EJ52-1998-183

Journal of the Chinese Chemical Society, **1998**, *45*, 183-188

Thermal Reactions of *N*-Acyl Phenylcyclobutylimines

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Flash vacuum thermolysis of the parent and phenyl substituted *N*-acyl cyclobutylimines **3** was under investigation. At 500 °C and 0.01 torr, **3d** with phenyl group on C-1 and **3e** with phenyl group on C-2 of cyclobutane ring underwent ring expansion processes to produce *N*-acyl 1,2,3,4-tetrahydropyridines **8d** and **8e**. Meanwhile the parent *N*-acyl cyclobutylimines **3a** together with the phenyl group on C-3 (**3c**) and imine carbon (**3b**) proceeded a hydrogen shift reaction to afford *N*-acylaminomethylenecyclobutanes **8a-c**. In addition, cycloreversion competed with ring expansion or hydrogen shift in all cases.

INTRODUCTION

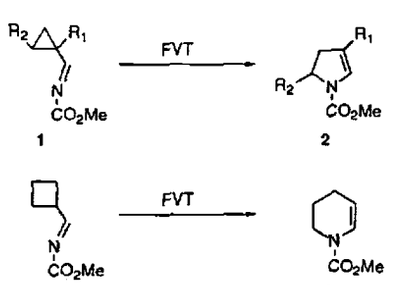
The thermal ring expansion of vinylcyclobutanes yielded cyclohexenes. Moreover, cycloreversion to alkenes competed with this rearrangement.[1-10] The free energy of activation energies ($\Delta G^{\ddagger}$, 286 °C) for the ring expansion (46.6 kcal/mol) and for cycloreversion (46.1 kcal/mol) were comparable.[1,2] At high reaction temperature, the population of cycloreversion products would be raised due to substantial increase of the entropy factor. Not only the temperature but also the solvent and the structure of the vinylcyclobutanes affected the ratio of ring expansion and cycloreversion.

Six-membered-nitrogen containing heterocycles are important intermediates in alkaloid synthesis. They can be synthesized by the Diels-Alder reaction of *N*-acyl 1-azadienes and alkene[11-13] as well as dienes and imines.[14,15] In connection with our earlier work on the ring expansion of *N*-acyl cyclopropylimines **1** to 2-pyrrolines **2**,[16] the analogous reaction of the *N*-acyl cyclobutylimine **3a** as a synthetic route to 1,2,3,4-tetrahydropyridine **4** is now investigated (Scheme I). The acyl group on the imine nitrogen serves to lower the activation energy of the process due to the formation of the amide functionality in the product and to stabilize the enamine derivative because endocyclic enamine without substituents on the double bond are extremely reactive.[17] We describe herein the thermal reaction of *N*-acyl cyclobutylimines and the substituent effect of the phenyl group.

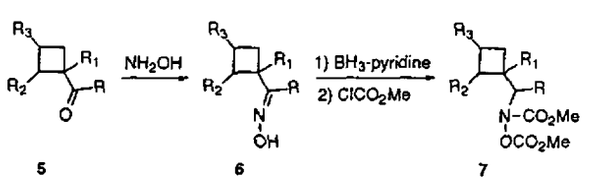
RESULTS AND DISCUSSION

N-acyl cyclobutylimines **3** were generated *via* flash vacuum thermolysis (FVT) of *N,O*-bis(methoxycarbonyl)cyclobutylhydroxylamines **7** by the thermal elimination of methanol and carbon dioxide. This FVT technique would be used to both prepare the reactive *N*-acyl imines and to induce the subsequently thermal reactions (Scheme III). The diacylated hydroxylamines **7**, were accessible from corresponding cyclobutanecarboxaldehydes **5a**, **5c-e** or ketone **5b**. Treatment of the aldehydes or ketone **5** with hydroxylamine gave the oximes **6**. Reduction with borane-pyridine complex followed by acylation with methyl chloroformate afforded the desired cyclobutylimine precursors **7**.

Scheme I



Scheme II

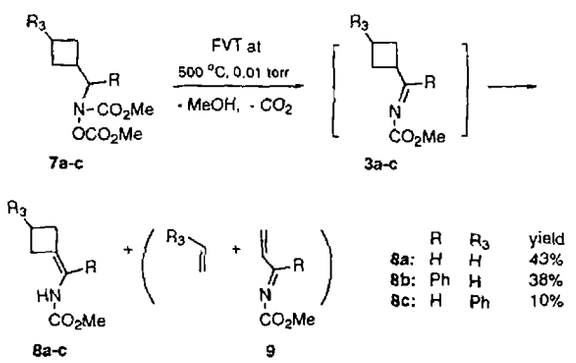


	R	R_1	R_2	R_3
a:	H	H	H	H
b:	Ph	H	H	H
c:	H	H	H	Ph
d:	H	Ph	H	H
e:	H	H	Ph	H

Dedicated to Professor Hsien-Ju Tien on the occasion of his 65th birthday.

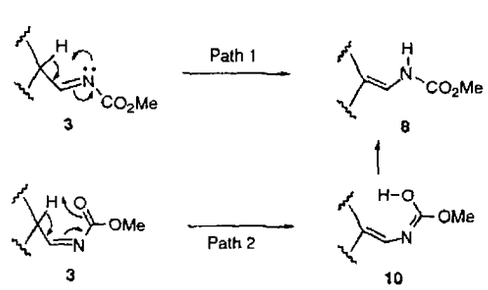
Then, the parent molecule **7a** was sent to FVT tube at 500 °C and 0.01 torr. According to GC-Ms analysis, none of the ring expansion product was formed, instead, an enamide, (*N*-methoxycarbonylamino)methylenecyclobutane (**8a**), was isolated in 43% yield. Compound **8a** is the product of hydrogen shift from the position α to the imine. Similar results were obtained for **7b**, phenyl substituent on imine carbon, and **7c**, phenyl substituent on C-3 of the cyclobutane ring. The FVT of **7b** and **7c** afforded enamides **8b** and **8c** in 38% and 10% yield, respectively.

Scheme III



The hydrogen shift reaction of the *N*-acyl imines **3a-c** to more stable enamides **8a-c** occurs in the gas phase unimolecularly. Although this isomerization is a known transformation,[18] the actual mechanism is obscure. The thermally forbidden suprafacial 1,3-hydrogen shift pathway[19] can be avoided by using the orbital involved with nitrogen lone pair electrons (Scheme IV, Path 1). Alternatively, a 1,5-hydrogen shift involving the carbonyl π bond could occur to give, initially, the imide **10** followed by tautomerization to the enamide **8** (Scheme IV, Path 2). This kind of reaction is not found in the rearrangement of vinylcyclobutane, suggesting that nitrogen or acyl substitution plays an important role in the hydrogen shift reaction.

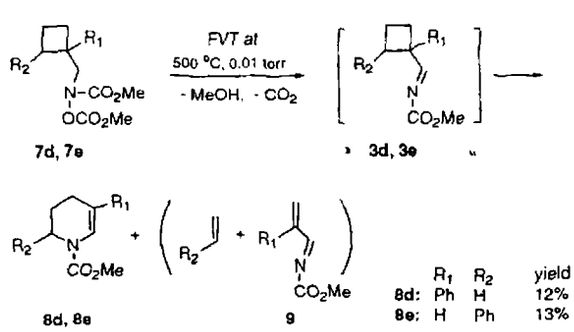
Scheme IV



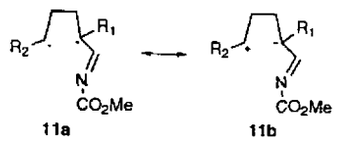
In addition, styrene, one of the cycloreversion products, was also isolated in 44% yield for the FVT of **7c**. However, we have not been able to identify unequivocally the second fragment, *N*-acyl 1-azadiene **9**, of the cycloreversion process. The azadiene **9** which belongs to the unstable *N*-acyl imine, probably decomposed or polymerized into unpurified compounds under high temperature. Therefore, the phenyl group on C-3 of the cyclobutane ring caused the thermal cycloreversion prior to the hydrogen shift. Even though ethene was not detected either because of the volatility, we believe the cycloreversion reaction in the FVT of **7a** and **7b** still took place. Based on the above results, we conclude that ring expansion of *N*-acyl cyclobutylimines **3a-c** can not compete with hydrogen shift and cycloreversion.

We have observed that the ring expansion reaction can be accelerated by suitable substituents.[16] For example, placement of a phenyl or an acyl substituent on the cyclopropane ring resulted in successful ring expansion. Consequently, the phenyl group substituted on C-1 or C-2 of the cyclobutane ling was prepared. Evaporation of **7d** with the phenyl group on C-1 and **7e** with the phenyl group on C-2 through the FVT tube produced the ring expansion products, *N*-acyl 1,2,3,4-tetrahydropyridines **8d** and **8e**, in 12% and 13% yield (Scheme V). In the latter case, styrene was found in 38% yield, suggesting that cycloreversion proceeded preferably to ring expansion. The phenyl substituent on C-1 (**7d**) apparently suppressed the occurrence of hydrogen shift. Furthermore, no hydrogen shift product was detected after the FVT of **7e** indicated that phenyl group on migrating C-C σ bond has the ability to stabilize the formation of the diradical intermediate **11a**, which may have a somewhat zwitterionic character **11b** because of the presence of the nitrogen heteroatom (Scheme VI). This intermediate **11** underwent ring expansion or cycloreversion reactions immediately. Although the mechanism of all carbon vinylcyclobutane has been the focus of a number of studies, disagreement persists regarding the mechanistic routes (concerted or step-

Scheme V



Scheme VI



wise) as well as the best electronic description of the transition state. We believe the reaction mechanism may be sensitive to substituent.

In summary, the products for the FVT of *N*-acyl cyclobutylimines **3** were formed by three pathways: (1) cycloreversion to *N*-acyl 1-azadienes and alkenes; (2) hydrogen shift to *N*-acylaminomethylenecyclobutanes; (3) ring expansion to *N*-acyl 1,2,3,4-tetrahydropyridines. The phenyl group on C-1 or C-2 of cyclobutane ring, e.g. **3d** and **3e**, did accelerate the ring expansion reaction whereas the parent *N*-acyl cyclobutylimine **3a** and the phenyl group on C-3 (**3c**) or imine carbon (**3d**) proceeded the reactions of hydrogen shift. The isolation of styrene supported that cycloreversion would accompany ring expansion or hydrogen shift.

EXPERIMENT SECTION

General

IR spectra were recorded as either thin films or solid dispersions in KBr. NMR spectra were recorded on 200 or 400 MHz spectrometers; all chemical shifts are reported in ppm from tetramethylsilane as an internal standard. MS spectra were recorded on a direct inlet system. Column chromatography was carried out using silica gel (70-230 mesh). Cyclobutyl phenyl ketone (**5b**) was obtained commercially (Aldrich Chemical Co.). 1-Phenylcyclobutanecarboxaldehyde (**5d**) was prepared from 1-phenylcyclobutanecarbonitrile[20] by the DIBAL-H reduction.[21] Cyclobutanecarboxaldehydes **5a**, **5c** and **5e** were prepared from the corresponding cyclobutanecarboxylic acid by the reduction with lithium aluminum hydride[22] followed by the oxidation with pyridinium chlorochromate;[23] 2-phenylcyclobutanecarboxylic acid[24] and 3-phenylcyclobutanecarboxylic acid[25] were yielded using procedures similar to those previously described in the literature.

General Procedure for the Preparation of Oximes

Sodium carbonate (0.80 g, 7.5 mmol) was added to a solution of hydroxylamine hydrochloride (1.04 g, 15 mmol) in a minimum amount of water. The cyclobutanecarboxaldehyde **5a** or **5c-e** or cyclobutyl phenyl ketone (**5b**) (10 mmol) in 3 mL of 95% ethyl alcohol was added to the aqueous solution and stirred at room temperature for 2 h. The resulting mixture was extracted with ethyl acetate. The combined extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Pure oxime **6** was purified by column chromatography over silica gel using EtOAc/hexane (1:5) as eluent. Generally this procedure produced an isomeric mixture of *syn* and *anti* oximes. This *syn* and *anti* mixture was not separated and was used for the further reaction.

Cyclobutanecarboxaldoxime (6a)

Yield 92%; IR (film) 3250, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8-2.4 (m, 6H), 3.0-3.2 (m, 1H of *anti* isomer), 3.6-3.8 (m, 1H of *syn* isomer), 6.81 (d, 1H of *syn* isomer, J = 6 Hz), 7.47 (d, 1H of *anti* isomer, J = 7 Hz), 8.0-10.0 (br s, 1H); MS *m/z* (relative intensity) 98 (5, $[M-H]^+$), 82 (60), 71 (100), 67 (43), 55 (74); HRMS Calcd for C_5H_8NO 98.0606, $[M^+-H]$. Found 98.0606.

Cyclobutyl Phenyl Ketoxime (6b)

Yield 90%; IR (film) 3240, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7-2.4 (m, 6H), 3.46 and 3.91 (q', 1H of *syn* and *anti* isomers, J = 9 Hz), 7.3-7.5 (m, 5H), 9.0-10.0 (br s, 1H); MS *m/z* (relative intensity) 175 (10, M^+), 158 (55), 143 (28), 130 (43), 104 (100), 77 (57); HRMS Calcd for $C_{11}H_{13}NO$ 175.0997, $[M]^+$. Found 175.0996.

3-Phenylcyclobutanecarboxaldoxime (6c)

Yield 86%; IR (film) 3252, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1-3.8 (m, 6H), 6.85, 7.23, 7.54 and 7.79 (d, 1H of four isomers, J = 6 Hz), 7.2-7.5 (m, 5H), 7.8-9.8 (br s, 1H); MS *m/z* (relative intensity) 175 (7, M^+), 158 (9), 115 (7), 104 (100), 91 (14), 78 (16), 77 (12); HRMS Calcd for $C_{11}H_{13}NO$ 175.0997, $[M]^+$. Found 175.0994.

1-Phenylcyclobutanecarboxaldoxime (6d)

Yield 86%; IR (film) 3260, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.9-2.8 (m, 6H), 7.1-7.5 (m, 5H), 7.63 (s, 1H), 8.5-9.5 (br s, 1H); MS *m/z* (relative intensity) 175 (10, M^+), 158 (55), 146 (46), 130 (100), 129 (100), 115 (41), 103 (60), 91 (84), 77 (73); ^{13}C NMR ($CDCl_3$) δ 16.1, 31.4, 47.8, 125.9, 126.4, 128.4, 145.0, 155.9; HRMS Calcd for $C_{11}H_{13}NO$ 175.0997, $[M]^+$. Found 175.0996.

2-Phenylcyclobutanecarboxaldoxime (6e)

Yield 84%; IR (film) 3250, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0-2.6 (m, 4H), 3.1-4.1 (m, 2H), 6.63, 6.87 and 7.56 (d, 1H of three isomers, J = 7 Hz), 7.1-7.5 (m, 5H), 7.5-9.0 (br s, 1H); MS *m/z* (relative intensity) 175 (2, M^+), 158

(4), 129 (6), 104 (100), 91 (14), 78 (13); HRMS Calcd for $C_{11}H_{13}NO$ 175.0997, $[M]^+$. Found 175.0998.

General Procedure for the Preparation of Diacylated Hydroxylamines

A mixture of cyclobutyl oxime **6** (5 mmol) and borane-pyridine (0.93 g, 10 mmol) in 8 mL of 95% ethanol was maintained at 0 °C. Then, 7.5 mL of 10% HCl solution was added over a 20 min period with vigorous mixing, and the mixture was stirred for 20 min at rt. Next, the solution was cooled to 0 °C, and NaOH pellets were carefully added until pH > 10. The mixture was extracted with etner. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to a volume of 50 mL. Triethylamine (1.01 g, 10 mmol), then methyl chloroformate (0.95 g, 10 mmol) were added dropwise to the ether solution at 0 °C. After stirring at rt for 2 h, the solution was acidified with 10% HCl solution. The ether layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography over silica gel eluting witn EtOAc/hexane (1:5) to yield diacylated hydroxylamine **7** as a colorless liquid.

***N,O*-Bis(methoxycarbonyl)-*N*-(cyclobutylmethyl)hydroxylamine (7a)**

Yield 59%; IR (film) 1794, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7-2.1 (m, 6H), 2.63 (septet, 1H, J = 7 Hz), 3.66 (d, 2H, J = 7 Hz), 3.77 (s, 3H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 18.2, 25.9, 33.1, 53.4, 55.4, 55.9, 154.6, 156.1; MS *m/z* (relative intensity) 217 (5, M^+), 173 (15), 118 (71), 105 (60), 91 (30), 59 (100); HRMS Calcd for $C_9H_{15}NO_5$ 217.0950, $[M]^+$. Found 217.0950.

***N,O*-Bis(methoxycarbonyl)-*N*-[(phenyl)(cyclopropyl)methyl]hydroxylamine (7b)**

Yield 60%; IR (film) 1800, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6-2.3 (m, 6H), 2.8-3.3 (br s, 1H), 3.74 (s, 3H), 3.82 (br s, 3H), 5.14 (br d, 2H, J = 11 Hz), 7.2-7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.5, 25.8, 26.6, 35.5, 53.6, 55.9, 69.0, 128.0, 128.3, 128.4, 136.8, 154.5, 156.6; MS *m/z* (relative intensity) 293 (1, M^+), 238 (79), 145 (78), 104 (57), 91 (100), 77 (29), 59 (32). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.56; H, 6.61; N, 4.76.

***N,O*-Bis(methoxycarbonyl)-*N*-[(3-phenylcyclopropyl)methyl]hydroxylamine (7c)**

Yield 74%; IR (film) 1797, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8-2.7 (m, 5H), 2.3-3.7 (m, 1H), 3.69 and 3.88 (d, 2H of *cis* and *trans* isomers, J = 7 Hz), 3.79 and 3.82 (s, 3H of *cis* and *trans* isomers), 3.92 (s, 3H), 7.1-7.4 (m, 5H); MS *m/z* (relative intensity) 293 (10, M^+), 218 (7), 131 (15), 104 (100), 91 (25), 77 (10), 59 (26). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.19; H, 6.73; N, 4.87.

***N,O*-Bis(methoxycarbonyl)-*N*-[(1-phenylcyclopropyl)methyl]hydroxylamine (7d)**

Yield 64%; IR (film) 1790, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8-2.5 (m, 6H), 3.53 (s, 3H), 3.74 (s, 3H), 3.99 (s, 2H), 7.1-7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.4, 30.7, 46.0, 52.9, 55.3, 59.6, 125.3, 125.6, 127.4, 146.5, 153.8, 155.6; MS *m/z* (relative intensity) 293 (2, M^+), 144 (48), 131 (100), 103 (49), 91 (21), 77 (3), 59 (8). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.47; H, 6.56; N, 4.86.

***N,O*-Bis(methoxycarbonyl)-*N*-[(2-phenylcyclopropyl)methyl]hydroxylamine (7e)**

Yield 55%; IR (film) 1794, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7-2.4 (m, 5H), 2.6-3.1 (m, 1H), 3.2-3.8 (m, 2H), 3.68 and 3.73 (s, 3H of *cis* and *trans* isomers), 3.85 and 3.87 (s, 3H of *cis* and *trans* isomers), 7.2-7.4 (m, 5H); MS *m/z* (relative intensity) 293 (4, M^+), 144 (6), 104 (100), 91 (17), 77 (7), 59 (20). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.57; H, 6.46; N, 4.88.

General Method for FVT

Diacylated hydroxylamine **7** (10-300 mg) was first frozen in a liquid nitrogen bath, and a vacuum was applied. Once the vacuum (0.01 torr) had been established, the heater was turned on. The temperature of the hot tube was regulated by a temperature controller. When the set temperature reached 500 °C, the receiver was placed in a liquid nitrogen bath. The reactant was thawed and evaporated through the hot tube. The product was condensed and collected in the receiver at liquid nitrogen temperature and washed out with diethyl ether. The crude products were purified by column chromatography over silica gel using EtOAc/hexane (1:8) as eluent to afford enamide **8**.

(*N*-Methoxycarbonylamino)methylenecyclobutane (8a)

Yield 43%; IR (film) 3320, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (*q'*, 2H, J = 8 Hz), 2.5-2.8 (m, 4H), 3.70 (s, 3H), 5.5-6.0 (br s, 1H), 6.1-6.4 (br s, 1H of two rotamers); ^{13}C NMR ($CDCl_3$) δ 17.6, 27.1, 28.1, 52.3, 114.8, 121.2, 154.0; MS *m/z* (relative intensity) 141 (11, M^+), 118 (43), 101 (39), 82 (84), 59 (100); HRMS Calcd for $C_7H_{11}NO_2$ 141.0790, $[M^+]$. Found 141.0792.

(*N*-Methoxycarbonylamino)benzylidenecyclobutane (8b)

Yield 38%; IR (film) 3280, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (qintet, 2H, J = 8 Hz), 2.7-2.9 (br t, 2H, J = 8 Hz), 2.9-3.1 (br t, 2H, J = 8 Hz), 3.67 (s, 3H), 5.7-6.0 (br s, 1H), 7.2-7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.1, 30.0, 31.1, 52.3, 124.9, 126.0, 126.8, 128.1, 136.7, 138.5, 155.3; MS *m/z* (relative intensity) 217 (29, M^+), 202 (15), 189 (58), 174 (69), 158 (53), 142 (92), 129 (57), 115 (40), 103 (100), 91 (28), 77 (89), 59 (24); HRMS Calcd for $C_{13}H_{15}NO_2$ 217.1103, [M^+]. Found 217.1102.

3-Phenyl-1-(*N*-Methoxycarbonylamino)methylenecyclobutane (8c)

Yield 10%; IR (film) 3324, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0-3.2 (m, 4H), 3.62 (q', 1H, J = 8 Hz), 3.73 (s, 3H), 4.8-5.5 (br s, 1H), 5.9-6.0 (br m, 1H), 6.3-6.4 (br s, 1H of two rotamers), 7.2-7.4 (m, 5H); MS *m/z* (relative intensity) 217 (8, M^+), 158 (19), 142 (100), 129 (18), 115 (16), 104 (81), 91 (26), 77 (19), 59 (19); HRMS Calcd for $C_{13}H_{15}NO_2$ 217.1103, [M^+]. Found 217.1101.

***N*-Methoxycarbonyl-5-Phenyl-1,2,3,4-tetrahydropyridine (8d)**

Yield 12%; IR (film) 1703, 1644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.9-2.1 (m, 2H), 2.4-2.5 (m, 2H), 3.6-3.8 (m, 2H), 3.81 (s, 3H), 7.2-7.5 (m, 6H, C_6H_5 and CH=C); ^{13}C NMR ($CDCl_3$) δ 21.6, 24.0, 41.9, 53.0, 117.6, 122.5, 124.4, 125.6, 126.9, 140.1, 154.1; MS *m/z* (relative intensity) 217 (100, M^+), 202 (32), 158 (12), 129 (24), 115 (19), 103 (11), 91 (42), 77 (13), 59 (13); HRMS Calcd for $C_{13}H_{15}NO_2$ 217.1103, [M^+]. Found 217.1102.

***N*-Methoxycarbonyl-2-Phenyl-1,2,3,4-tetrahydropyridine (8e)**

Yield 13%; IR (film) 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6-2.2 (m, 4H), 3.65 and 3.77 (br s, 3H of two rotamers), 4.9-5.1 (br m, 1H), 5.3-5.5 (br s, 1H of two rotamers), 6.9-7.1 (br m, 1H), 7.1-7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.1, 27.5, 53.0, 54.3, 106.4, 124.9, 125.4, 126.8, 128.3, 141.5, 154.0; MS *m/z* (relative intensity) 217 (54, M^+), 158 (22), 142 (58), 104 (100), 91 (27), 77 (20), 59 (14); HRMS Calcd for $C_{13}H_{15}NO_2$ 217.1103, [M^+]. Found 217.1102.

ACKNOWLEDGMENT

We would like to thank the National Science Council, R.O.C. (NSC 86-2113-M-006-012) for support of this research.

Received September 5, 1997.

Key Words

Flash vacuum thermolysis; Cycloreversion; Hydrogen shift; Ring expansion; *N*-Acyl cyclobutylimine; 1,2,3,4-Tetrahydropyridine; Aminomethylenecyclobutane.

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