A Facile Synthesis of Some Condensed Ring 1,3-Dialkyl-1,3,5-triazine-2,4-dione Derivatives

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Recently, we reported the preparation of 1,3-dialkyl-1,3,5-triazine-2,4-diones from 4-pyridones[1]. The overall reaction is characterized as a combination of successive addition of alkyl isocyanate and intramolecular Michael addition to afford a triazine-dione ring: a new sequence of cycloaddition to form a 6-membered ring[2,3]. We now describe a simple and easy synthesis of a variety of 1,3-dialkyl-1,2,3,4,5,8,9,9a-octahydropyrido[1,2-*a*]-*s*-triazine-2,4,8-triones **(5)** and benzo derivatives, 2,4-dialkyl-1,2,3,4,4a,5,6,11-octahydroquinolino[1,2-*a*]-*s*-triazine-1,3,6-triones **(4)**.

The general procedure consists of reaction of 4-pyridone **(1a)** or 4-quinolone **(1b)** and excess alkyl isocyanate (2–10 equiv) in the presence of 1,1,3,3-tetramethylguanidine as a base catalyst (0.1 equiv) in dry dimethylformamide solution at room temperature under nitrogen atmosphere. In most cases, the progress of the reaction was monitored by H.P.L.C.[4]. A series of 1:2 cycloadducts, **(4)** and **(5)**, which consist of one pyridone or quinolone and two alkyl isocyanate moieties, were observed to reach a maximum content during 5 to 25 minutes[5].

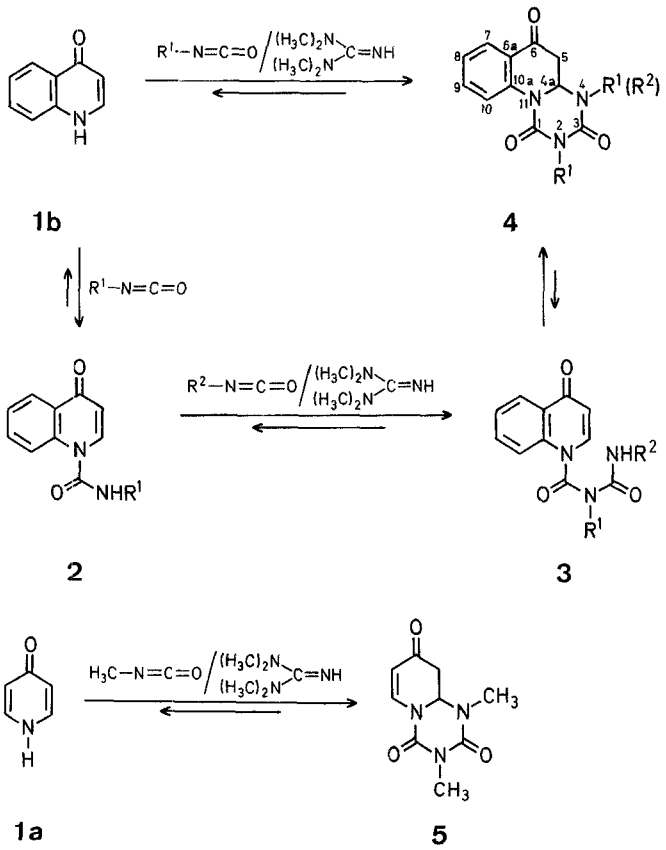

Table. Compounds **4a–c** prepared

Product No.	R^1/R^2	Equiv of Isocyanate	Yield[a] [%]	m.p. [°C][b]	Molecular Formula[c]	M.S. *m/e*	I.R. (Nujol) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	^{13}C-N.M.R. ($CDCl_3$) δ [ppm] (C=O)
4a	CH_3	2.3	78	188° (dec)	$C_{13}H_{13}N_3O_3$ (259.3)	259	1710, 1680, 1670	2.97 (d, 1H, J=10.5 Hz); 3.00 (d, 1H, J=4.9 Hz); 3.09 (s, 3H); 3.29 (s, 3H); 5.17 (dd, 1H, J=10.3 Hz, 4.9 Hz); 7.3–8.1 (m, 4H)	150.3; 150.5; 190.9
4b	C_2H_5	5.5	91	143–145°	$C_{15}H_{17}N_3O_3$ (287.3)	287	1730, 1700, (1690, sh)	1.24 (t, 3H, J=7.1 Hz); 1.27 (t, 3H, J=7.1 Hz); 2.9–3.0 (m, 2H); 3.23 (q, 1H, J=7.1 Hz); 3.80 (q, 1H, J=7.1 Hz); 3.90 (q, 2H, J=7.1 Hz); 5.0–5.3 (m, 1H); 7.3–8.1 (m, 4H)	149.7; 150.1; 191.2
4c	n-C_4H_9	5.7	~100	86–87°	$C_{19}H_{25}N_3O_3$ (343.4)	343	1720, 1690, 1670	0.93 (t, 3H, J=7.4 Hz); 0.95 (t, 3H, J=7.4 Hz); 1.2–1.8 (m, 8H); 2.9–3.0 (m, 2H); 2.9–3.2 (m, 1H); 3.6–3.9 (m, 1H); 3.85 (t, 2H, J=7.4 Hz); 5.0–5.3 (m, 1H); 7.3–8.1 (m, 4H)	150.2; 150.5; 191.3

[a] Yield of crude product.
[b] Recrystallized from chloroform/hexane.
[c] Satisfactory microanalyses obtained: C ±0.2, H ±0.2, N ±0.1.

A two-step addition of two different alkyl isocyanates gave successfully a 1,3-dialkyl-1,3,5-triazine derivative having different alkyl groups in the triazine skeleton.

Reaction conditions for the preparation are mild. Isolation procedures are simple and easy except for the case of **4e** and **4f**, where chromatographic separation is required to obtain the desired product from a mixture of by-products. The overall yields are 16% to quantitative, strongly depending on the structure of the alkyl isocyanate (primary alkyl > secondary alkyl). In contrast, the reaction of an aryl isocyanate such as phenyl isocyanate with 4-pyridone under the same basic conditions gives a cyclic trimer of phenyl isocyanate (triphenyl isocyanurate)[6] as the main product. The results are summarized in the Table.

2,4-Dibenzyl-1,2,3,4,4a,5,6,11-octahydroquinolino[1,2-*a*]-*s*-triazine-1,3,6-trione (4d; $R^1=R^2=C_6H_5CH_2$); Typical Procedure:

To a solution of 4-quinolone (**1b**; 0.50 g, 3.4 mmol) in dimethylformamide (7.5 ml) containing 1,1,3,3-tetramethylguanidine (40 mg, 0.35 mmol) is added benzyl isocyanate (2.34 g, 17.6 mmol) dropwise at room temperature under nitrogen. The solution is stirred for 1 h. After evaporation of the solvent and the excess isocyanate, the product is purified by column chromatography [silica gel 60, 40–63 μm; eluent: 7:3 chloroform/hexane]. After evaporation of the eluent, the adduct is recrystallized from chloroform/hexane to give colorless needles of **4d**; yield: 1.04 g (73%); m.p. 143 °C (dec).

$C_{25}H_{21}N_3O_3$	calc.	C 73.11	H 5.14	N 10.43
(411.5)	found	73.11	5.05	10.43

I.R. (Nujol): ν=1720, 1690, 1680 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): δ=2.8 (m, 2H); 4.29 (d, 1H, J=15.4 Hz); 5.07 (d, 1H, J=15.4 Hz); 5.0–5.1 (m, 1H); 5.08 (s, 2H); 7.2–8.0 ppm (m, 14H).

^{13}C-N.M.R. ($CDCl_3$): δ=150.4, 150.7, 190.0 ppm (C=O).

M.S.: m/e=411 (M^+).

2,4-Diisopropyl-1,2,3,4,4a,5,6,11-octahydroquinolino[1,2-*a*]-*s*-triazine-1,3,6-trione (4e; $R^1=R^2=i$-C_3H_7); Typical Procedure:

To a solution of 4-quinolone (**1b**; 1.50 g, 10 mmol) in dimethylformamide (22.5 ml) containing 1,1,3,3-tetramethylguanidine (0.12 g, 1.0 mmol) is added isopropyl isocyanate (9.5 g, 112 mmol) dropwise at room temperature under nitrogen. H.P.L.C. monitoring[7] shows that equilibrium is reached after 2 h, when the relative amounts of the components **1b**, **2e** (**2**; $R^1=i$-C_3H_7), and **4e**, do not change any more. Then, after stirring for 2 h and evaporation of excess isopropyl isocyanate and dimethylformamide at room temperature under reduced pressure, the yellow oily products obtained are purified by column chromatography on silica gel (eluent: 95:5 chloroform/ethyl acetate) to give colorless products; crude yield: 525 mg (16%). Recrystallization from chloroform/hexane affords the pure compound **4e**; yield: 370 mg (11%); m.p. 164–165 °C.

$C_{17}H_{21}N_3O_3$	calc.	C 64.74	H 6.71	N 13.32
(315.4)	found	64.54	6.85	13.20

I.R. (Nujol): ν=1720, 1690, 1670 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): δ=1.29 (d, 6H, J=6.8 Hz); 1.44 (d, 3H, J=6.8 Hz); 1.47 (d, 3H, J=6.8 Hz); 2.7–3.3 (m, 2H); 4.4–4.9 (m, 2H); 5.15 (dd, 1H, J=12.0 Hz, 3.2 Hz); 7.3–8.0 ppm (m, 4H).

^{13}C-N.M.R. ($CDCl_3$): δ=150.4, 151.2, 191.9 ppm (C=O).

M.S.: m/e=315 (M^+).

2-Methyl-4-benzyl-1,2,3,4,4a,5,6,11-octahydroquinolino[1,2-*a*]-*s*-triazine-1,3,6-trione (4f; $R^1=CH_3$, $R^2=C_6H_5CH_2$):

4-Quinolone (**1b**; 1.00 g, 7 mmol) is suspended in an excess of methyl isocyanate (5.5 g, 96 mmol) and the mixture is stirred for about 24 h at room temperature under nitrogen. After evaporation of methyl isocyanate under reduced pressure, the crude 1:1 adduct, *N-methylaminocarbonyl-4-oxo-1,4-dihydroquinoline* (**2a**), is obtained as colorless crystals which are pure according to ^{1}H-N.M.R. spectra; yield: 1.3 g (93%); m.p. 203–204 °C; which is used without further purification.

To a solution of **2a** (1.00 g, 5 mmol) in dimethylformamide (11 ml) is added an equimolar amount of benzyl isocyanate (0.67 g, 5 mmol) containing 1,1,3,3-tetramethylguanidine (59 mg, 0.5 mmol) dropwise at room temperature under nitrogen. The solution is stirred for 30 min

and poured into water (50 ml). The products are extracted with chloroform (3 × 50 ml), the extract is washed with water (3 × 30 ml), and dried with anhydrous magnesium sulfate. After evaporation of the solvent, the product is separated by column chromatography on silica gel (eluent: 9 : 1 chloroform/ethyl acetate) into the desired compound **4f** and the accompaning products **4d** and **4a**; yields: 0.66 g (40%), 0.36 g (18%), and 0.18 g (14%), respectively. Recrystallizations from chloroform/hexane give the pure adduct **4f**; yield: 0.44 g (26% yield); m.p. 176–177 °C.

$C_{19}H_{17}N_3O_3$	calc.	C 68.05	H 5.11	N 12.53
(335.4)	found	67.78	5.15	12.47

I.R. (Nujol): $\nu = 1720, 1680, 1670$ (sh) cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.8$–3.1 (m, 2H); 3.34 (s, 3H); 4.35 (d, 1H, $J = 15.3$ Hz); 5.08 (d, 1H, $J = 15.3$ Hz); 5.08 (dd, 1H, $J = 10.3$ Hz, 4.9 Hz); 7.32 (s, 5H); 7.2–8.0 ppm (m, 4H).

^{13}C-N.M.R. ($CDCl_3$): $\delta = 150.6, 150.9, 191.0$ ppm.

M.S.: $m/e = 335$ (M^+).

1,3-Dimethyl-1,2,3,4,5,8,9,9a-octahydropyrido[1,2-*a*]-*s*-triazine-2,4,8-trione (5):

To a solution of 4-pyridone (**1a**; 1.0 g, 11 mmol) in dimethylformamide (20 ml) containing triethylamine (1.1 mg, 1.08 mmol) is added methyl isocyanate (6.2 g, 109 mmol) dropwise at room temperature under nitrogen. The solution is stirred for 24 h and the excess methyl isocyanate and dimethylformamide are evaporated under reduced pressure. After addition of water, the crude precipitate is collected, washed with water, and dried in vacuo; yield: 2.73 g (~ 100%). Recrystallized from acetonitrile; yield: 1.02 g; m.p. 168 °C (dec).

$C_9H_{11}N_3O_3$	calc.	C 51.67	H 5.30	N 20.09
(209.2)	found	51.61	5.32	20.35

I.R. (Nujol): $\nu = 1720, 1670, 1660$ sh cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.6$–3.0 (m, 2H); 3.04 (s, 3H); 3.30 (s, 3H); 5.13 (dd, 1H, $J = 13.1$ Hz, 5.0 Hz); 5.58 (dd, 1H, $J = 8.3$ Hz, 1.0 Hz); 8.13 ppm (d, 1H, $J = 8.3$ Hz).

^{13}C-N.M.R. ($CDCl_3$): $\delta = 148.7, 151.6, 189.9$ ppm (C=O).

M.S.: $m/e = 209$ (M^+).

We are grateful to Mr. Hitoshi Yamada, Mrs. Fusako Fukuda, and Mr. Takanori Tanaka (Material Analysis Center in ISIR, Osaka University) for their kind measurements of mass spectral, microanalytical, TG-DTA, and other spectral analyses.

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[1] M. Sawada et al., *Tetrahedron Lett.* **23**, 3181 (1982).

[2] R. Richter, H. Ulrich, *The Chemistry of Cyanates and Their Thio Derivatives*, Part 2, John Wiley & Sons, New York, 1977, Chap. 12.

[3] R. Huisgen, K. Herbig, M. Morioka, *Chem. Ber.* **100**, 1107 (1967).

[4] H.P.L.C. eluent: 60 : 35 : 5 ether/chloroform/dimethyl sulfoxide or 90 : 5 : 5 ether/chloroform/dimethyl sulfoxide; column: Lichrosorb SI 100, 5 μm.

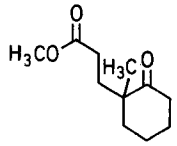
[5] In the case of **4e**, stirring for 2 h is required.

[6] J. I. Jones, N. G. Savill, *J. Chem. Soc.* **1957**, 4392.

[7] Toluene (3.4 g) was added as an internal standard for H.P.L.C. monitoring.

J. K. Whitesell, M. A. Whitesell, *Synthesis* **1983** (7), 517–536:

Compound **14** (p. 521) should be named 3-methoxycarbonylmethyl-8a-methyl-5-methylene-2-oxo-6-(2,2-dimethylpropanoyloxy)-*trans*-decalin. The structure of compound **25** (p. 522) should be:



25

T. Kolasa, *Synthesis* **1983** (7), 539:

The heading for the 6th column in the Table should be (*Z*/*E*)-Ratio.

S. Kano, Y. Yuasa, T. Yokomatsu, S. Shibuya, *Synthesis* **1983** (7), 585–587:

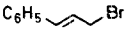
Compounds **5** should be named 3-oxo-2,3,4,5-tetrahydro-1*H*-azepino[4,3-*b*][1]benzothiophenes.

M. Sawada, Y. Furukawa, Y. Takai, T. Hanafusa, *Synthesis* **1983** (7), 593–595:

Compounds **4** and **5** should be named 2,4-dialkyl-1,3,6-trioxo-2,3,4,4a,5,6-hexahydro-1*H*-[1,3,5]triazino[1,2-*a*]quinolines and 1,3-dimethyl-2,4,8-trioxo-1,2,3,4,7,8-hexahydro-8a*H*-pyrido[1,2-*a*][1,3,5]triazine, respectively.

R. B. Cheikh, R. Chaabouni, A. Laurent, P. Mison, A. Nafti, *Synthesis* **1983** (9), 685–700:

The first substrate in Table 3 (p. 689) should be:



Y. Imai, A. Mochizuki, K. Kakimoto, *Synthesis* **1983** (10), 851:

The title compounds **4** should be named 4*H*-1,2,4-benzothiadiazine 1,1-dioxides.

R. Rastogi, S. Sharma, *Synthesis* **1983** (11); 861–882:

Compound **109** (p. 870) should be named: 7,12-dioxo-6,7-dihydro-12*H*-benzimidazo[1,2-*b*][2,4]benzodiazepine.

P. Kutschy, J. Imrich, J. Bernát, *Synthesis* **1983** (11), 929–931:

The title compounds **4** should be named 2-amino-4-oxo-4*H*-[1]benzothieno[2,3-*e*]-1,3-thiazines.

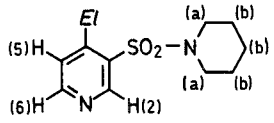
P. Breant, M. Marsais, G. Quéguiner, *Synthesis* **1983** (10), 822–824:

The following data should be added to the ^{1}H-N.M.R. spectra of compounds **3a–c** (p. 824):

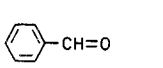
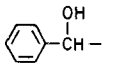
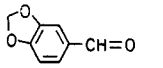
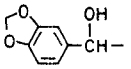
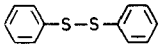
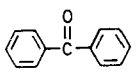
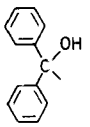
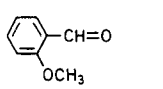
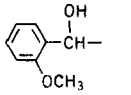
For compounds **3a–c**, $J_{H\text{-}4,H\text{-}5}$ = 8 Hz; $J_{H\text{-}5,H\text{-}6}$ = 5 Hz; $J_{H\text{-}4,H\text{-}6}$ = 2 Hz; $J_{H\text{-}4,H\text{-}2}$ = 2 Hz.

Tables 1 and 2 (p. 823) should be read as follows:

Table 1. 4-Substituted 3-Piperidinosulfonylpyridines prepared



5a, 7a-10a

Electrophile	*El*	Product	Yield [%]	m.p. [°C]	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm][b]
		**5a**	80	127°	$C_{17}H_{18}N_2O_3S$ (330.4)	1.5 [m, 6 H(b)]; 3.1 [m, 4 H(a)]; 4.0 (m, OH); 5.3 (m, 1 H); 6.7 (m, 5 H); 7.53 (d, H-5); 8.63 (d, H-6); 8.93 (s, H-2)
		**7a**	60	80° (dec)	$C_{18}H_{18}N_2O_5S$ (374.4)	1.6 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 5.96 (s, 2 H); 6.63 (s, 1 H); 6.9 (m, 3 H); 7.50 (d, H-5); 8.86 (d, H-6); 8.93 (s, H-2)
$(H_3C)_3Si-Cl$	$(H_3C)_3Si-$	**8a**	42	<50°	$C_{13}H_{20}N_2O_2SSi$ (296.5)	0.50 (s, 9 H); 1.7 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 7.70 (d, H-5); 8.70 (d, H-6); 8.95 (s, H-2)
		**9a**	80	82°	$C_{16}H_{16}N_2O_2S_2$ (332.4)	1.7 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 6.70 (d, H-5); 7.56 (s, 5 H); 8.30 (d, H-6); 8.93 (s, H-2)
		**6a**	95	195°	$C_{23}H_{22}N_2O_3S$ (406.5)	1.5 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 6.70 (s, OH); 6.75 (d, H-5); 7.30 (s, 10 H); 8.51 (d, H-6); 9.06 (s, H-2)
		**10a**	53	164°	$C_{18}H_{20}N_2O_4S$ (360.4)	1.7 [m, 6 H(b)]; 3.2 [m, 4 H(a)]; 3.70 (s, 3 H); 4.2 (m, OH); 6.70 (s, 1 H); 7.15 (d, H-5); 7.5 (m, 4 H); 8.80 (d, H-6); 9.06 (s, H-2)
–	–	**12**	–	–	–[c]	1.7 [m, 6 H(b)]; 3.3 [m, 4 H(a)]; 4.6 (m, OH); 5.96 (d, 1 H, J = 3 Hz); 7.85 (d, H-5); 8.86 (d, H-6); 9.00 (s, H-2)
–	–	**13**	–	–	–[c]	1.7 [m, 6 H(b)]; 3.3 [m, 4 H(a)]; 5.83 (d, 1 H, J = 3 Hz); 7.60 (d, H-5); 8.83 (d, H-6); 9.13 (s, H-2)

[a] Satisfactory microanalyses obtained: C ±0.38, H ±0.32, N ±0.14; exception: **7**: C −0.70%.

[b] $J_{H\text{-}5,H\text{-}6}$ = 5 Hz for all products.

[c] See text.