp 153° dec. The hydrogen oxalate (41.6 g, 0.20 mole) was added, in small portions with stirring, to an ice-cold solution of potassium hydroxide (44.9 g, 0.80 mole) in water (30 ml). After an additional 30 minutes of stirring, the mixture was extracted with eight 150-ml portions of ether. The ether extracts were dried over sodium sulfate, concentrated and distilled, giving 15.4 g (65%) of **6d**, bp 81.5-83° (0.5 mm Hg); ir (liquid film): 3320 cm^{-1}; ^{1}H-nmr (90 MHz, deuteriochloroform): δ 0.91 (6H, s, CH_3), 2.71 (2H, s, CH_2NH), 3.40 (2H, s, CH_2OH), 3.73 (4H, br s, NH_2, NH and OH); ms: (CI) m/z 119 (MH^+).

Hydrogen oxalate, mp 156° dec.

Anal. Calcd. for $C_7H_{16}N_2O_5$: C, 40.38; H, 7.75; N, 13.45. Found: C, 39.75; H, 7.41; N, 13.52.

Reaction of *N*-Isobutylidenemethylamine (**1a**) with Dimethyl Methoxymethylenemalonate (**2**).

A mixture of **1a** (34.1 g, 400 mmoles) and **2** (73.2 g, 420 mmoles) was heated with stirring at 170° for 1 hour in an autoclave. Distillation of the reaction mixture gave 62.4 g (69% based on **1a**) of **3a**.

Dimethyl *N*-Methyl-2-methyl-1-propenylaminomethylenemalonate (**3a**).

This compound was obtained as colorless prisms (hexane-ethyl acetate), mp 50-50.5°; bp 127-129° (0.25 mm Hg); ir (potassium bromide): 1715, 1693, 1590 cm^{-1}; ^{1}H-nmr (90 MHz, deuteriochloroform): δ 1.63 (3H, d, J = 1.1 Hz, $CH_3C=C$), 1.70 (3H, d, J = 1.3 Hz, $CH_3C=C$), 3.02 (3H, br s, NCH_3), 3.70 and 3.72 (each 3H, s, CO_2CH_3), 5.73 (1H, m, $(CH_3)_2C=CH$), 7.48 (1H, s, $CH=C(CO_2CH_3)_2$); ms: m/z 227 (M^+).

Anal. Calcd. for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.98; H, 7.40; N, 6.17.

Reaction of *N*-Isobutylideneisopropylamine (**1b**) with Dimethyl Methoxymethylenemalonate (**2**).

A mixture of **1b** (45.3 g, 400 mmoles) and **2** (73.2 g, 420 mmoles) was heated with stirring at 170° for 3 hours in an autoclave. Fractional distillation of the reaction mixture through a 50-cm spinning band column gave **3b** (40.3 g, 39% based on **1b**), **4b** (14.7 g, 14%) and **5** (12.1 g, 12%).

Dimethyl *N*-Isopropyl-2-methyl-1-propenylaminomethylenemalonate (**3b**).

This compound was obtained as colorless prisms (hexane-ethyl acetate), mp 39-40°; bp 126-129° (0.2 mm Hg); ir (potassium bromide): 1719, 1689, 1581 cm^{-1}; ^{1}H-nmr (90 MHz, deuteriochloroform): δ 1.22 (6H, d, J = 6.6 Hz, $CH(CH_3)_2$), 1.53 (3H, d, J = 1.3 Hz, $CH_3C=C$), 1.72 (3H, d, J = 1.5 Hz, $CH_3C=C$), 3.64 (1H, septet, J = 6.6 Hz, $CH(CH_3)_2$), 3.67 and 3.68 (each 3H, s, CO_2CH_3), 5.59 (1H, m, $(CH_3)_2C=CH$), 7.57 (1H, s, $CH=C(CO_2CH_3)_2$); ms: m/z 255 (M^+).

Anal. Calcd. for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.88; H, 8.32; N, 5.57.

Dimethyl 3-Isopropylimino-2,2-dimethylpropylidenemalonate (**4b**).

This compound was obtained as a colorless liquid, bp 84-87° (0.2 mm Hg); ir (liquid film): 1734, 1663, 1640 cm^{-1}; ^{1}H-nmr (90 MHz, deuteriochloroform): δ 1.13 (6H, d, J = 6.4 Hz, $CH(CH_3)_2$), 1.27 (6H, s, $C(CH_3)_2$), 3.30 (1H, septet, J = 6.4 Hz, $CH(CH_3)_2$), 3.78 and 3.80 (each 3H, s, CO_2CH_3), 7.06 (1H, s, CH = C), 7.55 (1H, s, CH = N); ms: (CI) m/z 256 (MH^+).

Anal. Calcd. for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.87; H, 8.33; N, 5.46.

Methyl 1-Isopropyl-6-methoxy-5,5-dimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate (**5**).

This compound was obtained as a colorless liquid, bp 147-149° (0.3 mm Hg); ir (liquid film): 1740, 1666, 1630 cm^{-1}; ^{1}H-nmr (90 MHz, deuteriochloroform): δ 1.14 and 1.27 (each 3H, s, CH_3), 1.28 and 1.38 (each 3H, d, J = 6.8 Hz, $CH(CH_3)_2$), 3.35 (3H, s, OCH_3), 3.80 (3H, s, CO_2CH_3), 4.28 (1H, d, J = 2.1 Hz, $CHOCH_3$), 4.56 (1H, septet, J = 6.8 Hz, $CH(CH_3)_2$), 7.03 (1H, d, J = 2.1 Hz, CH = C); ms: (CI) m/z 256 (MH^+).

Anal. Calcd. for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.03; H, 8.27; N, 5.53.

Reaction of *N*-Isobutylidene-*t*-butylamine (**1c**) with Dimethyl Methoxymethylenemalonate (**2**).

A mixture of **1c** (50.9 g, 400 mmoles) and **2** (73.2 g, 420 mmoles) was heated with stirring at 170° for 5 hours in an autoclave. Fractional distillation of the reaction mixture through a 50-cm spinning band column gave **3c** (5.80 g, 5% based on **1c**) and **4c** (70.9 g, 66%).

Dimethyl *N*-(*t*-Butyl)-2-methyl-1-propenylaminomethylenemalonate (**3c**).

This compound was obtained as a colorless liquid, bp 138-140° (0.9 mm Hg); ir (liquid film): 1722, 1690, 1580 cm^{-1}; ^{1}H-nmr (90 MHz, deuteriochloroform): δ 1.33 (9H, s, $C(CH_3)_3$), 1.49 and 1.70 (each 3H, d, J = 1.5 Hz, $CH_3C=C$), 3.67 and 3.69 (each 3H, s, CO_2CH_3), 5.65 (1H, septet, J = 1.5 Hz, $(CH_3)_2C=CH$), 7.81 (1H, s, $CH=C(CO_2CH_3)_2$); ms: m/z 269 (M^+).

Anal. Calcd. for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.15; H, 8.41; N, 5.42.

Dimethyl 3-(*t*-Butylimino)-2,2-dimethylpropylidenemalonate (**4c**).

This compound was obtained as a colorless liquid, bp 107-110° (0.6 mm Hg); ir (liquid film): 1732, 1668, 1640 cm^{-1}; ^{1}H-nmr (90 MHz, deuteriochloroform): δ 1.15 (9H, s, $C(CH_3)_3$), 1.25 (6H, s, $C(CH_3)_2$), 3.78 and 3.80 (each 3H, s, CO_2CH_3), 7.13 (1H, s, CH = C), 7.47 (1H, s, CH = N); ms: (CI) m/z 270 (MH^+).

Anal. Calcd. for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.19; H, 8.44; N, 5.25.

General Procedure for the Reaction of Michael Adduct **4c** with Hydrazinoalkanols **6**.

Method A.

To a refluxing solution of **4c** (70.0 mmoles) in methanol (150 ml) was added a solution of **6** (73.5 mmoles) in methanol (50 ml) over a period of 30 minutes. Refluxing was continued for an additional 8 hours. The solvent was removed *in vacuo* and the residue was distilled to give a mixture of dimethyl malonate and **9**. The mixture was dissolved in ether (30 ml). To the solution cooled in an ice bath was added dropwise with stirring concentrated hydrochloric acid (10 ml). The layers were separated and the aqueous layer was extracted with two 30-ml portions of ether. The combined ether solutions were dried over sodium sulfate and evaporated, leaving dimethyl malonate. To the aqueous layer cooled in an ice bath was added dropwise with stirring aqueous 12 *M* sodium hydroxide (11 ml). The mixture was extracted with three 30-ml portions of ether. The ether extracts were dried over sodium sulfate and evaporated, leaving **9**.

Method B.

To a refluxing solution of **4c** (70.0 mmoles) in acetonitrile (70 ml) was added a solution of **6** (73.5 mmoles) in acetonitrile (30 ml) over a period of 30 minutes. Refluxing was continued for an additional 15 hours. The reaction mixture was worked up as described above.

The purity of **9** obtained was higher than 97%, as determined by gc analysis with a Hitachi 263-30 instrument on an SE-30 column. The yields listed in Table 1 are based on **4c**.

7,7-Dimethyl-2,3,7,7a-tetrahydropyrazolo[5,1-*b*]oxazole (**9a**).

This compound was obtained as a colorless liquid, bp 64-65° (6.5 mm Hg); ir (liquid film): 3045, 1593 cm^{-1}; ^{1}H-nmr (400 MHz, deuteriochloroform): δ 1.17 and 1.23 (each 3H, s, CH_3), 3.31, 3.50, 3.78 and 3.85 (each 1H, m, CH_2), 4.56 (1H, s, CH), 6.70 (1H, d, J = 1.1 Hz, CH=N); ms: m/z 140 (M^+).

Anal. Calcd. for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.70; H, 8.58; N, 20.08.

2,2,7,7-Tetramethyl-2,3,7,7a-tetrahydropyrazolo[5,1-*b*]oxazole (**9b**).

This compound was obtained as a colorless liquid, bp 68-69° (6 mm Hg); ir (liquid film): 3050, 1595 cm^{-1}; ^{1}H-nmr (400 MHz, deuteriochloroform): δ 1.15, 1.19, 1.23 and 1.28 (each 3H, s, CH_3), 3.21 (1H, dd, J = 12.7, 1.3 Hz, CH_2), 3.67 (1H, d, J = 12.7 Hz, CH_2), 4.66 (1H, s, CH), 6.57 (1H, d, J = 1.3 Hz, CH=N); ms: m/z 168 (M^+).

Anal. Calcd. for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 63.69; H, 9.60; N, 16.26.

3,3-Dimethyl-3,3a,6,7-tetrahydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine (**9c**).

This compound was obtained as a colorless liquid, bp 71-72° (5.5 mm Hg); ir (liquid film): 3055, 1579 cm^{-1}; ^{1}H-nmr (400 MHz, deuteriochloroform): δ 1.07 and 1.17 (each 3H, s, CH_3), 1.32, 1.95, 3.42, 3.64, 3.86 and 3.97 (each 1H, m, CH_2), 4.35 (1H, s, CH), 6.55 (1H, d, J = 0.9 Hz, CH=N); ms: m/z 154 (M^+).

Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.04; H, 9.09; N, 18.02.

3,3,6,6-Tetramethyl-3,3a,6,7-tetrahydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine (**9d**).

This compound was obtained as colorless prisms (hexane), mp 43-44.5° (lit [5], 32°), bp 84-85° (6.5 mm Hg); ir (liquid film): (*cf.* lit [5]) 3055, 1580 cm^{-1}; ^{1}H-nmr (400 MHz, deuteriochloroform): (*cf.* lit [5]) δ 0.74, 1.02, 1.07 and 1.19 (each 3H, s, CH_3), 3.13 (1H, d, J = 14.7 Hz, CH_2), 3.32 (1H, d, J = 11.2 Hz, CH_2), 3.45-3.55 (2H, m, CH_2), 4.25 (1H, s, CH), 6.40 (1H, d, J = 0.9 Hz, CH=N); ms: m/z 182 (M^+).

3,3-Dimethyl-3,3a,5,6,7,8-hexahydropyrazolo[5,1-*b*][1,3]oxazepine (**9e**).

This compound was obtained as a colorless liquid, bp 82-83° (5 mm Hg); ir (liquid film): 3055, 1585, 1572 cm^{-1}; ^{1}H-nmr (400 MHz, deuteriochloroform): δ 1.12 and 1.14 (each 3H, s, CH_3), 1.60-1.95 (4H, m, CH_2), 3.35-3.65 (4H, m, CH_2), 4.41 (1H, s, CH), 6.52 (1H, s, CH=N); ms: m/z 168 (M^+).

Anal. Calcd. for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 63.96; H, 9.33; N, 16.70.

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