REACTION OF LITHIUM TRIMETHYLSILYLDIAZOMETHANE WITH *N,N*-DIALKYLAMIDES OF α-KETO ACIDS AND *N,N*-DISUBSTITUTED α-AMINO KETONES§

Hideki Ogawa, Toyohiko Aoyama,* and Takayuki Shioiri*

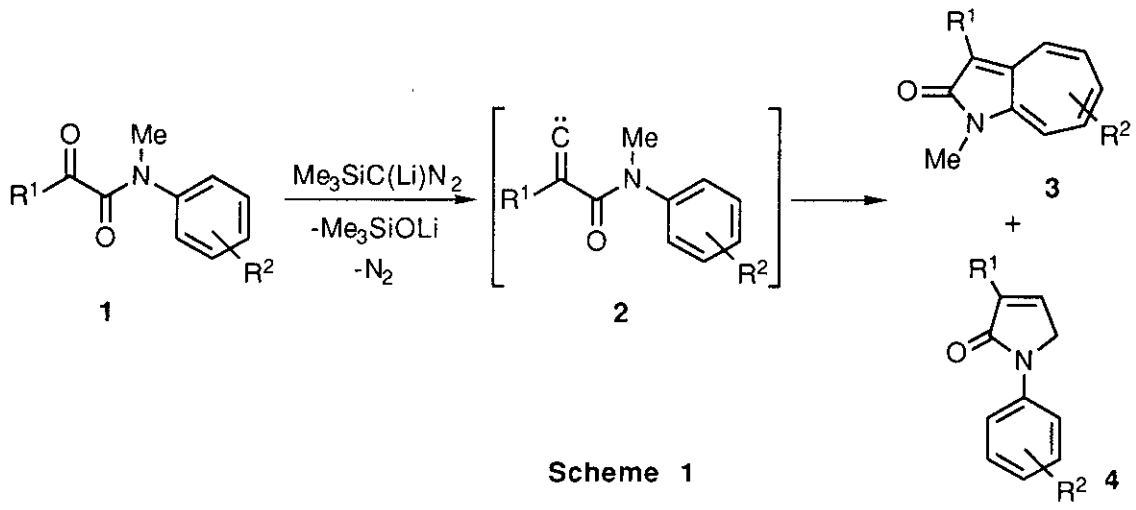
Faculty of Pharmaceutical Sciences, Nagoya City University
Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

Abstract — Lithium trimethylsilyldiazomethane smoothly reacted with *N,N*-dialkylamides of α-keto acids and *N,N*-disubstituted α-amino ketones to give 2-oxo-3-pyrrolines and 3-pyrrolines, respectively, in good to moderate yields.

In our previous communication,[1] we reported that lithium trimethylsilyldiazomethane (TMSC(Li)N_2), a useful reagent for generating alkylidenecarbenes from carbonyl compounds,[2] smoothly reacted with *N*-methylanilides (**1**) of α-keto acids to give cyclohepta[*b*]pyrrol-2-ones (**3**) via alkylidenecarbene intermediates (**2**), as shown in Scheme 1. In some cases, small amounts of 2-oxo-3-pyrrolines (**4**) (1,5 C-H insertion products) were formed as by-products. We thought that 2-oxo-3-pyrrolines could be obtained exclusively if *N,N*-dialkylamides of α-keto acids were used as substrates. Here we wish to report our results on the reaction of TMSC(Li)N_2 with *N,N*-dialkylamides of α-keto acids and *N,N*-disubstituted α-amino ketones.

First, treatment of TMSC(Li)N_2 with 1-(α-oxopropionyl)piperidine (**5a**) in ether

§ Dedicated to the memory of the late Professor Yoshio Ban.

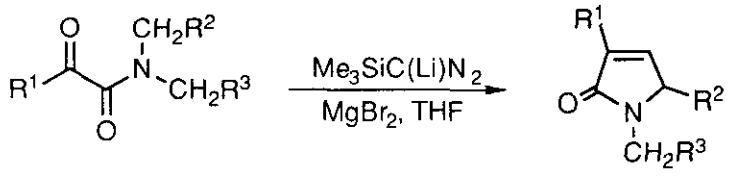


Scheme 1

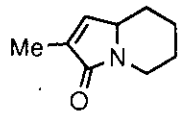
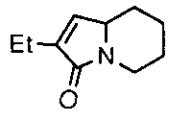
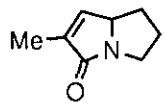
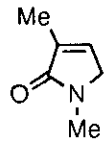
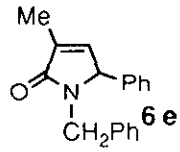
under the same reaction conditions for the preparation of **3** gave the desired 3(5*H*)-indolizinone (**6a**) though the yield was only 13%. However, changing the reaction solvent to tetrahydrofuran (THF) and addition of magnesium bromide as an additive led to a significant improvement of the yield. The reaction has been found to have generality, as summarized in Table 1. Various *N*,*N*-dialkylamides (**5**) including acyclic and cyclic ones smoothly underwent the reaction with $TMSC(Li)N_2$ to give the corresponding **6** as sole isolable products. Magnesium bromide seems to be the additive of choice since the use of magnesium chloride showed a remarkable decrease in the yield. Although analogous reaction with the potassium salt of diethyl diazomethylphosphonate (DAMP)[3] has been reported, the product is a mixture of **6** and considerable amounts of *N*,*N*-dialkyl-2-butynamides, the latter of which is formed by migration of the carbamoyl group in the alkylidenecarbene intermediate. Further, two equivalents of DAMP is required to conduct the reaction smoothly. Thus the reaction with $TMSC(Li)N_2$ is much more effective than that with DAMP.

Next, the reaction of $TMSC(Li)N_2$ with *N*,*N*-disubstituted α-amino ketones was investigated. We found that $TMSC(Li)N_2$ also reacted with 1-(*N*-methylanilino)-2-propanone (**7a**) to give 3-pyrroline (**8a**) in good yield. In this case, the reaction smoothly proceeded in the absence of magnesium bromide. It should be

Table 1



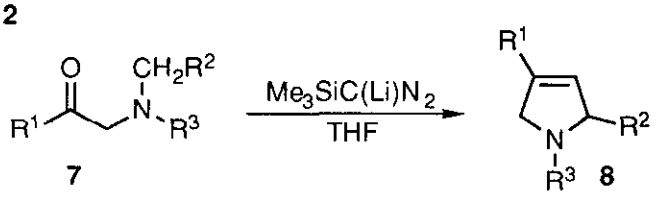
5 **6**

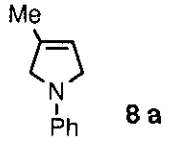
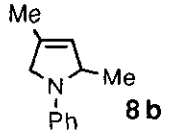
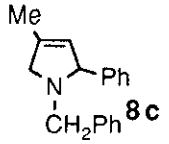
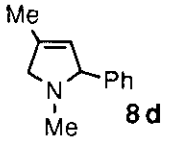
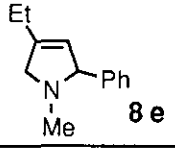
Starting ketone	R^1	R^2	R^3	Product	Yield (%)[a]	bp (°C/mmHg)[b]
5a	Me	-$(CH_2)_3$-		 **6a**	58 (67)[c]	115-120/1.5
5b	Et	-$(CH_2)_3$-		 **6b**	62	145-150/4
5c	Me	-$(CH_2)_2$-		 **6c**	41	85-90/1
5d	Me	H	H	 **6d**	37 (50)[c]	pale yellow oil
5e	Me	Ph	Ph	 **6e**	56	195-200/0.8

a) Isolated yield. b) By Kugelrohr distillation. c) Yields (determined by ^{1}H-Nmr) in parentheses refer to the reaction with DAMP.[3] The corresponding *N*,*N*-dialkyl-2-butynamides were also formed in 23~32% yields.

noted that no 2*H*-cyclohepta[*b*]pyrrole *similar to the product obtained by the* reaction with anilides (**1**) could be detected at all. Analogs (**7b-e**) bearing phenyl or benzyl group as an *N*-substituent also underwent the similar reaction with TMSC(Li)N_2 to furnish the 3-pyrrolines (**8b-e**), as shown in Table 2. However, *N*,*N*-dialkylamino derivatives such as 1-(*N*,*N*-dimethyl(or diethyl)-

Table 2



Starting ketone	R^1	R^2	R^3	Product	Yield (%)[a]	mp (°C) or bp (°C/mmHg)[b]
7a	Me	H	Ph	 **8a**	73	83-85 (MeOH)
7b	Me	Me	Ph	 **8b**	46	colorless oil
7c	Me	Ph	CH_2Ph	 **8c**	80	165-170/2.5
7d	Me	Ph	Me	 **8d**	53	120-125/6
7e	Et	Ph	Me	 **8e**	46	130-135/6

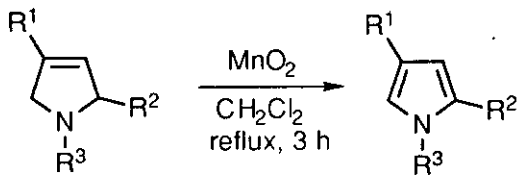
a) Isolated yield. b) By Kugelrohr distillation.

amino)-2-propanones afforded a complex mixture.

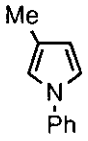
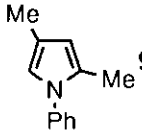
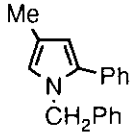
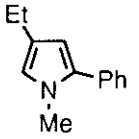
Incidentally, we found that 3-pyrrolines (**8**) were easily oxidized with manganese dioxide (CMD, chemical manganese dioxide[4]) to give the pyrroles (**9**) in high to moderate yields,[5] as shown in Table 3.

In conclusion, the present method using commercially available $TMSCHN_2$ will provide a new and convenient method for the preparation of 2-oxo-3-pyrrolines and 3-pyrrolines.

Table 3



8 **9**

Starting **8**	R^1	R^2	R^3	Product	Yield (%)	mp (°C)
8a	Me	H	Ph	 **9a**	88	55-57 (benzene-hexane)
8b	Me	Me	Ph	 **9b**	64[a]	pale yellow oil
8c	Me	Ph	CH_2Ph	 **9c**	83	pale pink oil
8e	Et	Ph	Me	 **9e**	45	colorless oil

a) Reflux for 6 h.

General procedure for the preparation of 6 and 8 : $TMSCHN_2$[6] (1.56 M hexane solution, 0.77 ml, 1.2 mmol) was added dropwise to a solution of LDA, prepared from diisopropylamine (141 mg, 1.2 mmol) and *n*-butyllithium (1.63 M hexane solution, 0.74 ml, 1.2 mmol) in THF (8 ml), at -78 °C under argon and the mixture was stirred for 20 min. $MgBr_2$ (1 M ether-benzene (ca. 1:1) solution, 1.2 ml, 1.2 mmol) was added and the mixture was stirred at -78 °C for 30 min. To this mixture was added dropwise a solution of **5** in THF (2 ml) and the whole was stirred at -78 °C for 3 h, then heated under reflux for 2 h. After addition of cold water, the mixture was filtered off and the filtrate was extracted with benzene.

The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (BW-200, Fuji Davison) using ethyl acetate or ethyl acetate-hexane (1:5-2:1) to give **6**.[7]

3-Pyrrolines (**8**)[7] were prepared from **7** according to the general procedure, except the reaction was carried out in the absence of $MgBr_2$.

REFERENCES AND NOTES

1. H. Ogawa, T. Aoyama, and T. Shioiri, *Synlett*, 1994, 757.
2. a) K. Miwa, T. Aoyama, and T. Shioiri, *Synlett*, 1994, 107. b) K. Miwa, T. Aoyama, and T. Shioiri, *Synlett*, 1994, 109. c) K. Miwa, T. Aoyama, and T. Shioiri, *Synlett*, 1994, 461.
3. J. C. Gilbert and B. K. Blackburn, *J. Org. Chem.*, 1986, **51**, 3656.
4. a) Y. Hamada, M. Shibata, T. Sugiura, S. Kato, and T. Shioiri, *J. Org. Chem.*, 1987, **52**, 1252. b) N. Irako, Y. Hamada, and T. Shioiri, *Tetrahedron*, 1992, **48**, 7251. c) J. Matsubara, K. Nakao, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.*, 1992, **33**, 4187. d) Available from Chuo Denki Kogyo, Co., Ltd. (272 Taguchi, Myokokogen-machi, Nakakubiki-gun, Niigata 949-21, Japan)
5. For example, a mixture of **8a** (159 mg, 1 mmol) and CMD (869 mg, 10 mmol) in dichloromethane (10 ml) was heated under reflux for 3 h to give **9a** in 88% yield.
6. T. Shioiri, T. Aoyama, and S. Mori, *Org. Synth.*, Coll. Vol., 1993, **8**, 612.
7. **6a** : Ir (neat) : 2938, 2857, 1671, 1642, 1429, 1287 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.96 (1H, dq, J=3.63, 12.87 Hz), 1.28 (1H, ddq, J=3.63, 5.27, 12.87 Hz), 1.50 (1H, tq, J=3.3, 12.87 Hz), 1.69-1.89 (1H, m), 1.90 (4H, t, J=1.65 Hz), 2.01-2.10 (1H, m), 2.84 (1H, dt, J=3.63, 12.87 Hz), 3.70 (1H, dt, J=1.65, 11.88 Hz), 4.28 (1H, dd, J=5.28, 13.2 Hz), 6.62 (1H, t, J=1.65 Hz).

   The spectral data were identical with that reported.[3]

   6b : Ir (neat) : 2938, 2859, 1682, 1640, 1447, 1429, 1314, 1289 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.96 (1H, dq, J=3.3, 12.87 Hz), 1.14 (3H, t, J=7.59 Hz), 1.29 (1H, ddq, J=3.3, 4.95, 12.87 Hz), 1.50 (1H, tq, J=3.3, 12.87 Hz), 1.72-1.78 (1H, m),

1.86-1.94 (1H, m), 2.03-2.11 (1H, m), 2.30 (2H, tq, J=1.65, 7.59 Hz), 2.84 (1H, dt, J=3.63, 12.87 Hz), 3.68-3.73 (1H, m), 4.29 (1H, dd, J=5.28, 13.2 Hz), 6.58 (1H, q, J=1.65 Hz.)

6c : Ir (neat) : 2972, 2888, 1682, 1636, 1447, 1375, 1337, 1244 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.09 (1H, dq, J=3.96, 11.55 Hz), 1.87 (3H, t, J=1.65 Hz), 1.99-2.09 (1H, m), 2.17-2.45 (2H, m), 3.24-3.32 (1H, m), 3.41-3.51 (1H, m), 4.07-4.13 (1H, m), 6.80 (1H, t, J=1.65 Hz).

6d : Ir (neat) : 2923, 1674, 1644, 1455, 1402 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.90 (3H, q, J=1.98 Hz), 3.05 (3H, s), 3.82 (2H, t, J=1.98 Hz), 6.64 (1H, q, J=1.65 Hz).

6e : Ir (neat) : 3030, 2922, 2867, 1688, 1651, 1603, 1495, 1455, 1408, 1358, 1211 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 2.00 (3H, t, J=1.65 Hz), 4.40 (2H, ABq, J=14.85 Hz), 4.72-4.73 (1H, m), 6.62 (1H, t, J=1.65 Hz), 7.03-7.38 (10H, m).

8a : Ir (nujol) : 2924, 1609, 1509, 1219, 1157 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.85 (3H, s), 3.98-4.07 (4H, m), 5.54 (1H, q, J=1.65 Hz), 6.51 (2H, d, J=8.58 Hz), 6.67 (1H, t, J=7.26 Hz), 7.24 (2H, dd, J=7.26, 8.58 Hz).

8b : Ir (neat) : 3031, 2969, 2818, 1599, 1507, 1470, 1368, 1347 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.26 (3H, d, J=6.27 Hz), 1.82 (3H, s), 3.87-4.17 (2H, m), 4.49-4.54 (1H, br s), 5.45 (1H, quint., J=1.65 Hz), 6.55-6.59 (2H, m), 6.66 (1H, t, J=7.26 Hz), 7.20-7.27 (2H, m).

8c : Ir (neat) : 3026, 2870, 2786, 1601, 1493, 1453, 1291, 1169, 1111 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.73 (3H, s), 3.19-3.26 (1H, m), 3.59 (1H, dd, J=4.62, 13.19 Hz), 3.73 (2H, ABq, J=13.2 Hz), 4.57 (1H, s), 5.33 (1H, s), 7.19-7.44 (10H, m).

8d : Ir (neat) : 3061, 2936, 2768, 1601, 1491, 1453, 1352, 1300, 1281 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.80 (3H, s), 2.38 (3H, s), 3.28-3.36 (1H, m), 3.77 (1H, dd, J=4.29, 12.87 Hz), 4.25-4.30 (1H, m), 5.33 (1H, s), 7.23-7.38 (5H, m).

8e : Ir (neat) : 3029, 2965, 2772, 1601, 1491, 1455, 1350, 1291 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.10 (3H, t, J=7.26 Hz), 2.12-2.17 (2H, m), 2.40 (3H, s), 3.30-3.39 (1H, m), 3.81 (1H, dd, J=3.96, 12.87 Hz), 4.31 (1H, br s), 5.34 (1H, s), 7.24-7.39 (5H, m).

9a : Ir (nujol) : 2926, 2855, 1603, 1510, 1350, 1073, 1051 cm^{-1}. ^1H-Nmr

($CDCl_3$) δ: 2.17 (3H, s), 6.18 (1H, t, J=2.31 Hz), 6.87 (1H, s), 7.00 (1H, t, J=2.31 Hz), 7.16-7.43 (5H, m).

The ^{1}H-Nmr spectrum was identical with that reported.[8]

9b : Ir (neat) : 2923, 2897, 1599, 1512, 1499, 1406, 1352, 1225, 1188 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.12 (3H, s), 2.18 (3H, s), 5.90 (1H, s), 6.55 (1H, s), 7.27-7.44 (5H, m).

The ^{1}H-Nmr spectrum was identical with that reported.[8]

9c : Ir (neat) : 3063, 2924, 2869, 1605, 1510, 1495, 1474, 1455, 1406, 1345, 1331, 1300, 1211 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.13 (3H, s), 5.07 (2H, s), 6.11 (1H, s), 6.50 (1H, s), 7.01-7.32 (10H, m).

9e : Ir (neat) : 2961, 2924, 1605, 1512, 1478, 1462, 1404, 1379, 1310 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.23 (3H, t, J=7.59 Hz), 2.52 (2H, q, J=7.59 Hz), 3.61 (3H, s), 6.10 (1H, s), 6.51 (1H, s), 7.26-7.39 (5H, m).

8. T. Tsuchiya, H. Arai, and H. Igeta, *Chem. Pharm. Bull.*, 1973, **21**, 1516.

Received, 10th March, 1995