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COPPER CATALYZED CYCLOPROPANATION OF 1,2,3,4-TETRAHYDROPYRIDIN-2-ONES WITH TRIMETHYLSILYLDIAZOMETHANE: A FACILE AND SELECTIVE SYNTHESIS OF 2-AZA-3-OXOBICYCLO[4.1.0]HEPTANES

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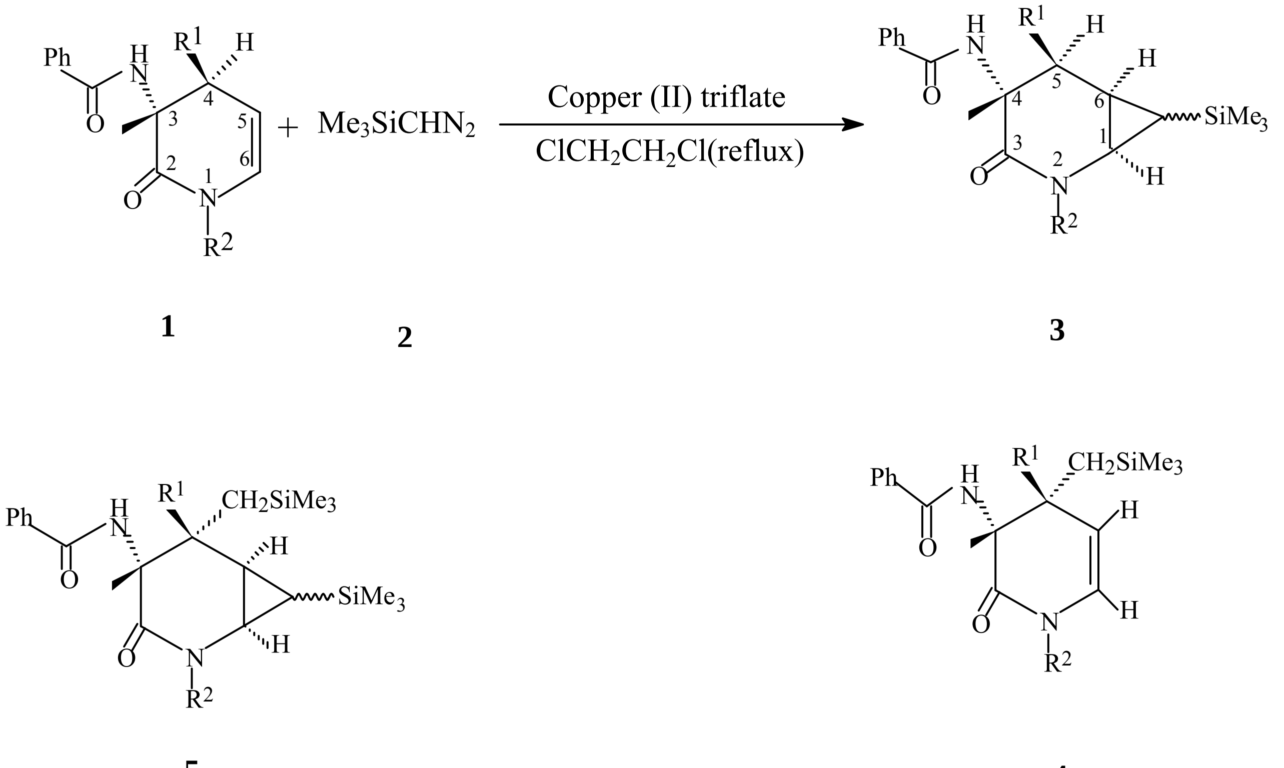
Abstract – The reactions of a series of 1,2,3,4-tetrahydropyridin-2-ones with trimethylsilyldiazomethane using catalytic amounts of copper(II) triflate in refluxing 1,2-dichloroethane yielded exclusively 3-oxo-2-azabicyclo[4.1.0]-heptanes in good yields. The application of ultrasonic radiation enhanced the reaction rate and allowed the reactions to be conducted at room temperature.

INTRODUCTION

Cyclopropanation of olefins is an important synthetic transformation as the cyclopropyl ring is present in many natural products, pharmaceuticals and could be transformed into a variety of useful products by cleavage of the strained three membered ring.[1] Silylcyclopropanes in particular are very important and versatile synthones because silyl group can potentially control ring opening, metalation reactions and can itself also be substituted by electrophiles.[2] The transition metal catalyzed decomposition of trimethylsilyldiazomethane in the presence of olefins is a simple and direct approach for the preparation of silylcyclopropanes and few reports available in literature describe the use of palladium,[3] polymeric ruthenium complex $[Ru_2(CO)_4(\mu\text{-OAC})_2]_{n,}$[4] copper bis(oxazoline),[5] CuCl[6] and iron complexes[7] as catalysts. In these reports the use of substrates is limited to simple aliphatic and aromatic olefins, and to the best of our knowledge there is no literature report which describes the use of enamine double bond or address the chemoselectivity in these reactions. Cyclopropanation of enamine double bond has also gained importance in view of the conflicting literature reports, wherein Wenkert *et al.*[8] and Wang *et al.*[9] reported cyclopropanation of enamine double bond and in contrast, Augusti *et al.*[10] reported the formation of product derived from C-H insertion in the reaction of acyclic enaminones with carbethoxycarbene. 1,2,3,4-Tetrahydropyridin-2-ones,[11] easily accessible from reaction of 1-aza-1,3-butadiene with 2-oxazolin-5-ones, are typical enamides containing pyridin-2-one ring, which comprise of an important feature of many alkaloids and biologically active substances. Earlier we reported copper-bronze catalyzed cyclopropanation of 1,2,3,4-tetrahydropyridin-2-ones (**1**) with diazoacetate[12] and now herein we report for the first time the reactions of **1** with trimethylsilyldiazomethane (**2**) in presence of copper based catalysts to yield 3-oxo-2-azabicyclo[4.1.0]heptanes (**3**) chemoselectively without any evidence for the formation of the products (**4**) which could arise from allylic C-H insertion or product (**5**) formed by cyclopropanation and insertion (Scheme 1) .



1 **2** **3**

5 **4**

Scheme

RESULTS AND DISCUSSION

3-Benzoylamino-1,4-diphenyl-3-methyl-1,2,3,4-tetrahydropyridin-2-one (**1**, $R^1=R^2=C_6H_5$) was reacted with excess of trimethylsilyldiazomethane (**2**) in presence of catalytic amount of copper(II) triflate in refluxing dichloroethane for 4 h. After evaporation of the solvent under vacuum, the residue left was purified by thin layer chromatography (SiO_2) to give exclusively 4-benzoylamino-2,5-diphenyl-4-methyl-3-oxo-7-trimethylsilyl-2-azabicyclo[4.1.0]heptane (**3a**) as white crystalline solid, yield 75%, mp 250-251 ^{0}C (recrystallized with benzene). The structural assignment of **3a** rests on elemental as well as spectral data. The FAB MS spectra showed (M^++1) at m/z 469. The 300 MHz ^{1}H NMR spectra of **3a** taken in $CDCl_3$ showed signal at δ: 0.07 (m, 1H, H-7), 0.11 (s, 9H, $(CH_3)_3Si$) , 0.89 (m, 1H, J=7.1, 8.2 Hz, H-6), 1.29 (s, 3H, CH_3), 1.62 (m, 1H, H-1), 4.37 (d, 1H, J=7.1Hz, H-5), 5.85 (br s, 1H, NH), 7.20-7.50 (m, 13H, Ar-H), 7.68 (m, 2H, Ar-H). The higher values of coupling constants for H-5 and H-6 confirmed their *cis* stereochemistry. The reaction was generalized by reacting a series of 1,2,3,4-tetrahydropyridin-2-ones (**1**) with trimethylsilyldiazomethane (**2**) in presence of catalytic amount of copper(II) triflate to yield corresponding 3-oxo-2-azabicyclo[4.1.0]heptanes (**3**) chemoselectively, without any evidence for the formation of products (**4**) which could arise from allylic C-H insertion or product (**5)** formed by the cyclopropanation and insertion. These results are presented in Table 1. In general 1,2,3,4-tetrahydropyridin-2-ones with *N*-aryl substituents were found to be more reactive than having *N*- alkyl substituents. Among the various *N*-aryl substituted 1,2,3,4-tetrahydropyridin-2-ones studied, those substituted with electron donating groups were found to be most reactive.

To evaluate the effect of various catalysts in these reactions, the reaction of 3-benzoylamino-1,4-diphenyl-3-methyl-1,2,3,4-tetrahydropyridin-2-one (**1**, R^1=R^2=C_6H_5) with trimethylsilyldiazomethane (**2**) was conducted in presence of different catalysts. These results are presented in Table 2 (Entries 1-6) and show that while copper based catalysts are good for this transformation, rhodium chloride and ruthenium chloride did not catalyze the reaction. Among the various copper based catalysts, copper(II) triflate was found to be most promising catalyst for these transformations. Reaction of 3-benzoylamino-3-methyl-1,4-diphenyl-1,2,3,4-tetrahydropyridin-2-one (**1**, R^1=R^2=C_6H_5) with trimethylsilyldiazomethane in presence of catalytic amount of copper(II) triflate was studied in different solvents with a view to evaluate the effect of various solvents in these reactions. These results are presented in Table 2 (Entries 4, 7-10) and show that among the various solvents like dichloroethane, benzene, xylene, chlorobenzene and acetonitrile studied, dichloroethane is the best solvent for this reaction.

Table 1 Copper (II) triflate catalyzed cyclopropanation of 1,2,3,4-tetrahydropyridin-2-ones (1) with trimethylsilyldiazomethane (2)

Compd 1	**R^1**	**R^2**	**Yield (%)**	**Reaction Time (h)**	**mp (^{0} C)**
a	C_6H_5	C_6H_5	75	4	250-251
b	C_6H_5	C_6H_4OMe (*p*)	78	4	280-281
c	C_6H_5	C_6H_4Me (*p*)	76	4	265-266
d	C_6H_5	C_6H_4Cl (*p*)	65	6	274-275
e	C_6H_5	C_6H_{11}	55	8	218-219
f	C_6H_5	Me	50	8	236-237
g	Me	C_6H_{11}	40	12	175-176

Table 2 Effect of various catalysts and solvents on cyclopropanation of 1,2,3,4-tetrahydropyridin-2-one (1a) with TMSCHN$_2$

Entry	Catalyst	Solvent (Refluxing)	Reaction Time (h)	Yield (%)
1	Copper bronze	1,2-Dichloroethane	6	75
2	$CuSO_4$	1,2-Dichloroethane	8	65
3	Cu(acac)$_2$	1,2-Dichloroethane	5	72
4	Cu(II) triflate	1,2-Dichloroethane	4	75
5	$RuCl_3 . xH_2O$	1,2-Dichloroethane	12	Trace
6	$RhCl_3 . xH_2O$	1,2-Dichloroethane	12	-
7	Cu(II) triflate	Benzene	12	20
8	Cu(II) triflate	Xylene	8	55
9	Cu(II) triflate	Chlorobenzene	15	-
10	Cu(II) triflate	Acetonitrile	8	65

Ultrasonic radiations have been found to be very effective in promoting various types of reactions and are finding increasing applications in synthetic organic transformations.[13-14] To evaluate the effect of ultrasonic radiation, the reaction of 1,2,3,4-tetrahydropyridin-2-one (**1a**) with trimethylsilyldiazomethane in presence copper catalysts in 1,2-dichloroethane was carried out under sonochemical conditions. The results of these experiments are presented in Table 3.

Table 3. Effect of ultrasonic radiation on cyclopropanation of 1,2,3,4-tetrahydropyridin-2-one (1a) at room temperature

Entry	Catalyst	Reaction time (h)	Yield (%)
1	Cu(II) triflate	3.0	85
2	Cu(acac)$_2$	4.5	5
3	Cu bronze	5.0	75

Substrate (1 mmol), catalyst (0.1 mmol), 1,2-dichloroethane (15 mL), TMSCHN$_2$ (5 mmol)

In summary 1,2,3,4-tetrahydropyridin-2-ones, typical enamides undergo highly chemoselective reaction with carbene generated from copper catalyzed decomposition of trimethylsilyldiazomethane to yield corresponding 3-oxo-2-azabicyclo[4.1.0]heptanes in good yields without any evidence for the formation of product which could arise from C-H insertion or product formed by cyclopropanation and insertion.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on Bruker 300 MHz spectrometer and chemical shift values are recorded in δ units (parts per million) relative to TMS. IR spectra were recorded on a Perkin Elmer 1760X FTIR spectrophotometer in potassium bromide disc or neat thin film. MS spectra were recorded on matrix assisted laser desorption ionization (MALDI) mass spectrometer. Soniprep-150 with exponential microprobe was used for carrying out experiments under sonochemical conditions.

MATERIALS

1,2,3,4-Tetrahydropyridin-2-ones (**1**) were prepared by reacting 1-aza-1,3-butadienes with 4-methyl-2-phenyl-2-oxazolin-5-one. Trimethylsilyldiazomethane used was 2M solution in hexane and purchased from Aldrich. All the solvents and catalysts were commercially available.

Reaction of 1,2,3,4–tetrahydropyridin-2-ones (1) with TMSCHN$_2$ (2) (Typical procedure): To the stirred and refluxing solution of 3-benzoylamino-1,4-diphenyl-3-methyl-1,2,3,4-tetrahydropyridin-2-one (**1a**, R^1=R^2=C_6H_5, 382 mg, 1 mmol) in dry dichloroethane (15 mL), containing copper(II) triflate (36 mg, 0.1 mmol), the solution of trimethylsilyldiazomethane (2.5 mL 2M solution in hexane, 5 mmol) in dry dichloroethane (5 mL) was added drop wise over a period of 0.5 h. The stirring was further continued with refluxing for a period of 4 h till the reaction was completed (TLC, SiO_2, ethyl acetate:benzene 1:4). The solvent of the reaction mixture was then evaporated under vacuum and the residue left was purified on TLC (SiO_2) using ethyl acetate/benzene (1:4) as eluent to yield 4-benzoylamino-2,5-diphenyl-4-methyl-3-oxo-7-trimethylsilyl-2-azabicyclo[4.1.0]heptane (**3a**) as white crystalline solid (351 mg 75%) mp 250-251 ^{0}C. Other 3-oxo-2-azabicyclo[4.1.0] heptanes (**3b-3g**) were similarly prepared and their reaction times and yields are presented in Table 1.

PRODUCT IDENTIFICATION

4-Benzoylamino–2,5-diphenyl-4-methyl–3-oxo-7–trimethylsilyl-2-azabicyclo[4.1.0]heptane (3a): White crystalline solid, mp 250-251 ^{0}C (recrystallized with benzene). IR (KBr): 3325, 1685, 1645 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ) 0.07 (m, 1H, H-7), 0.11 (s, 9H, $(CH_3)_3Si$), 0.89 (m, 1H, H-6), 1.29 (s, 3H, CH_3), 1.62 (m, 1H, H-1), 4.37 (d, 1H, *J*=7.1Hz, H-5), 5.85 (br s, 1H, NH), 7.20-7.50 (m, 13H, Ar-H), 7.68 (m, 2H, Ar-H). MS m/z 469 (M^+ + 1). Anal Calcd for $C_{29}H_{32}N_2O_2Si$: C, 74.32; H, 6.88; N, 5.97. Found: C, 74.21; 6.89; N, 6.02.

2-*p*-Anisoyl-4-benzoylamino–4-methyl-5-phenyl–3-oxo-7–trimethylsilyl-2-azabicyclo[4.1.0]heptane (3b):

white crystalline solid, mp 280-281 ^{0}C (recrystallized with benzene). IR (KBr): 3360, 1690, 1643 cm^{-1}. ^{1}H NMR (CDCl$_3$, δ) 0.08 (m, 1H, H-7), 0.10 (s, 9H, (CH$_3$)$_3$Si), 0.89 (m, 1H, H-6), 1.28 (s, 3H, CH$_3$), 1.61 (m, 1H, H-1), 3.81 (s, 3H, OCH$_3$), 4.39 (m, 1H, H-5), 5.90 (br s, 1H, NH), 7.12-7.50 (m, 12H, Ar-H), 7.67 (m, 2H, Ar-H). MS m/z 499 (M$^+$ + 1). Anal Calcd for $C_{30}H_{34}N_2O_3Si$: C, 72.25; H, 6.87; N, 5.61. Found: C, 72.39; H, 6.79; N, 6.82.

4-Benzoylamino–4-methy-3-oxo-5-phenyl–2-*p*-tolyl-7–trimethylsilyl-2-azabicyclo[4.1.0]heptane (3c):

White crystalline solid, mp 265-266 ^{0}C (recrystallized with benzene). IR (KBr) 3355, 1690, 1645 cm^{-1}. ^{1}H NMR (CDCl$_3$, δ) 0.06 (m, 1H, H-7), 0.10 (s, 9H, (CH$_3$)$_3$Si), 0.88 (m, 1H, H-6), 1.32 (s, 3H, CH$_3$), 1.61 (m, 1H, H-1), 2.35 (s, 3H, $C_6H_5C\mathbf{H}_3$), 4.35 (m, 1H, H-5), 5.82 (br s, 1H, NH), 7.10-7.50 (m, 12H, Ar-H), 7.67 (m, 2H, Ar-H) MS m/z 483 (M$^+$ + 1). Anal. Calcd for $C_{30}H_{34}N_2O_2Si$: C, 74.64; H, 7.09; N, 5.80. Found: C, 74.60; H, 7.08; N, 5.79.

4-Benzoylamino-2–*p*-chlorophenyl-4-methyl-3-oxo-5-phenyl-7–trimethylsilyl-2-azabicyclo[4.1.0] heptane (3d):

White crystalline solid, mp 274-275 ^{0}C (recrystallized with benzene). IR (KBr) 3350, 1687, 1648 cm^{-1}. ^{1}H NMR (CDCl$_3$, δ) 0.06 (m, 1H, H-7), 0.10 (s, 9H, (CH$_3$)$_3$Si), 0.90 (m, 1H, H-6), 1.30 (s, 3H, CH$_3$), 1.64 (m, 1H, H-1), 4.40 (m, 1H, H-5), 5.90 (br s, 1H, NH), 7.20-7.50 (m, 12H, Ar-H), 7.70 (m, 2H, Ar-H) M$_1$S m/z 503 (M$^+$ + 1). Anal. Calcd for $C_{29}H_{31}N_2O_2ClSi$: C, 69.23; H, 6.21; N, 5.56. Found: C, 69.28; H, 6.23; N, 5.47.

4-Benzoylamino-2–cyclohexyl-4-methyl-5-phenyl-3-oxo-7–trimethylsilyl-2-azabicyclo[4.1.0]heptane (3e):

White crystalline solid, mp 218-219 ^{0}C (recrystallized with benzene). IR (KBr) 3335, 1685, 1645 cm^{-1}. ^{1}H NMR (CDCl$_3$, δ) 0.05 (m, 1H, H-7), 0.10 (s, 9H, (CH$_3$)$_3$Si), 0.88 (m, 1H, H-6), 1.20-2.05 (m, 14H, CH$_3$, H-1, cyclohexyl H), 4.08 (m, 1H, N-CH of cyclohexyl), 4.34 (m, 1H, H-5), 5.67 (br s, 1H, NH), 7.18-7.48 (m, 8H, Ar-H), 7.66 (m, 2H, Ar-H) MS m/z 475 (M$^+$ + 1). Anal. Calcd for $C_{29}H_{38}N_2O_2Si$: C, 73.37; H, 8.06; N, 5.90. Found: C, 73.31; H, 8.03; N, 5.93.

4-Benzoylamino-2,4-dimethyl-3-oxo-5-phenyl-7–trimethylsilyl-2-azabicyclo[4.1.0]heptane (3f):

White crystalline solid, mp 236-237 ^{0}C (recrystallized with benzene). IR (KBr) 3330, 1681, 1648 cm^{-1}. ^{1}H NMR (CDCl$_3$, δ) 0.05 (m, 1H, H-7), 0.11(s, 9H, (CH$_3$)$_3$Si), 0.82 (m, 1H, H-6), 1.28(s, 3H, CH$_3$), 1.62 (m, 1H, H-1), 3.14 (s, 3H, N-CH$_3$), 4.35(m, 1H, H-5), 5.68 (br s, 1H, NH), 7.15-7.48(m, 8H, Ar-H), 7.65 (m, 2H, Ar-H) MS m/z 407 (M$^+$ + 1). Anal. Calcd for $C_{24}H_{30}N_2O_2Si$: C, 70.89; H, 7.43; N, 6.89. Found: C, 71.02; H, 7.42; N, 6.88.

4-Benzoylamino-2-cyclohexyl-4,5-dimethyl-3-oxo-7–trimethylsilyl-2-azabicyclo[4.1.0]heptane (3g): White crystalline solid, mp 175-176 ^{0}C (recrystallized with benzene). IR (KBr) 3335, 1685, 1645 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ) 0.06 (m, 1H, H-7), 0.12(s, 9H, $(CH_3)_3Si$), 0.86 (m, 1H, H-6), 1.04 (d, *J*=7.0 Hz, 3H), 1.28-2.06 (m, 15H, CH_3, H-1, H-5, cyclohexyl H), 4.18 (m, 1H, N-CH of cyclohexyl), 5.78 (br s, 1H, NH), 7.25-7.48 (m, 3H, Ar-H), 7.68 (m, 2H, Ar-H). MS m/z 401 (M^+ + 1). Anal. Calcd for $C_{24}H_{36}N_2O_2Si$: C, 69.85; H, 8.79; N, 6.79. Found: C, 69.95; H, 8.69; N, 6.62

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