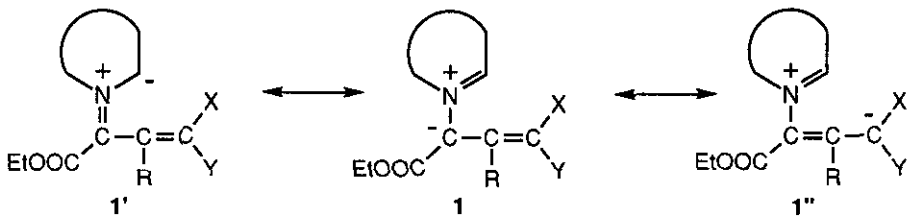
THERMAL REACTION OF 1,2,4-TRIAZOLIUM *N*-ALLYLIDES: FORMATION OF MESOMERIC BETAINES, 1,2,4-TRIAZOLO[4,3-*a*]PYRIDINIUMIDES, *VIA* BACK-DONATED 1,6-CYCLIZATION

Yoshiro Matsuda,* Yasushige Chiyomaru, Chieko Motokawa, and
Takanobu Nishiyori

School of Pharmaceutical Sciences, Nagasaki University,
1-14 Bunkyo-machi Nagasaki 852, Japan

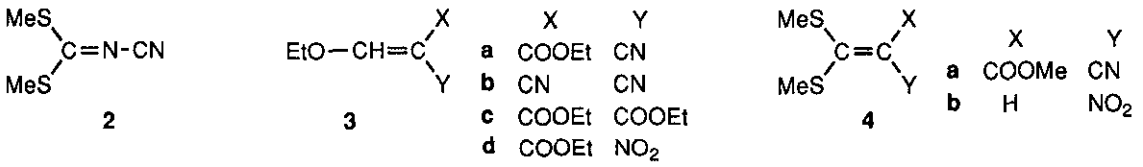
Abstact —— The reaction of 1,2,4-triazolium salt (**7**) with polarized olefins (**2, 3a,b**) in the presence of K_2CO_3 in $CHCl_3$-EtOH gave the corresponding triazolium *N*-allylides (**8a-c**). Thermolyses of the *N*-allylides (**8a,c**) afforded the mesomeric betaine (**9a**) and the 8-amino-1,2,4-triazolo[4,3-*a*]pyridine derivative (**10**). Similar treatment of the salt (**7**) with polarized olefins (**3c,d, 4a**) directly yielded mesomeric betaines (**9c-e**), while the reaction of the salt (**7**) with polarized olefin (**4b**) gave the pyrrolo[1,2-*d*]-1,2,4-triazine derivative (**11**). The formation of mesomeric betaines is suggested to proceed *via* back-donated 1,6-cyclization.

Polarized olefins (ethoxymethylene compounds and ketene dithioacetals) that have appropriately functionalized groups (cyano, methoxycarbonyl, nitro, sulfonyl, pyridyl, etc.) are versatile reagents which have been extensively utilized in heterocyclic synthesis.[1] As a part of our continuing interest in such olefins, we carried out extensive studies on the reaction of heteroaromatic compounds with various polarized olefins and their analogues.[2] In particular, it is well known that heterocyclic salts react with polarized olefins to produce heterocyclic *N*-allylides (**1**). These allylides (**1**), acting as extended dipoles, are of interest in heterocyclic chemistry.[3] These *N*-allylides may be considered to be resonance hybrids of the representative structures (**1, 1', 1"**) shown in Scheme 1.

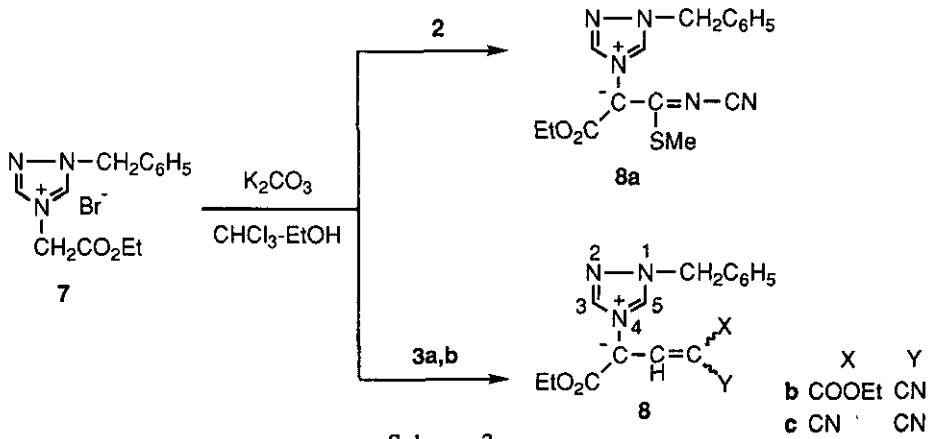


Scheme 1

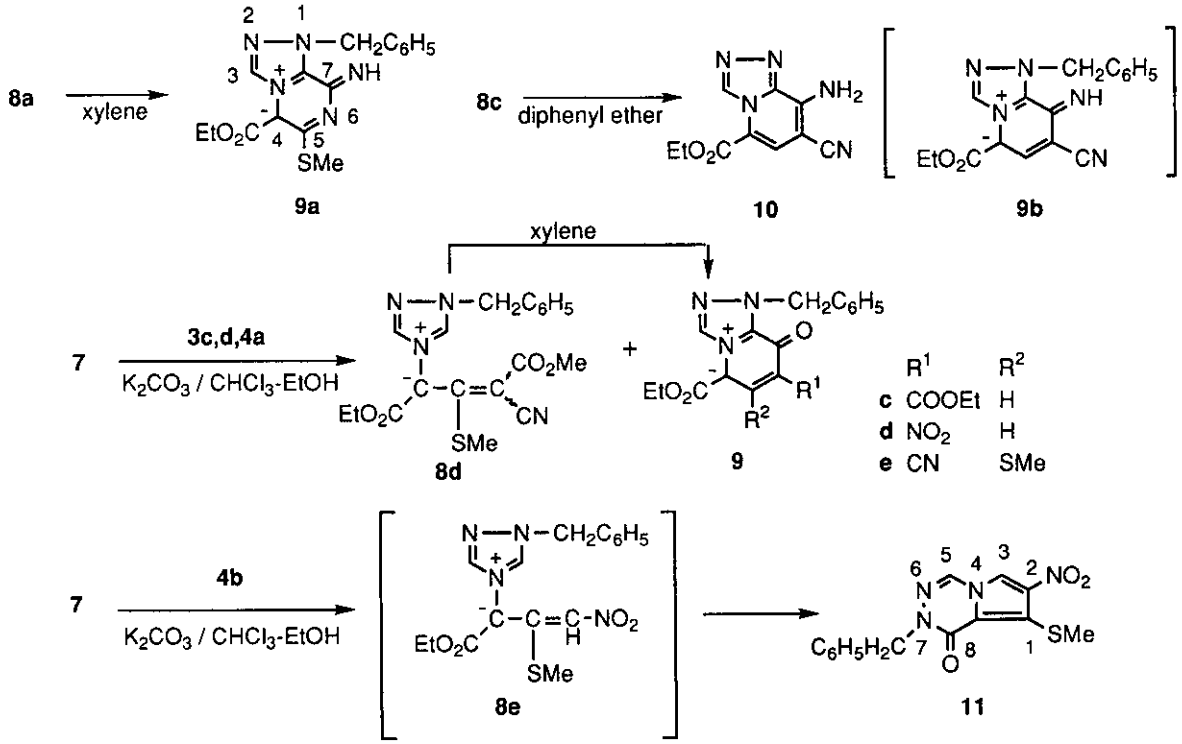
However, a number of previous studies on *N*-allylides (**1**) have been mainly concerned with the synthesis of bicyclic compounds with bridgehead nitrogen, indolizines by 1,5-dipolar cyclization due to the resonance structure (**1"**). We have taken advantage of an alternative *N*-allylide form (resonance structure **1'**) to realize a novel reaction which we have termed a 'back-donated 1,6-cyclization'. Our preliminary studies[4] on the thermolyses of imidazolium *N*-allylides and *N*-vinylimino ylides have led to a new heterocyclic ring closure proceeding by back-donated 1,6-cyclization onto carbonyl or cyano carbon at X to produce the mesomeric betaines, imidazo[1,2-*a*]pyridiniumides or imidazo[1,2-*b*]pyridaziniumides. The purpose of the present investigation was to extend this back-donated 1,6-cyclization to the synthesis of 1,2,4-triazolo[4,3-*a*]-pyraziniumide (**9a**) and 1,2,4-triazolo[4,3-*a*]pyridinumide (**9c-e**). The polarized olefins (**2-4**)[5] used in the present work are shown in Scheme 2.



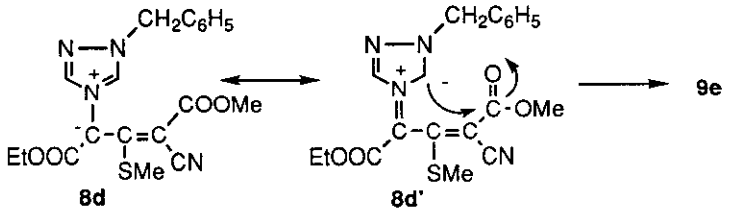
Scheme 2



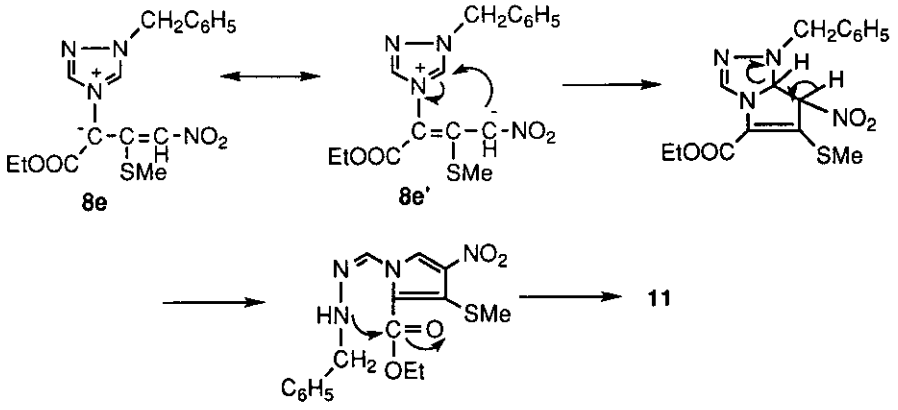
Scheme 3



Scheme 4



Scheme 5



Scheme 6

By Couture's method[6] the starting material, 1,2,4-triazolium salt (**7**), was prepared from the reaction of ethyl bromoacetate with 1-benzyl-1,2,4-triazole (**6**), which was obtained by the reaction of 1,2,4-triazole (**5**) with benzyl bromide in the presence of sodium hydride in THF. The reaction of the salt (**7**) with polarized olefins (**2**, **3a**,**b**) in the presence of K_2CO_3 gave triazolium *N*-allylides (**8a-c**) (Scheme 3).

A solution of **8a** in xylene was refluxed to afford the desired mesomeric betaine, 7-imino-1,2,4-triazolo[4,3-*a*]pyraziniumide (**9a**). Attempts to obtaine the mesomeric betaine from **8b**,**c** by thermolysis in refluxing xylene, trimethylbenzene or acetic acid were fruitless. After much investigation, we found that refluxing of **8c** in diphenyl ether did not give the mesomeric betaine (**9b**), but gave 8-amino-1,2,4-triazolo[4,3-*a*]pyridine (**10**) with debenzylation. In addition, the reaction of the salt (**7**) with polarized olefins (**3c,d, 4a**) in the presence of K_2CO_3 directly afforded the back-donated 1,6-cyclization products (**9c-e**) together with the *N*-allylide (**8d**). The compound (**9e**) was also obtained by the thermolysis of **8d** in refluxing xylene. On the other hand, similar treatment of **7** with 2,2-bis(methylthio)-1-nitroethylene (**4b**) afforded the 1,5-dipolar cyclization product, pyrrolo[1,2-*d*]-1,2,4-triazine (**11**) without 1,2,4-triazolium *N*-allylide (**8e**) (Scheme 4).

As pointed out in our previous paper,[4] a reasonable mechanism for the formation of the back-donated 1,6-cyclization product (**9e**) involves the resonance structure (**8d'**), as outlined in Scheme 5. As pointed out by Acheson and Elmore[3k] and Meth-Cohn,[3e] the formation of **11** may be rationalized as outlined in Scheme 6.

In conclusion the 1,2,4-triazolium *N*-allylide (**8**) which had two electron-withdrawing groups at the 3-position of the allylide group participated in back-donated 1,6-cyclization to produce the mesomeric betaine (**9**). The high efficiency of the back-donated 1,6-cyclization, due to the resonance structure (**1'**), in thermolysis of the *N*-allylide of the resulting mesomeric betaine, 1,2,4-triazolo[4,3-*a*]pyridiniumide, presents interesting synthetic possibilities.

EXPERIMENTAL

Melting points were determined with a Mitamura Mel-Temp and are uncorrected. Ir spectra were recorded in KBr pellets on a JASCO IRA-2 spectrophotometer. Uv spectra were recorded on a Hitachi 323 spectrophotometer. ^{1}H-Nmr spectra were obtained on JNM-FX-90Q spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ). Elemental analyses (C,H,N) of all compounds described here were performed on a Yanagimoto MT-2 CHN recorder.

The preparation of 7

By Couture's method,[6] to a stirred solution of 1,2,4-triazole (**5**) (34.5 g, 0.5 mol) and Na (23 g, 1 mol) in EtOH (300 ml) at 0 °C was added dropwise benzyl bromide (85.5 g, 0.5 mol) and left to warm up to room tempetature. After standing overnight the reaction mixture was poured into ice-water (2 l) and extracted with $CHCl_3$ (4x100 ml). The organic extracts were combined and dried (Na_2SO_4). The solvent was evaporated and the residue was distilled in vacuum (bp 129-133 °C/ 3 mm Hg) to give 1-benzyl-1,2,4-triazole (**6**) (38.2 g, 48 %) which solidified, mp 52-54 °C (lit. bp 110 °C/ 0.001 mm Hg,[7] mp 54-55 °C[8]). A mixture of **6** (15.9 g, 0.1 mol) and ethyl bromoacetate (16.7 g, 0.1 mol) in acetone (200 ml) was stirred at room temperature for a week. The precipitate was collected by filtration, washed with acetone, dried and recrystallized from EtOH to give **7**.

7 : mp 187-190 °C (17.9 g, 55 %). Ir (KBr) cm^{-1} : 1725 (CO). ^{1}H-Nmr ($CDCl_3$) : 1.27 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.23 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 5.65 (2H, s, CH_2Ar), 5.71 (2H, s, CH_2CO), 7.33-7.50 (5H, m, Ar-H), 9.23 (1H, s, C_3-H), 11.32 (1H, s, C_5-H). *Anal.* Calcd for $C_{13}H_{16}N_3O_2Br$: C, 47.87; H, 4.94; N, 12.88. Found : C, 47.78; H, 4.96; N, 12.66.

General procedure for the preparation of 8

A mixture of the salt (**7**) (1.30 g, 4 mmol), a polarized olefin (**2, 3a,b**) (4 mmol) and K_2CO_3 (1.21 g, 8 mmol) in $CHCl_3$-EtOH(1:1, 50 ml) was stirred at room temperature for a week and the mixture was then poured into ice-water (100 ml). The mixture was extracted with $CHCl_3$ (4x30 ml) and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was recrystallized from $CHCl_3$-MeOH to give **8a-c**, respectively.

8a : mp 173-176 °C (0.75 g, 55 %). Ir (KBr) cm^{-1} : 2140 (CN), 1650 (CO). Uv (EtOH) λmax (log ε) nm : 202 (4.41), 268 (4.11), 305 (4.34). ^{1}H-Nmr ($CDCl_3$) : 1.14 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.33 (3H, s, SCH_3), 4.07 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 5.52 (2H, s, CH_2Ar), 7.48 (5H, s, Ar-H), 8.26 (1H, s, C_3-H), 8.27 (1H, s, C_5-H). *Anal.* Calcd for $C_{16}H_{17}N_5O_2S$: C, 55.96; H, 4.99; N, 20.39. Found : C, 56.04; H, 4.96; N, 20.43.

8b : mp 168-170 °C (0.29 g, 20 %). Ir (KBr) cm^{-1} : 2180 (CN), 1680 (CO), 1660 (CO). Uv (EtOH) λmax (log ε) nm : 340 (4.62), 239 (4.04) sh. ^{1}H-Nmr ($CDCl_3$) : 1.26 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.16 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 5.50 (2H, s, CH_2Ar), 7.49 (5H, s, Ar-H), 8.23 (1H, s, CH=), 8.30 (1H, s, C_3-H), 8.31 (1H, s, C_5-H). *Anal.* Calcd for $C_{19}H_{20}N_4O_4$: C, 61.95; H, 5.47; N, 15.21. Found : C, 61.66; H, 5.47; N, 15.15.

8c : mp 199-201 °C (1.03 g, 80 %). Ir (KBr) cm^{-1} : 2200 (CN), 1665 (CO). Uv (EtOH) λmax (log ε) nm : 278 (3.70), 355 (4.47), 405 (4.10). ^{1}H-Nmr ($CDCl_3$) : 1.43 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.30 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 6.41 (2H, s, CH_2Ar), 7.28-7.30 (5H, m, Ar-H), 7.37 (1H, s, CH=), 8.30 (1H, s, C_3-H), 8.31

(1H, s, C_5-H). *Anal.* Calcd for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.71; N, 21.79. Found : C, 63.47; H, 4.73; N, 21,67.

4,7-Dihydro-1-benzyl-4-ethoxycarbonyl-7-imino-5-methylthio-1,2,4-triazolo[4,3-*a*]pyrazin-3a-ium-4-ide (9a)

A solution of *N*-allylide (**8a**) (0.69 g, 2 mmol) in xylene (60 ml) was refluxed for 24 h and the solution was then evaporated under reduced pressure. To the residue was added ice-water (50 ml) and the mixture was extracted with $CHCl_3$ (4x30 ml). The combined extracts were washed with water (50 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was submitted to column chromatography on silica gel. From a benzene-$CHCl_3$ (20:1) fraction, **9a** was obtained.

9a : mp 160-163 °C (0.27 g, 40 %). Ir (KBr) cm^{-1} : 3130 (=NH), 1650 (CO). Uv (EtOH) λmax (log ε) nm : 254 (4.24), 282 (3.98), 327 (4.14), 369 (4.09). ^{1}H-Nmr ($CDCl_3$) : 1.41 (3H, t, *J*=7Hz, $CH_2C\underline{H}_3$), 2.43 (3H, s, SCH_3), 4.36 (2H, q, *J*=7Hz, $C\underline{H}_2CH_3$), 6.27 (2H, s, CH_2Ar), 7.51-7.26 (5H, m, Ar-H), 9.69 (1H, s, C_3-H). *Anal.* Calcd for $C_{16}H_{17}N_5O_2S$: C, 55.96; H, 4.99; N, 20.39. Found : C, 55.90; H, 5.00; N, 20.34.

8-Amino-7-cyano-5-ethoxycarbonyl-1,2,4-triazolo[4,3-*a*]pyridine (10)

A solution of *N*-allylide (**8c**) (0.64 g, 2 mmol) in diphenyl ether (60 ml) was refluxed for 4 h and hexane was then added to the solution. The precipitate was collected by filtration, washed with hexane, dried, and recrystallized from $CHCl_3$-MeOH to give **10**.

10: mp 230-231 °C (0.09 g, 20 %). Ir (KBr) cm^{-1} : 2215 (CN), 1640 (CO). Uv (EtOH) λmax (log ε) nm : 227 (4.36), 251 (4.15), 312 (4.08), 341 (4.30), 352 (4.25). ^{1}H-Nmr (DMSO-d_6) : 1.36 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.37 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 7.71 (1H, s, C_3-H), 8.40 (2H, s, NH_2), 9.69 (1H, s, C_6-H). *Anal.* Calcd for $C_{10}H_9N_5O_2$: C, 51.95; H, 3.92; N, 30.29. Found : C, 51.92; H, 4.08; N, 29.22.

General procedure for the preparation of 9c-e

A mixture of the salt (**7**) (1.30 g, 4 mmol) with a polarized olefin (**3c,d, 4a**) in the presence of K_2CO_3 (1.21 g, 8 mmol) in $CHCl_3$-EtOH (1:1, 30 ml) was stirred at room temperature for a week and the mixture was then poured into ice-water (100 ml). The mixture was extracted with $CHCl_3$ (4x30 ml) and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was submitted to column chromatography on silica gel. From a benzene-$CHCl_3$ (20:1) fraction, **8d** was obtained. From a benzene-$CHCl_3$ (1:1) fraction, **9c-e** were obtained. In addition, thermolysis of **8d** (0.40 g, 1 mmol) in refluxing xylene gave also **9e** (0.16 g, 43%).

8d : *mp* 116-118 °C (1.04 g, 65 %). Ir (KBr) cm^{-1} : 2190 (CN), 1690 (CO), 1660 (CO). Uv (EtOH) λmax (log ε) nm : 205 (4.27), 300 (3.93), 383 (4.24). ^{1}H-Nmr ($CDCl_3$) : 1.24 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.50 (2H, s, SCH_3), 3.37 (3H, s, OCH_3), 4.17 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 5.45 (2H, s, CH_2Ar), 7.42 (5H, s, Ar-H), 8.18 (1H, s, C_3-H), 9.21 (1H, s, C_5-H). *Anal.* Calcd for $C_{19}H_{20}N_4O_4S$: C, 56.99; H, 5.03; N, 13.99. Found : C, 57.22; H, 5.11; N, 13.79.

9c : mp 256-259 °C (0.14 g, 10 %). Ir (KBr) cm^{-1} : 1675 (CO), 1605(CO). Uv (EtOH) λmax (log ε) nm : 321 (4.36), 355 (4.30). ^{1}H-Nmr ($CDCl_3$) : 1.40 (3H, t, *J*=7Hz, $CH_2C\underline{H}_3$), 1.42 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.39 (2H, q, *J*=7Hz, $C\underline{H}_2CH_3$), 4.42 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 6.29 (2H, s, CH_2Ar), 7.22-7.62 (5H, m, Ar-H), 8.59 (1H, s, C_3-H), 9.84 (1H, s, C_5-H). *Anal.* Calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38. Found : C, 61.58; H, 5.10; N, 11.49.

9d : mp 154-155 °C (0.27 g, 20 %). Ir (KBr) cm^{-1}: 1700 (CO), 1625 (CO). Uv (EtOH) λmax (log ε) nm : 225 (4.17), 329 (4.35), 390 (4.12). ^{1}H-Nmr ($CDCl_3$) : 1.42 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 4.42 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 6.72 (2H, s, CH_2Ar), 7.39-7.57 (5H, m, Ar-H), 8.83 (1H, s, C_3-H), 9.91 (1H, s, C_5-H). *Anal.* Calcd for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.37. Found : C, 55.93; H, 4.18; N, 16.32.

9e : mp 143-146 °C (0.12 g, 8 %). Ir (KBr) cm^{-1} : 2200 (CN), 1680 (CO), 1590 (CO). Uv (EtOH) λmax (log ε) nm : 207 (4.04), 345 (3.95). ^{1}H-Nmr ($CDCl_3$) : 1.45 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 2.63 (3H, s, SCH_3), 4.47 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 6.18 (2H, s, CH_2Ar), 7.29-7.64 (5H, m, Ar-H), 9.54 (1H, s, H). *Anal.* Calcd for $C_{18}H_{16}N_4O_3S$: C, 58.68; H, 4.38; N, 15.21. Found : C, 58.56; H, 4.41; N, 15.17.

7,8-Dihydro-7-benzyl-1-methylthio-2-nitro-8-oxopyrrolo[1,2-*d*]-1,2,4-triazine (11)

A mixture of the salt (**7**) (1.30 g, 4 mmol) with polarized olefin (**4b**) (0.53 g, 4 mmol) in the presence of K_2CO_3 (1.21 g, 8 mmol) in $CHCl_3$-EtOH (1:1, 30 ml) was stirred at room temperature for a week and the mixture was poured into ice-water (100 ml). The mixture was extracted with $CHCl_3$ (4x30 ml) and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was submitted to column chromatography on silica gel. From a benzene-$CHCl_3$ (*20:1*) fraction, **11** was obtained.

11: mp 203-205 °C (0.43 g, 34 %). Ir (KBr) cm^{-1} : 1650 (CO). Uv (EtOH) λmax (logε) nm : 209 (4.36), 240 (4.18), 277 (4.20). ^{1}H-Nmr ($CDCl_3$) : 2.64 (3H, s, SCH_3), 5.17 (2H, s, CH_2Ar), 7.26-7.39 (5H, m, Ar-H), 7.90 (1H, s, C_3-H), 7.91 (1H, s, C_5-H). *Anal.* Calcd for $C_{14}H_{12}N_4O_3S$: C, 53.16; H, 3.82; N, 17.71. Found : C, 53.22; H, 3.83; N, 17.79.

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