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Studies on *as*-Triazine Derivatives. XVI.[1] Reaction of 1,2,4-Triazinecarbonitriles with Carbanions

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A cyano group in 1,2,4-triazines, regardless of its position, acted as an effective leaving group in reactions with carbanions. Thus, the reactions gave the corresponding substituted products in place of the compounds formed by addition reaction of carbanions to the cyano group. Grignard reaction of these carbonitriles is also described.

Keywords active methylene compound; addition; carbanion; cyano group; Grignard reagent; ketone; substitution; 1,2,4-triazine

Like Grignard reagents, enolate anions, in principle, add to cyano groups in π-electron-deficient *N*-heteroaromatic nuclei, and this represents a versatile method for the preparation of *N*-heteroaromatic enaminoketones.[2] A typical example is the reaction of 2,6-dimethylpyrimidine-4-carbonitrile with these reagents, as shown in Chart 1.

On the other hand, it is also known that 4-quinazolinecarbonitrile (**1**) reacts with Grignard reagents to give 4-alkyl (or 4-aryl) quinazoline (**2**) and that the reaction with methylketones gives rise to the formation of 4-quinazolyl-

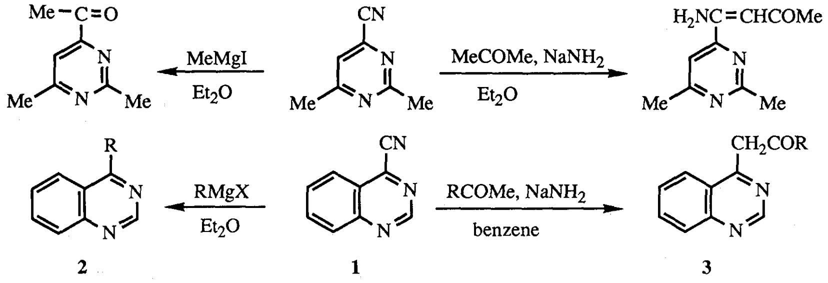

Chart 1

TABLE I. Reactions of **4**, **6**, and **8** with Active Methylene Compounds or with Ketones

Substrate Compd. No.	Nucleophile X-$\bar{C}$H-Y X	Y	Reaction conditions Temp.[a]	Time (h)	Product Compd. No.	Yield (%)	mp (°C)	Recryst. solvent
4	H	COPh	B	10	**5a**	47	128—130[b]	Ethyl acetate
	$-CO(CH_2)_4-$		B	10	**5b**	51	170—172[c]	Ethyl acetate
	CN	CN	R	18	**5c**	73	219—220 (dec.)[d]	Acetone
	CN	CO_2Et	B	3	**5d**	51	231(dec.)[e]	Ethyl acetate
	CO_2Et	CO_2Et	B	10	**5e**	21	65—66	Hexane
6	H	COPh	B	5	**7a**	61	192—194[f]	Ethyl acetate
	$-CO(CH_2)_4-$		B	5	**7b**	61	135—136	Ether
	CN	CN	R	18	**7c**	76	261—263 (dec.)[g]	Acetone
	CN	CO_2Et	R	18	**7d**	68	181—183[h]	Ethyl acetate
	CO_2Et	CO_2Et	B	3	**7e**	63	95—97	Hexane
8	H	COPh	B	18	**9a**	51	178—180	Ethyl acetate
	$-CO(CH_2)_4-$		B	18	**9b**	36	120—121	Ether
	CN	CN	B	6	**9c**	71	265—267 (dec.)	Acetone
	CN	CO_2Et	B	24		0 (76)[i]		
	CO_2Et	CO_2Et	B	24		0 (71)[i]		

a) B: boiling point of tetrahydrofuran. R: room temperature. *b*) Lit.[5] mp 130—132 °C. *c*) Lit.[5] mp 172—173 °C. *d*) Lit.[6] mp 220 °C. *e*) Lit.[5] mp 235 °C (dec.). *f*) Lit.[7] mp 192—194 °C. *g*) Lit.[8] mp 261—263 °C. *h*) Lit.[7] mp 181—183 °C. *i*) The figures in parentheses show the recoveries of substrates.

TABLE II. Reactions of **4**, **6**, and **8** with Grignard Reagents

Substrate No.	Temp.	Reagent	Product No.	Yield (%)	mp (°C)	Recryst. solvent
4	R[a]	MeMgI	**10a**	62	162—163[b]	Ethyl acetate
4	R[a]	PhMgBr	**10b**	70	130—132	Ethyl acetate
6	0 °C	MeMgI	**11a**	41	123—125[c]	Ethyl acetate
6	0 °C	PhMgBr	**11b**	46	144—146[d]	Ethyl acetate
8	R[a]	PhMgBr	**12**	66	115—116	Ethyl acetate

a) Room temperature. *b*) Lit.[9] mp 159.5—161.5 °C. *c*) Lit.[10] mp 122—124 °C. *d*) Lit.[11] mp 145—146 °C.

methyleneketones (**3**).[3] Such abnormal behavior of **1** is caused by the extraordinary susceptibility of the C_4–N_3 double bond in the quinazoline ring to nucleophilic reagents, and a few examples in this category have been reported in fused pyrimidine ring systems.[4]

In this paper, we describe the reactions of three positional isomers of 1,2,4-triazinecarbonitriles with various carbanion, in which the cyano group at the 3-, 5- or 6-position acts as an efficient leaving group, together with ketone formation from the 3-cyano and 6-cyano derivatives by means of Grignard reactions.

As listed in Table I, the reaction of diphenyl-1,2,4-triazinecarbonitriles (**4**, **6**, **8**) with acetophenone, cyclohexanone, or active methylene compounds under basic conditions gave the substituted products (**5**, **7**, **9**) corresponding to **3**. Reactions of 3, 5-diphenyl-1,2,4-triazine-6-carbonitrile (**8**) with ethyl cyanoacetate and with diethyl malonate are exceptional, and most of **8** was recovered unchanged. In all cases, no formation of the addition compound(enaminoketone) was detected.

On the other hand, the reactions of **4**, **6**, and **8** with Grignard reagents gave somewhat mixed results as regards the subsitution and addition reactions. The reactions of the 3-carbonitrile (**4**) and the 6-carbonitrile (**8**) with Grignard reagents under traditional conditions, like that of the pyrimidinecarbonitrile, yielded the corresponding ketones (**10a**, **b** and **12**), whereas the reaction of the 5-carbonitrile (**6**) with Grignard reagents gave the substitution products (**11a** and **11b**) corresponding to **2**. The results of these reactions illustrated in Chart 3 are summarized in Table II.

The observations in the present investigation suggest that the chemical properties of the 5-position of 1,2,4-triazine resemble those of the 4-position of quinazoline, while pyrimidine-like character still remains at the 3- and 6-positions of 1,2,4-triazines.

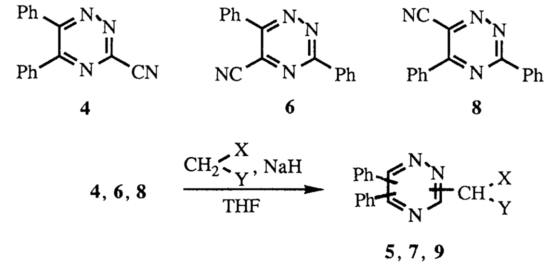

Chart 2

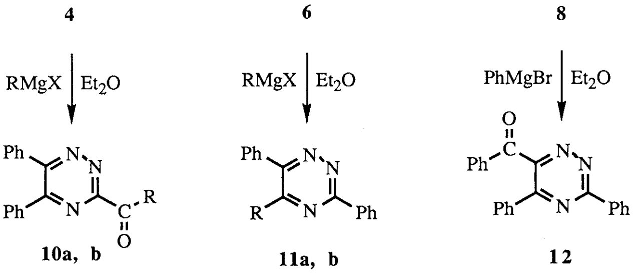

Chart 3

Experimental

All melting points were determined by the capillary method and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded at either 60 MHz on a JEOL JNM-PMX 60 spectrometer or 100 MHz on a JEOL FX-100 spectrometer. Chemical shifts are quoted in δ values (ppm) with tetramethylsilane (TMS) or 2,2-dimethyl-2-silapentanesulfonic acid sodium salt (DSS) as an internal standard, and coupling constants (J) are given in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Infrared (IR) spectra were obtained on a JASCO IR 810 spectrophotometer.

General Procedure for the Reaction of 1,2,4-Triazinecarbonitriles with Active Methylene Compounds or with Ketones A 50% oil dispersion of NaH (0.12 g, 2.5 mmol) was washed with hexane and the oil-free NaH was suspended in dry tetrahydrofuran (THF) (10 ml). A solution of an active methylene compound or a ketone (2.5 mmol) in dry THF (10 ml) was added to the above suspension and the mixture was stirred at room temperature (in the case of phenylacetonitrile; refluxed) for 15 min. Then, a triazinecarbonitrile (0.53 g, 2 mmol) in dry THF (10 ml) was added, and the whole was stirred at an appropriate temperature. After removal of the solvent under reduced pressure, the residue was dissolved in H_2O and neutralized with diluted HCl. The mixture was extracted with $CHCl_3$ (in the case of malononitrile, precipitated crystals were collected by suction and washed with H_2O). The $CHCl_3$ solution was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated. The product was pu-

Table III. Spectral Data for the Products of the Reaction of **4**, **6**, and **8** with Carbanions

Compd. No.	IR ($CDCl_3$) ν ($C\equiv N$, $C=O$; cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (ppm)
5a	1690	14.3—13.4 (br, 1H), 8.3—7.9 (m, 2H), 7.8—7.3 (m, 13H), 6.54 (s, 1H)
5b	1710	13.7—13.4 (br, 1H), 7.7—7.2 (m, 10H), 2.9—2.5 (m, 8H)
5c	2220, 2200[a]	9.1—8.8 (br, 1H), 7.6—7.1 (m, 10H)[b]
5d	2200, 1650	14.0—13.8 (br, 1H), 7.7—7.2 (m, 10H), 4.35 (q, $J=8$, 2H), 1.39 (t, $J=8$, 3H)
5e	1735	7.8—7.2 (m, 10H), 5.34 (s, 1H), 4.32 (q, $J=7$, 4H), 1.31 (t, $J=7$, 6H)
7a	1620	16.0—15.8 (br, 1H), 8.6—8.3 (m, 2H), 8.0—7.2 (m, 13H), 6.39 (s, 1H)
7b	1720	8.9—8.5 (m, 2H), 7.8—7.3 (m, 8H), 4.2—3.9 (m, 1H), 2.9—1.4 (m, 8H)
7c	2220, 2200[a]	8.3—8.0 (m), 7.9—7.3 (m)[b,c]
7d	2200, 1650	15.0—14.7 (br, 1H), 8.4—7.9 (m, 2H), 7.9—7.3 (m, 8H), 4.35 (q, $J=7$, 2H), 1.37 (t, $J=7$, 3H)
7e	1760	8.8—8.5 (m, 2H), 7.8—7.4 (m, 8H), 5.13 (s, 1H), 4.21 (q, $J=7$, 4H), 1.23 (t, $J=7$, 6H)
9a	1615	15.1—15.0 (br, 1H), 8.8—8.4 (m, 2H), 8.1—7.3 (m, 13H), 6.38 (s, 1H)
9b	1720	8.9—8.5 (m, 2H), 7.8—7.3 (m, 8H), 4.3—4.0 (m, 1H), 2.9—1.5 (m, 8H)
9c	2220, 2190[a]	8.2—8.0 (m), 7.8—7.4 (m)[b,c]
10a	1720	7.8—7.2 (m, 10H), 2.95 (s, 3H)
10b	1680	8.5—8.2 (m, 2H), 8.0—7.3 (m, 13H)
11a		8.8—8.5 (m, 2H), 7.9—7.3 (m, 8H), 2.63 (s, 3H)
11b		8.8—8.6 (m, 2H), 7.8—7.3 (m, 13H)
12	1675	8.9—8.5 (m, 2H), 8.2—7.2 (m, 13H)

a) KBr disc. *b*) DMSO-d_6. *c*) The integration ratio is 1 : 4.

Table IV. Analytic Data for the New Compounds

No.	Formula	Analysis (%) Calcd (Found)			No.	Formula	Analysis (%) Calcd (Found)		
		C	H	N			C	H	N
5e	$C_{22}H_{21}N_3O_4$	67.51	5.41	10.74	**9a**	$C_{23}H_{17}N_3O$	78.61	4.88	11.96
		(67.37	5.22	10.85)			(78.38	4.68	11.77)
7a	$C_{23}H_{17}N_3O$	78.61	4.88	11.96	**9b**	$C_{21}H_{19}N_3O$	76.57	5.81	12.76
		(78.75	4.92	11.85)			(76.35	5.73	12.59)
7b	$C_{21}H_{19}N_3O$	76.57	5.81	12.76	**9c**	$C_{18}H_{11}N_5$	72.72	3.73	23.56
		(76.40	5.80	12.74)			(72.60	3.56	23.26)
7e	$C_{22}H_{21}N_3O_4$	67.51	5.41	10.74	**10b**	$C_{22}H_{15}N_3O$	78.32	4.48	12.45
		(67.56	5.19	10.69)			(78.55	4.49	12.56)
8	$C_{16}H_{10}N_4$	74.40	3.90	21.70	**12**	$C_{22}H_{15}N_3O$	78.32	4.48	12.45
		(74.56	4.16	21.59)			(78.05	4.32	12.19)

rified by recrystallization from an appropriate solvent.

General Procedure for the Reaction of 1,2,4-Triazinecarbonitriles with Grignard Reagents A solution of a carbonitrile (0.52 g, 2 mmol) in dry Et_2O (20 ml) was added to a solution of a Grignard reagent in Et_2O, prepared from a halide (2.2 mmol) and metallic magnesium (0.06 g, 2.4 mmol) in dry Et_2O (20 ml). The mixture was vigorously stirred for 2 h and poured into ice-HCl solution. The ethereal phase was separated, washed with H_2O, and dried over $MgSO_4$. After evaporation of the solvent, the residue was recrystallized from AcOEt to give the product.

5,6-Diphenyl-1,2,4-triazine-3-carbonitrile[12] (4) $KMnO_4$ (6.4 g, 40 mmol) was added to a solution of 3-methylthio-5,6-diphenyl-1,2,4-triazine[13] (5.6 g, 20 mmol) in AcOH (20 ml) and acetone (200 ml) under cooling in an ice bath. The mixture was stirred for 2 h at room temperature, decolorized by addition of $NaHSO_3$ and H_2O, then poured into H_2O (2.5 l). The separated solid was collected by suction, washed well with H_2O, and dissolved in $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated. After removal of $CHCl_3$, the residue was recrystallized from AcOEt to give 3-methylsulfonyl-5,6-diphenyl-1,2,4-triazine as pale yellow prisms (5.8 g, 93%). mp 140—141 °C (lit.[5] mp 139—140 °C). A solution of the above methylsulfonyl derivative (1.24 g, 4 mmol) in dimethylformamide (DMF) (5 ml) was added in one portion to a solution of NaCN (0.22 g, 4.5 mmol) in DMF (5 ml) under cooling in an ice bath. The mixture was stirred at room temperature for 1 h, diluted with H_2O, and extracted with benzene. The benzene solution was washed well with H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from AcOEt to give yellow needles (0.80 g, 78%), mp 158—159 °C (lit.[5] mp 154—155 °C).

3,6-Diphenyl-1,2,4-triazine-5-carbonitrile[12] (6) Compound **6** was prepared according to our previous report.[7]

3,5-Diphenyl-1,2,4-triazine-6-carbonitrile[12] (8) 6-Methylthio-3,5-diphenyl-1,2,4-triazine[1] (5.6 g, 20 mmol) was treated with $KMnO_4$ (6.4 g, 40 mmol) as described for the preparation of the 3-methylsulfonyl derivative. Recrystallization from AcOEt gave 6-methylsulfonyl-3,5-diphenyl-1,2,4-triazine as pale yellow prisms (5.8 g, 93%), mp 148—149 °C (lit.[1] mp 150—152 °C). The above methylsulfonyl derivative (1.24 g, 4.0 mmol) was treated with NaCN (0.22 g, 4.5 mmol) as described for the preparation of **4**. Recrystallization from AcOEt gave yellow prisms (0.73 g, 71%), mp 117—119 °C. ^{1}H-NMR ($CDCl_3$–TMS): 8.9—8.7 (m), 8.5—8.3 (m), 8.0—7.6 (m); the integration ratio is 1 : 1 : 3.

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