CROSSS-CONJUGATED AND PSEUDO-CROSS-CONJUGATED MESOMERIC BETAINES, 19.[1] CYCLOADDITION PRODUCTS FROM MESOMERIC PYRIMIDINIUMOLATES AND TCNE AND THEIR THERMAL RING TRANSFORMATION REACTION

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This paper is dedicated with great admiration to Professor Rolf Huisgen who introduced the concept of 1,4-dipolar cycloaddition reactions in 1965-67 to heterocyclic chemistry.[2a] It is also dedicated to the memory of Professor Hans Gotthardt (1932-1989), his former student, who added so much to our knowledge of cycloadditions with mesomeric pyrimidine betaines (see introduction).

Abstract - The bicyclic pyrido-pyrimidine mesoion (**2**) reacts with TCNE under the loss of HCN to yield the tricyanovinylated derivative (**3**). However, monocyclic pyrimidine betaines (**4a-d**) (substituted at C-5) afford with TCNE 1,4-dipolar cycloaddition products (**5a-d**). Compounds (**5c,d**) (with CH_2 groups at the malonyl moiety) rearrange above 200 °C under the loss of HCN and phenyl isocyanate to yield cyclopenta[*d*]pyrimidines (**6a,b**).

Introduction

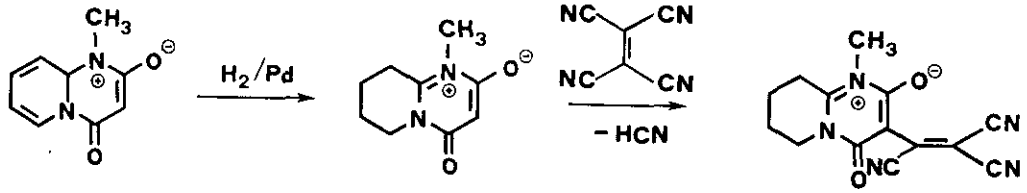
Six-membered mesoionic heterocycles of the pyrimidine, 1,3-oxazine, and 1,3-thiazine series - be they mono- or bicyclic - may be looked upon as 1,4-dipolar systems.[2] Therefore they appear to be suitable candidates for 1,4-dipolar cycloadditions. This assumption has already been verified in 1971 by Kappe[3a] and Potts[4] using electron-poor dipolarophiles such as acetylene dicarboxylates,[3a,4] maleic anhydride,[3a] and benzyne.[3b] The relevant literature until 1982 has been summari-

zed by review articles.[2b] However, new results have emerged more recently. For instance, intramolecular 1,4-dipolar cycloadditions using mesoionic thiazines[5] and pyrimidines[6] have been reported. Gotthardt and his group showed in a series of papers that mono- and bicyclic mesoionic pyrimidines are capable of cycloaddition reactions with singlet oxygen[7] as well as with electron-poor multiple bond systems such as nitriles,[8] 1,2,4-triazolin-3,5-diones,[9] ketenes and ketones,[10] *cis*- and *trans*- ethenedicarboxylates[12], methyl propiolate[12], and (more surprisingly) with electron-rich multiple bond systems, such as bis(dialkylamino)ethynes,[12] diethylaminopropyne,[13,14] enol ethers,[11] enamines,[11] and ketene acetals.[11,13] Furthermore, valuable contributions concerning the mechanism of these 1,4-dipolar cycloadditions were made by establishing the regio-[12] and stereochemistry[11,12] of the reaction products.

These results prompt us to report our earlier work[2b,15] on the cycloaddition of tetracyanoethene (TCNE) to mesomeric pyrimidine betaines after we were recently successful in establishing the structure of compounds resulting from thermolysis of the primary addition products by X-ray crystal structure analysis.

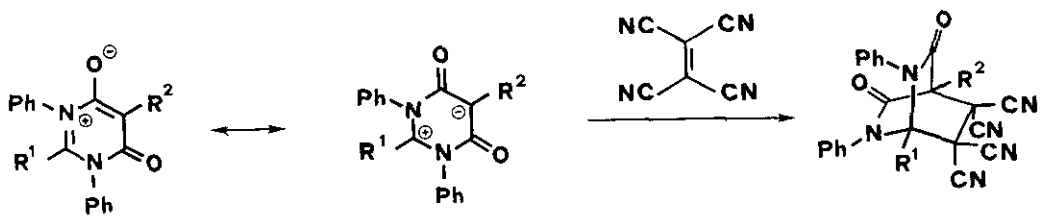
Results and Discussion

The reaction of a mesomeric pyrimidine betaine with tetracyanoethene has already been tested some time ago.[4] However, the substrate molecule (**1**) had no substitution at the C-atom of the malonyl moiety, thus only "tricyanovinylation"[16] at the nucleophilic site of the mesoion occurred. We found another example for this type of reaction: when the bicyclic mesoion (**2**), obtained by catalytic hydrogenation of the well-known[17] betaine (**1**), was heated with TCNE in boiling benzene, the tricyanovinyl derivative (**3**) was formed under loss of hydrogen cyanide. It should be mentioned that ethyl azodicarboxylate also gives an "ene-type" adduct with **1**,[4] and that dimethyl acetylenedica rboxylate adds in a first step in a similar fashion to bicyclic mesoionic 1,3-thiazines yielding dimethyl fumarate derivatives.[18]



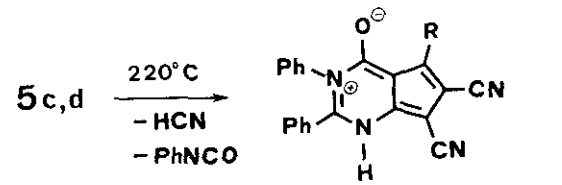
1 **2** **3**

However, when the monocyclic mesoionic pyrimidines (**4a-d**) were allowed to react with TCNE in boiling benzene for about 16 hours the cycloadducts (**5a-d**) could be isolated as colorless prisms. The structure of compounds (**5**) as 2,6-diazabicyclo[2.2.2]octane-3,5-dione derivatives is in agreement with their elemental analyses and spectroscopic data. However, it is noteworthy that they show no nitrile absorption in the infrared spectra.[19] The yields seem to be dependent on the bulkiness of the substituents, especially in the 5-position (R^2) of **4**: while **5a** and **5b** could be obtained in 85% and 71% yield, respectively, **5c** was obtained in 28% and **5d** in 41% yield. Attempts to perform the cycloaddition with samples of **4** with R^1 = phenyl and R^2 = phenyl or isopropyl failed.



4a–d **5a–d**

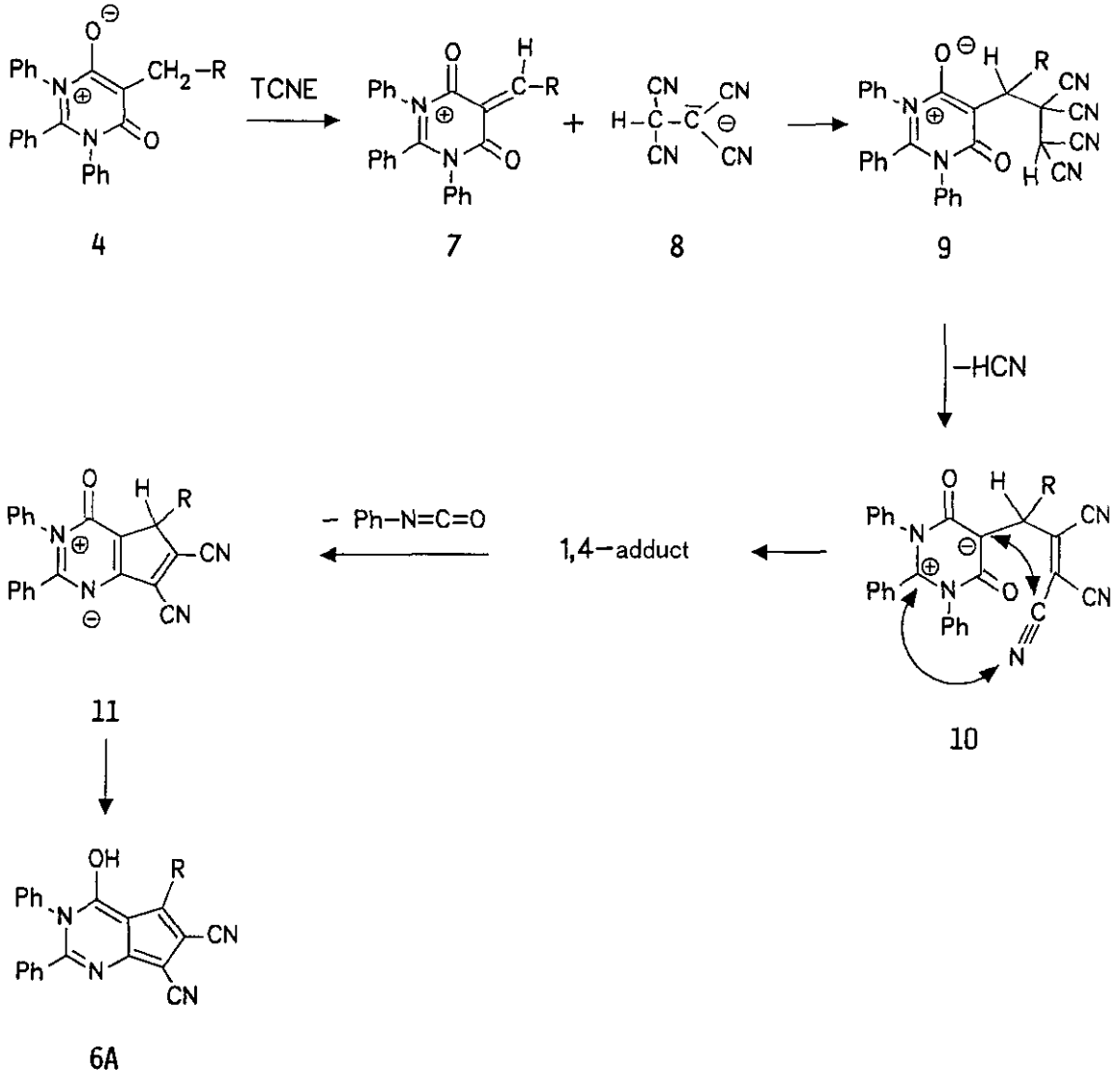
4,5	R^1	R^2
a	H	H
b	CH_3	CH_3
c	C_6H_5	C_2H_5
d	C_6H_5	$CH_2C_6H_5$



6a: R = CH_3
6b: R = $CH_2C_6H_5$

All cycloaddition products (**5**) melt at about 190 °C under slow decomposition. While **5a** and **5b** decompose uncontrolled to a number of products, the thermolysis of **5c** and **5d** (preferentially performed *in vacuo* at 220 °C) leads to new, bright yellow colored products in 85% yield. Elemental analysis shows that both compounds are formed from **5** under loss of hydrogen cyanide and phenyl isocyanate. This is substantiated by the mass spectra of **5** which show also the loss of phenylisocyanate as predominant fragmentation pathway. Now the infrared spectra show the presence of nitrile groups and a carbonyl absorption at 1720 cm^{-1} for **6a** and 1710 cm^{-1} for **6b**. The proton magnetic resonance spectra are most informative: they show clearly that the CH_2-group of the side chain (R^2) must have been attacked and converted to a sp^2 hybridized C-atom - thus the ethyl group of **5c** is converted to a methyl group in **6a**, and the benzyl

group of **5d** to a phenyl substituent in **6b**. These findings are also substantiated by the ^{13}C-nmr of **6a** (see Experimental). However, with all spectroscopic data available the structure of the new yellow compounds remained unsolved. Actually, some information led into wrong directions; for instance the high carboxamide bands in the ir together with the loss of phenyl isocyanate in the mass spectra suggested a five-membered *N*-phenyl substituted lactam ring as partial structure.[15] Having solved the constitution of **6a** by X-ray structure analysis of a crystal containing one equivalent of dimethyl sulfoxide associated by a hydrogen bridge to the zwitterionic structure of **6a**, it should be emphasized that in solution also the tautomeric non-zwitterionic 4-hydroxypyrimidine (**6A**) may be present, which complicates the interpretation of the ^{13}C-nmr data.



The reaction mechanism yielding the cyclopenta[*d*]pyrimidines (**6**) by thermolysis of **5** is quite interesting. The fact that isocyanates are eliminated from primary cycloadducts derived from pyrimidine betaines (leading to pyridones) has been frequently observed, especially if acetylenic dipolarophiles are used.[2-4] Cycloadducts derived from mesoionic 1,3-oxazines and 1,3-thiazines eliminate CO_2 or COS even more readily to the 2-pyridone system.[2b,5] In our case the formation of a pyrimidine nucleus requests the incorporation of a nitrile group into the system. Since Gotthardt has already shown that the cyano group can act as a dipolarophile with pyrimidine betaines,[8] structure (**10**) would be a logical precursor for such a reaction affording **11** (after extrusion of phenyl isocyanate from the primary 1,4-adduct) which to the final product (**6A**), or its tautomer (**6**), by hydrogen shift. However, there is no decent mechanistic pathway thinkable which would lead from **5** to **10**. The only possibility rests in the assumption of a *retro*-Diels-Alder reaction of **5** (which seems not unlikely at 200 °C!) giving back **4** and TCNE which now attacks **4c,d** in a thermodynamically controlled reaction at the CH_2-group of the side chain. Tricyanovinylation reactions at carbon with TCNE under loss of HCN are well known.[16] In our case the reaction sequence may start with a hydride transfer from **4** to TCNE (maybe preceded by SET) followed by a Michael type reaction of the cation (**7**) with the anion (**8**) to give **9** which after loss of HCN affords the postulated intermediate (**10**). Analogous reactions have been described in the literature.[21,22] (We thank Prof. R. Huisgen for drawing our attention to the possibility of the ion pair intermediate, and for providing literature references.)

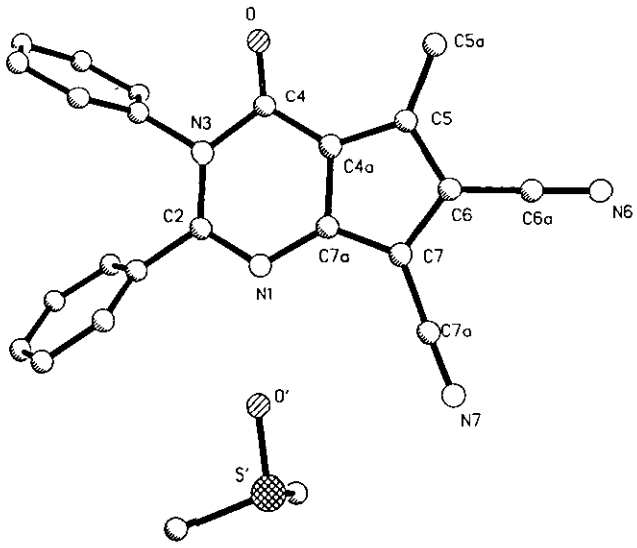


Figure 1. X-Ray structure of **6a** (with 1 molecule of *DMSO*).

Table 1. Bond length and angles of **6a**.

C5	-C6	1.385			C6	-C5	1.385		
C5	-C4A	1.415	106.4		C6	-C7	1.428	110.8	
C5	-C5A	1.496	127.3	126.3	C6	-C6A	1.418	124.8	124.3
			C6	C4A				C5	C7
C7	-C6	1.428			C7A	-C7	1.397		
C7	-C7A	1.397	105.5		C7A	-N1	1.386	131.0	
C7	-C7A	1.425	124.1	130.4	C7A	-C4A	1.416	109.1	119.9
			C6	C7A				C7	N1
N1	-C7A	1.386			C2	-N1	1.329		
N1	-C2	1.329	121.2		C2	-N3	1.368	120.1	
			C7A		C2	-C16	1.468	118.8	121.1
								N1	N3
N3	-C2	1.368			C4	-N3	1.437		
N3	-C4	1.437	123.9		C4	-C4A	1.423	113.9	
N3	-C22	1.457	120.4	115.5	C4	-O	1.229	118.4	127.7
			C2	C4				N3	C4A
C4A	-C5	1.415			O	-C4	1.229		
C4A	-C7A	1.416	108.2						
C4A	-C4	1.423	130.9	120.8					
			C5	C7A					
C5A	-C5	1.496			C6A	-C6	1.418		
					C6A	-N6	1.167	178.7	
								C6	
N6	-C6A	1.167			C7A	-C7	1.425		
					C7A	-N7	1.151	177.6	
								C7	
N7	-C7A	1.151			N1	-O'	2.678		

Experimental

Melting points (uncorrected): Tottoli (Büchi) or Gallenkamp melting point apparatus, Mod. MFB-595. - Ir spectra: Perkin-Elmer 424. - ^{1}H-Nmr: Varian A-60A, HA-100D, or XL-200 (TMS as internal standard). - ^{13}C-Nmr: Varian XL-200. - Mass spectra: MS 20 (AEI Manchester).

1-Methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-1-ium-2-olate (**2**): The solution of 5.0 g (28 mmol) of **1**[17] in 250 ml of methanol was hydrogenated over 5% Pd/charcoal (200 mg) at room temperature for about 24 h. After removal of the catalyst and evaporation to dryness the resulting oil was recrystallized from benzene yielding colorless plates (4.6 g, 90%), mp 180 °C. - Ir (KBr). 2950 (CH), 1720-1630 (C=O) cm^{-1}. - ^{1}H-Nmr (DMSO-d_6): δ = 1.80 (m, 4 H at C-7 and C-8), 2.90 (m, 2 H, C-9), 3.25 (s, 3 H, CH_3), 3.70 (m, 2 H, C-6), 4.55 (s, 1 H, H-3). Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6,71; N, 15.54. Found : C, 59.56; H, 6.68; N, 15.32.

3-Tricyanoethene-1-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido-[1.2-a]pyrimidin-1-ium-2-olate (**3**): The mixture of 1.8 g (10 mmol) **2** and 1.28 g (10 mmol) of TCNE in 75 ml of benzene was refluxed for 20 min. The solution was evaporated and the residue dissolved in 50 ml of hot acetone, charcoal was added and after filtration the acetone was removed. Crystallization from ether/acetonitrile (2:1) afforded 400 mg (14%) **3** in form of slightly yellow plates, mp 95 °C. - Ir (KBr): 2210 (CN), 1655 (C=O), 1496 (C=C) cm^{-1}. - ^{1}H-Nmr (DMSO-d_6): δ = 1.60-2.00 (m, 4 H, at C-7 and C-8), 3.00 (m, 2 H, C-8), 3.40 (s, 3 H, CH_3), 3.80 (m, 2 H, C-6). Anal. Calcd for $C_{14}H_{11}N_5O_2$: C, 59.79; H, 3.94; N, 24.89. Found : C, 59.63; H, 3.70; N, 24.84.

3,5-Dioxo-2,6-diphenyl-2,6-diazabicyclo[2.2.2]octane-7,7,8,8-tetracarbonitrile (**5a**): An intimate mixture of 2.94 g (7.5 mmol) of **4a** and 0.96 g (7.5 mmol) of TCNE was refluxed in 75 ml of absol. benzene for 20 h. The resulting new precipitate was isolated, washed with petroleum ether (bp 30-60 °C) and ether. Yield 2.50 g (85%); colorless prisms, mp 195 °C (methanol). - Ir (KBr): 3000 (CH), 1740, 1710 (C=O), 1590 (aromat). - ^{1}H-Nmr (DMSO-d_6): δ = 5.25 (s, 1 H, H-4), 7.10-7.45 (m, 10 H, arom. H), 7.55 (s, 1 H, H-4). - Anal. Calcd for $C_{22}H_{12}N_6O_2$: C, 67.35; H, 3.08; N 21.42. Found : C, 67.08; H, 3.25; N 21.20.

1,4-Dimethyl-3,5-dioxo-2,6-diphenyl-2,6-diazabicyclo[2.2.2]octane-7,7,8,8-tetracarbonitrile (**5b**): The mixture of 2.92 g (10 mmol) of **4b** and 1.28 g (10 mmol) of TCNE was refluxed in dry benzene (100 ml) for 16 h. The solution is concentrated to a small volume yielding 3.00 g (71%) of colorless prisms; mp 195 °C (acetonitrile). - Ir (KBr): 1735, 1705 cm^{-1} - ^{1}H-Nmr (DMSO-d_6): δ = 1.45 (s, 3 H, CH_3 at C-4), 1.75 (s, 3 H, CH_3 at C-1) Anal. Calcd for $C_{24}H_{16}N_6O_2$: C, 68.57; H, 3.84; N, 19.99 Found : C, 68.89; H, 3.91; N, 20.20.

4-Ethyl-3,5-dioxo-1,2,6-triphenyl-2,6-diazabicyclo[2.2.2]octane-7,7,8,8-tetracarbonitrile (**5c**): The mixture of 0.92 g (2.5 mmol) of **4c** and 0.315 g (2.5 mmol) of TCNE was refluxed in 75 ml of dry benzene. After evaporation of the solvent the residue was digested with petroleum ether. Crystallization from methanol afforded 0.35 g (28%) of colorless prisms, mp 190 °C (decomp.). - Ir (KBr): 1700 cm^{-1} (C=O), 1590 (Arom.). - Anal. Calcd for $C_{30}H_{20}N_6O_2$: C, 72.57; H, 4.06; N, 16.93. Found : C, 72.90; H, 4.36; N, 17.38.

4-Benzyl-3,5-dioxo-1,2,6-triphenyl-2,6-diazabicyclo[2.2.2]octane-7,7,8,8-tetracarbonitrile (**5d**): The mixture of 1.07 g (2.5 mmol) **4d** and of 0.315 g (2.5 mmol) of TCNE was refluxed in dry benzene (50 ml) for 16 h. The solution was evaporated and the residue digested with petroleum ether. Crystallization from methanol yielded 0.55 g (28%) of colorless prisms, mp 192 °C (decomp.). - Ir (KBr): 1700 (C=O), 1600 (arom.) cm^{-1}; ir (DMSO): 2240 (CH), 1690 (C=O),

1600, 1510 cm^{-1}. - Ms (70 eV): *m/z* = 439 (100%, M^+ - C_6H_5NCO). - Anal. Calcd for $C_{35}H_{22}N_6O_2$: C, 75.26; H; 3.97; N, 15.04. Found : C, 75.60; H; 3.94; N, 15.27.

6,7-Dicyano-5-methyl-2,3-diphenyl-1H-cyclopenta[d]pyrimidin-3-ium-4-olate **(6a)**: Compound (**5c**) (300 mg) was heated *in vacuo* for 20 min at 220 °C. The product was digested with cyclohexane and then crystallized fom a small amount of DMF yielding 180 mg (86%) of yellow prisms; mp 250 °C (dec.). - Ir (KBr): 2220 (CN), 1720 (C=O), 1625 (C=C) cm^{-1}. - ^{1}H-Nmr (DMSO-d_6): δ = 2.40 (s, 3 H, CH_3), 6.80-7.50 (m, 10 H, 2 phenyl), 8.40 (s, 1 H, NH). - ^{13}C-Nmr (DMSO-d_6): δ = 12.68 (CH_3), 77.05 (C-7), 97.46 (C-6), 106.42 (C-4a), 116.22 (CN), 117.24 (CN), 127.18 (C-5), 129.98 (Ph-ipso C-2), 132.85 (C-7a), 136.34 (Ph-ipso N-3), 154.32 (C-2), 156.47 (C-4). - Ms (70 eV): *m/z* (%) = 350 (55, M^+), 258 (19), 231 (34, M^+ - PhNCO), 180 (75, PhN=CPh), 105 (25), 77 (100, Ph), 51 (34). - Anal. Calcd for $C_{22}H_{14}N_4O$: C, 75.42; H, 4.03; N, 15.99 Found : C, 75.17; H, 4.19; N, 15.59.

5-Benzyl-6,7-dicyano-2,3-diphenyl-1H-cyclopenta[d]pyrimidin-3-ium-4-olate **(6b)**: Cycloadduct (**5d**) (300 mg) was heated for 15 min to 220 °C *in vacuo*. The melt is digested with cyclohexane and crystallized from DMF yielding 170 mg (85%) of yellow needles, mp 350 °C. - Ir (KBr): 2200 (CN), 1710 (C=O), 1620 (C=C) cm^{-1}. - Ms (70 eV): *m/z* (%) = 412 (80, M^+), 320 (45), 294 (30), 293 (10, M^+ - PhNCO), 180 (100, PhN=CPh), 92 (70). - Anal. Calcd for $C_{27}H_{16}N_4O$: C, 78.62; H, 3.89; N, 13.59. Found : C, 78.68; H, 4.16; N, 13.67.

Structure Determination of* 6a *by X-Ray Diffraction: Spacegroup $P\bar{1}$, a = 9.942(2), b = 11.143 (2), c = 20.525(30) Å, α = 83.29(2), β = 88.73(3), γ = 75.33(1)°, V = 2184.5 Å, Z = 4 ($C_{22}H_{14}N_4O$ x C_2H_6SO), d_{obs} = 1.249 g cm^{-3} (flotation technique, H_2O/CsCl), d_{calc} = 1.205 g.cm^{-3}, approximate crystal dimension 0.3 x 0.3 x 0.25 mm. All diffraction experiments were made on a modified STOE 4-circle diffractometer with MoK_α-radiation (graphite monochromator, λ = 0.71069 Å) using a NONIUS low temperature device (temperature of data collection 100(1) K). Cell dimensions by least-squares from the diffractometer angles of 36 well-centered reflections Intensity data collection for one hemisphere with $4 \leq 2\vartheta \leq 50°$ (ω/ϑ scan, scan width 1.5°). The 7592 independent reflections were processed (Lp-correction, no absorption- or extinction correction) to yield 5074 significant observations ($|F_{obs}| > 3\sigma(F_{obs})$). Least-squares refinement in a blocked mode due to the large number of parameters. All non-hydrogen atoms were refined with anisotropic, hydrogen atoms with isotropic temperature coefficients. Bonded C-H distances were constrained in the terminal refinement cycles: 1.05 Å (sp^2-C), 1.07 Å (sp^3-C). The refinement converged at a residual of R = 0.065 (589 parameters, 5112 observations). The highest maximum in a final difference fouriersynthesis was 0.5 $eÅ^{-3}$.

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