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Generation and Properties of N^7-Xanthinium Ylides: Reactions of N^7-Xanthinium Ylides with Diphenylcyclopropenone and Acetylenic Compounds

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Xanthinium N^7-ylides were generated *in situ* from 7-substituted 9-methylxanthinium tosylates (**2**) using *n*-BuLi in tetrahydrofuran or Et_3N in MeCN. The xanthinium N^7-ylides (**3**) generated using Et_3N in MeCN reacted with diphenylcyclopropenone to give pyrone derivatives and isocaffeine in good yields. The reactions of **3a**—**b** with dimethyl acetylenedicarboxylate or methyl propiolate (MP) afforded 5-pyrrol-1-yluracils in moderate yields. N^7-Methoxycarbonylmethylide (**3c**) reacted with MP to give a pyrrolopteridine derivative together with a 5-pyrrol-1-yluracil derivative. Furthermore, the dihydropyrrolopurine derivative (**7**), a primary 1,3-dipolar cycloaddition product, was detected by nuclear magnetic resonance measurement of the products.

Keywords——xanthinium N^7-ylide; cycloaddition; dimethyl acetylenedicarboxylate; methyl propiolate; diphenylcyclopropenone; 5-pyrrol-1-yluracil; pyrrolopteridine; isocaffeine

Although xanthine derivatives are widely distributed, and some are used as pharmaceutical agents, only limited applications in synthetic chemistry have been reported.[1] We have already reported that the 8,9-dihydroxanthines react with acetylenic compounds to give propellanes and pyrimidodiazepines.[2] This report describes the generation and reactions of xanthinium N^7-ylides as 1,3-dipoles with diphenylcyclopropenone (DPP), dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate (MP) in detail.[3]

7-Substituted xanthines **1a**—**c**, prepared from theophylline and alkyl halides by a modification of the method of Zelnick *et al.*,[4] were allowed to react with methyl *p*-toluenesulfonate[5] at 140 °C for 2 h to give tosylates (**2a**—**c**) in good yields.

When the ylides generated from **2a**—**c** using *n*-BuLi in tetrahydrofuran (THF) were allowed to stand at room temperature in air, hydrolytic decomposition occurred to give ring-opened products (**4a**—**c**). The structures of **4a**—**c** were determined from the mass spectra (MS), elemental analyses and proton nuclear magnetic resonance (^{1}H-NMR) spectra.

We then searched for simple ylide-generation method that can be conducted on a gram scale. As the tosylates (**2**) were insoluble in non-polar solvents, the reaction solvents must be selected from polar aprotic solvents. Generation of ylides (**3**) from **2a**—**c** did not occur in pyridine at room temperature and degradation at N^9-Me occurred under reflux conditions to give **1a**—**c** in 77.7, 77.5 and 61.1% yields, respectively. Similar demethylation was observed in boiling dimethylformamide (DMF) or DMF-Et_3N. We then selected MeCN as the solvent and Et_3N as the base. A stirred suspension of **1** and 1.1 eq of Et_3N in MeCN at room temperature formed a clear yellowish solution within one minute and afforded **4** after usual work-up. This result clearly showed that the ylides (**3**) were generated under these conditions and compounds **3** were hydrolyzed to give **4**.

Reactions of 3 with DPP

It is well known that various types of carbonyl-stabilized ylides react with DPP to give

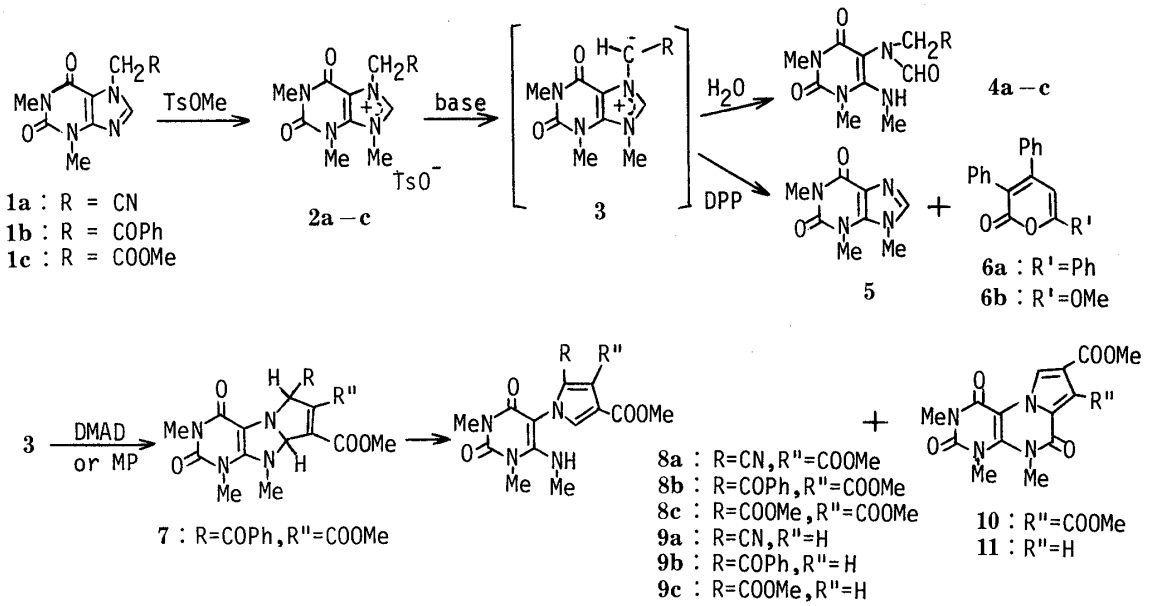

Chart 1

TABLE I. Reactions of 2 with Acetylenic Compounds in the Presence of Et_3N

Run	Compd.	R	Acetylenic Compd.	Et_3N (eq)	Temp.	Time (h)	Products (Yield %)	Yields (%) by reported method[3]
1	**2a**	CN	DMAD	1.5	r.t.	2	**8a** (44.5)	(65)
2	**2a**	CN	DMAD	1.5	Reflux	0.5	**8a** (60)	
3	**2b**	COPh	DMAD	1.5	r.t.	10	**8b** (75)	(41)
4	**2c**	$COOCH_3$	DMAD	2.0	r.t.	0.5	**8c** (60.9)	(81 as **10**)
5	**2a**	CN	MP	1.0	r.t.	22	**9a** (7.9)	(39)
6	**2a**	CN	MP	1.0	Reflux	5	**9a** (20.8)	
7	**2a**	CN	MP	2.0	Reflux	10	**9a** (18.3)	
8	**2b**	COPh	MP	1.0	r.t.	3.5	**9b** (26.3)	(37)
9	**2b**	COPh	MP	2.0	Reflux	6	**9b** (61.8)	
10	**2c**	$COOCH_3$	MP	1.0	r.t.	5	**9c** (8.0), **11** (7.5)	(51 as **11**)
11	**2c**	$COOCH_3$	MP	0.5	Reflux	5	**9c** (42.6), **11** (7.5)	
12	**2c**	$COOCH_3$	MP	1.5	Reflux	6	**9c** (49.2), **11** (8.7)	
13	**2c**	$COOCH_3$	MP	5.0	Reflux	6	**9c** (48.2), **11** (21.7)	

r.t.; room temperature.

heterocyclic compounds.[6-8] First, the reactions of **3** with DPP were conducted in order to investigate the reactivities of **3** as 1,3-dipoles. Isocaffeine[9] (**5**) was precipitated from the reaction mixture and 6-substituted 3,4-diphenyl-2-pyrones[6] (**6**) were obtained from the filtrate in good yields. However, **2a** did not react with DPP and DPP was recovered. Isocaffeine has been synthesized in several steps from expensive 5,6-diamino-1,3-dimethyluracil.[9] Our result thus provides a new synthetic route to isoxanthine analogues from xanthines in only three steps.

Reactions with Acetylenic Compounds

As the ylides **3** proved to be reactive, like pyridinium phenacylide,[6] the reactions with DMAD and MP were investigated. The results are summarized in Table I.

The structures of the ring-cleaved products (**8**,**9**) were determined from the MS, elemental analyses, ^{1}H-NMR and infrared (IR) spectra as described in the previous report.[3] The yields

of the product from the reactions with DMAD were better than those with MP. Treatment of **2c** with Et_3N in the presence of DMAD afforded 6-methylamino-5-(pyrrol-1-yl)uracil (**8c**) in 60.9% yield (run 4), whereas the reaction of the ylides generated from **2c** and *n*-BuLi with DMAD gave **10** in 81% yield.[3] Formation of **10** can be explained in terms of lactam formation of **8c** with *n*-BuLi. In fact, treatment of **8c** with *n*-BuLi at −60 °C afforded **10** in 18.3% yield together with recovered **8c** (68.5%).

The reaction of **2b** with MP at room temperature gave **9b** in poor yield (run 8). Under reflux conditions, the yields were greatly improved to 61.8% (run 9). Reaction of **2c** with MP at room temperature afforded **9c** in 8.0% yield along with 7.5% yield of the pteridine derivative, 8-methoxycarbonyl-2,4-5-trimethylpyrrolo[1,2-*f*]pteridine-1(2*H*),3(4*H*),6(5*H*)-trione (**11**) (run 10). Under reflux, the yield of **9c** was raised to about 50% but that of **11** was unchanged (8%) (run 12). On the other hand, the yield of **11** increased to 21.7% with excess Et_3N under reflux for 6 h (run 13). It is interesting that the recyclized product (**11**) was obtained when Et_3N was used as base in contrast to the result of the reaction with DMAD, which afforded only pyrrolyluracil (**8c**) and no pteridine derivative (**10**)[3] (run 4). However the formation mechanism of **11** is not yet clear, because **11** or **10** was detected in only a trace amount in the reaction of **9c** or **8c** with Et_3N at room temperature or under reflux.

In order to detect the intermediate (**7**) we reacted **2b** and DMAD in the presence of 0.5 eq of Et_3N under monitoring by thin layer chromatography (TLC) or by NMR measurement. Compound **7** was clearly observed in addition to **8b** and the ratio of **7**:**8b** was 3:1. Characteristic signals of C_{5a}-H and C_8-H (δ 5.80, 6.38 each doublet, J=2.3 Hz) were detected together with other signals at δ 3.02, 3.30, 3.35 (3H × 3, each singlet, NCH_3 × 3) and 3.55, 3.85 (3H × 2, each singlet, OCH_3 × 2). Compound **7** was not sufficiently stable to be isolated and changed into **8b**.

Further studies on the reactivities of xanthinium N^7-ylides are in progress.

Experimental[10]

Syntheses of 7-Substituted 1,3-Dimethylxanthines (1a—c)——Compounds **1a—c** were obtained from theophylline and corresponding halides in the presence of NaH in DMF with stirring overnight at room temperature. DMF was evaporated off, and the residual crystals were collected and recrystallized. **1a**: yield 82.9%, mp 187—188 °C (EtOH) (lit.[11] mp 188 °C). *Anal.* Calcd for $C_9H_9N_5O_2$: C, 49.31; H, 4.14; N, 31.94. Found: C, 49.40; H, 4.09; N, 31.94. **1b**: yield 92.5%, mp 190—191 °C (EtOH) (lit.[4] mp 193 °C). *Anal.* Calcd for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.55; H, 4.77; N, 18.80. **1c**: yield 87.3%, mp 147.5—148.5 °C (MeOH) (lit.[12] mp 148 °C). *Anal.* Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.69; H, 4.72; N, 22.29.

Syntheses of 7-Substituted 1,3,9-Trimethylxanthinium *p*-Toluenesulfonates (2a—c); General Procedure——A suspension of **1** (2 g) in 16 ml of methyl *p*-toluenesulfonate was heated for 2 h at 140 °C. After cooling, the reaction mixture was added to ether with stirring. The crude crystals were filtered off and recrystallized from EtOH. **2a**: yield 82%, mp 259—260 °C, colorless prisms. NMR (DMSO-d_6) δ: 2.44 (3H, s, Ar-CH_3), 3.54, 3.98, 4.38 (each 3H, 3 × NCH_3) 5.84 (2H, s, N^7-CH_2), 7.31—7.89 (4H, m, Ar-H) 9.21 (1H, s, C_8-H). MS *m/z*: 219 ($M^+ - 186$). *Anal.* Calcd for $C_{17}H_{19}N_5O_5S$: C, 50.37; H, 4.72; N, 17.28. Found: C, 50.12; H, 4.68; N, 17.27. **2b**: yield 80%, mp 130—132 °C, colorless needles. NMR (DMSO-d_6) δ: 2.41 (3H, s, Ar-CH_3), 3.49, 4.02, 4.42 (each 3H, 3 × NCH_3), 6.32 (2H, s, N^7-CH_2), 7.25—8.15 (9H, m, Ar-H), 9.06 (1H, s, C_8-H). MS *m/z*: 298 ($M^+ - 186$). *Anal.* Calcd for $C_{23}H_{24}N_4O_6S \cdot 1/2\ C_2H_5OH$: C, 56.79; H, 5.36; N, 11.04. Found: C 56.31; H, 5.29; N, 10.89. **2c**: 83%, mp 224 °C, colorless needles. NMR (DMSO-d_6) δ: 2.27 (3H, s, Ar-CH_3), 3.21, 3.71, 3.75 (each 3H, 3 × NCH_3) 4.20, (3H, s, OCH_3), 5.41 (2H, s, N^7-CH_2), 7.00—7.50 (4H, m, Ar-H), 9.40 (1H, s, C_8-H). MS *m/z*: 252 ($M^+ - 186$). *Anal.* Calcd for $C_{18}H_{22}N_4O_7S$: C, 49.31; H, 5.06; N, 12.78. Found: C, 49.15; H, 5.03; N, 12.68.

Reaction of 2 in Pyridine under Reflux; General Procedure——Compound **2b** (484.5 mg) was suspended in 8 ml of dry pyridine and refluxed for 3.5 h under N_2. The solvent was evaporated off and 10% K_2CO_3 solution–$CHCl_3$ was added. The $CHCl_3$ layer was dried ($MgSO_4$) and the solvent was evaporated off. The residue was recrystallized from AcOEt to give colorless needles of **1b** (148 mg); 83 mg more was obtained from the filtrate (total yield 77.5%).

Generation of the Ylides (2) and Detection of Hydrolyzed Products (4a—c); General Procedure——Under N_2, 1.1 N *n*-BuLi was added to a dry THF (15 ml) suspension of **2c** (220 mg) at −60 °C. The pale yellow solution was stirred for 10 min and the temperature was gradually raised. At −20 °C, sat. NH_4Cl solution was added and the mixture was extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give 92 mg of

crude 5-(*N*-methoxycarbonylmethyl-*N*-methyl)amino-6-(*N*-formyl-*N*-methyl)amino-1,3-dimethyluracil (**4c**, yield 64.5%). **4a**: yield 53.0%, mp 205—206 °C (dec.), colorless prisms (acetone). NMR ($CDCl_3$) δ: 3.04 (3H, d, CH_3NH, $J=5.8$ Hz), 3.32, 3.50 (3H, 3H, each s, NMe × 2), 4.15, 4.78 (1H, 1H, dd, CH_2, $J=19$ Hz), 8.05 (1H, s, CHO). MS *m/z*: 251 (M^+), 183 (base). *Anal.* Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.87. Found: C, 47.58; H, 5.20; N, 27.58. **4b**: yield 56.4%, oil. NMR ($CDCl_3$) δ: 2.98 (3H, d, CH_3NH, $J=5.3$ Hz), 3.30, 3.48 (3H, 3H, each s, $NCH_3 \times 2$), 4.32, 5.68 (1H, 1H, dd, CH_2, $J=18$ Hz), 7.35—7.70 (3H, m, Ar-H), 7.85—8.20 (3H, m, Ar-H, CHO). MS *m/z*: 330 (M^+), 105 (base). High-resolution MS Calcd for $C_{16}H_{18}N_4O_4$: 330.1328. Found: 330.1347. **4c**: yield 64.5%, mp 134—136.5 °C, colorless prisms (MeOH–ether). NMR ($CDCl_3$), δ: 2.94 (3H, d, CH_3NH, $J=5.5$ Hz), 3.32, 3.53 (3H, 3H, each s, $NCH_3 \times 2$), 3.82 (3H, s, OCH_3), 4.25, 4.60 (1H, 1H, dd, CH_2, $J=19$ Hz), 8.08 (1H, s, CHO). MS *m/z*: 284 (M^+) 195 (base). *Anal.* Calcd for $C_{11}H_{16}N_4O_5$: C, 46.48; H, 5.67; N, 19.71. Found: C, 46.35; H, 5.71; N, 19.77.

The Reaction of 3 with DPP——1,3,9-Trimethyl-7-phenacylxanthinium *p*-toluenesulfonate (**2b**, 480 mg) was suspended in 10 ml of MeCN and then 220 mg of Et_3N was added. The reaction mixture was stirred for 1 h. DPP (206 mg) was added, and the whole was stirred for 2 h. The precipitate **5** was filtered off and recrystallized from MeCN. Yield 239 mg (71%), mp 296 °C (lit.[9a] mp 285—287 °C). The filtrate was evaporated and the resulting crystals were recrystallized from benzene. Yield 322 mg (100%) of 3,4,6-triphenyl-2-pyrone (**6b**), pale yellow needles, mp 182—186 °C (lit.[6] mp 183—184 °C). IR ν_{max}^{KBr} cm^{-1}: 1705 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 6.82 (1H, s, vinyl H), 7.00—8.00 (15H, m, Ar-H). MS *m/z*: 324 (M^+), 296 (base).

By the same procedure, 109 mg of isocaffeine (56%) and 121 mg (44%) of 6-methoxy-3,4-diphenyl-2-pyrone (**6c**) were obtained from 440 mg of **2c**. **6c**: colorless prisms (from benzene), mp 135—136 °C (lit.[7] mp 134—135 °C). IR ν_{max}^{KBr} cm^{-1}: 1651, 1715, 1738 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.99 (3H, s, OCH_3), 5.55 (1H, s, vinyl H), 6.90—7.40 (10H, m, arom H). MS *m/z*: 278 (M^+).

When **2a** and DPP were reacted under the same reaction conditions as noted above, isocaffeine was not obtained but DPP was recovered (81%).

Reactions of 3 with Acetylenic Compounds. General Procedure——The salt **2** (1 mmol) and 1 mmol of DMAD or MP were suspended in 10 ml of dry MeCN, then Et_3N was slowly added with stirring. The reaction conditions were adjusted as shown in Table I. After the reaction, the solvent was evaporated and dil. NaCl was added. After extraction with $CHCl_3$, the organic layer was dried ($MgSO_4$), then evaporated. The crude product was separated and purified by silica-gel column chromatography (mixture of AcOEt–hexane as eluent, Table II). **11**[3]: ^{13}C-NMR (CF_3COOH) δ: 30.5, 38.8, 41.2 (3 × NCH_3), 54.5 (OCH_3), 104.9 (C-10a), 117.4 (C-6a), 121.6 (C-7), 123.7 (C-8), 128.8 (C-9), 145.3, 154.8, 160.0, 161.3 (C-3, 1, 6, 4a), 169.3 (COO).

Reaction of 8c with *n*-BuLi——Under N_2, 201 mg of **8c** was suspended in 5 ml of dry THF, 0.5 ml of 1.1 N *n*-BuLi was added with stirring at −60 °C. After 2 h the temperature was gradually raised to −10 °C. An NH_4OH solution was added and the mixture was extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and evaporated, and the residue was purified by TLC (AcOEt as the developing solvent) to give crystalline **10**. Recrystallization from MeOH

TABLE II. Properties of **8** and **9**

Compd.	R	mp (°C)[a]	Recryst solv.	Formula	Analysis (%) Calcd (Found)		
					C	H	N
8a	CN	204—206[b]	MeOH	$C_{16}H_{17}N_5O_6$	51.20	4.57	18.66
					(51.22	4.57	18.56)
8b	COPh	217—218[c]	AcOEt	$C_{22}H_{22}N_4O_7 \cdot 0.5CH_3COOC_2H_5$	57.83	5.26	11.24
					(57.92	5.25	11.33)
8c	$COOCH_3$	211.5—212.7	AcOEt	$C_{17}H_{20}N_4O_8$	50.01	4.94	13.72
					(49.77	4.88	13.58)
9a	CN	262—264 (dec.)[d]	AcOEt	$C_{14}H_{15}N_5O_4$	52.99	4.77	22.07
					(53.25	4.77	22.07)
9b	COPh	143—145	AcOEt–acetone	$C_{20}H_{20}N_4O_5 \cdot 0.25CH_3COOC_2H_5 \cdot 0.5CH_3COCH_3$	60.39	5.63	12.52
					(60.26	5.42	12.85)
9c	$COOCH_3$	209.5 (dec.)	AcOEt	$C_{15}H_{18}N_4O_6$	51.43	5.18	15.99
					(51.28	5.16	15.91)
11		287—288.5	EtOH	$C_{14}H_{14}N_4O_5$	52.83	4.43	17.60
					(52.81	4.51	17.39)

a) We found new features of the melting points of **8** and **9** after our preliminary communication.[3] Compounds **8a**, **8b** and **9a** showed double melting point. Some errors in that communication are corrected in this paper. The lower values of melting points were as follows. *b*) 140—142 °C. *c*) 99—102 °C. *d*) 220 °C.

gave 34 mg of pure **10** (yield 18.3%). The IR spectrum of the product was identical with that of authentic **10** obtained from **2c** and DMAD with *n*-BuLi in THF. From another fraction of the TLC, 136 mg of **8c** (68.5%) was recovered.

Detection of 8-Benzoyl-6,7-bis(methoxycarbonyl)-5a,8-dihydro-5*H*-pyrrolo[2,1-*f*]purine-1(2*H*),3(4*H*)-dione (7) ——Et_3N (50 mg) was added to a suspension of **2b** (242 mg) and DMAD (85 mg) in $CHCl_3$ (10 ml) and the mixture was stirred for 20 min. The solution was quenched with water and extracted with $CHCl_3$. After drying ($MgSO_4$) and evaporation of the extract, the residue was analyzed by ^{1}H-NMR spectroscopy ($CDCl_3$). The ratio of **7** and **8b** was calculated to be 3 : 1. Signals of **7**: 3.02 (3H, s, N^5-CH_3), 3.30 (3H, s, N^4-CH_3), 3.35 (3H, s, N^2-CH_3), 3.55, 3.83 (each 3H, s, s, $OCH_3 \times 2$), 5.80 (1H, d, C_{5a}-H, J=2.3 Hz), 6.38 (1H, d, C_8-H, J=2.3 Hz).

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10) Melting points were taken on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra were determined with a Hitachi R-20B spectrometer and chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard. ^{13}C-NMR spectra were determined with a JEOL FX-90Q spectrometer. IR spectra were recorded with a JASCO IRA-1 spectrometer. MS were recorded with a JEOL JMS D-300 spectrometer.
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