A New Synthesis of Fused 1,2,4-Triazine Derivatives

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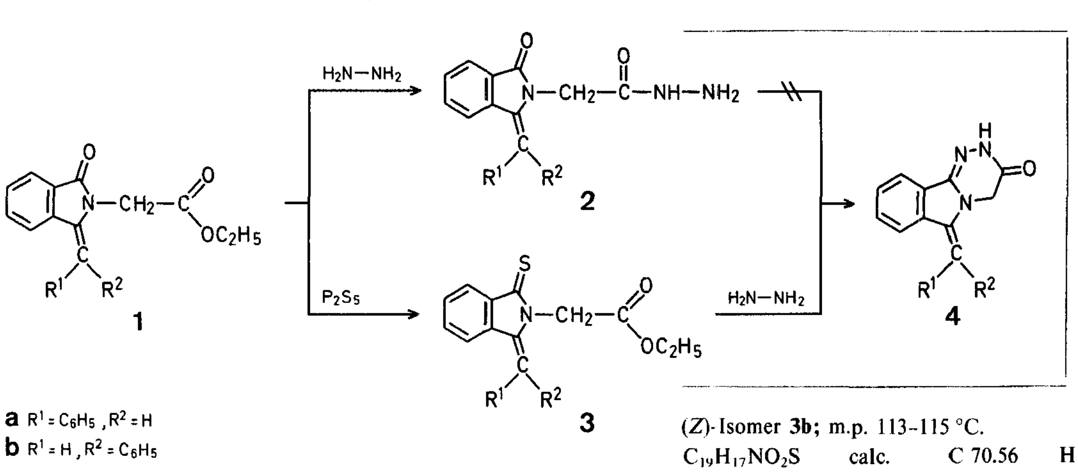
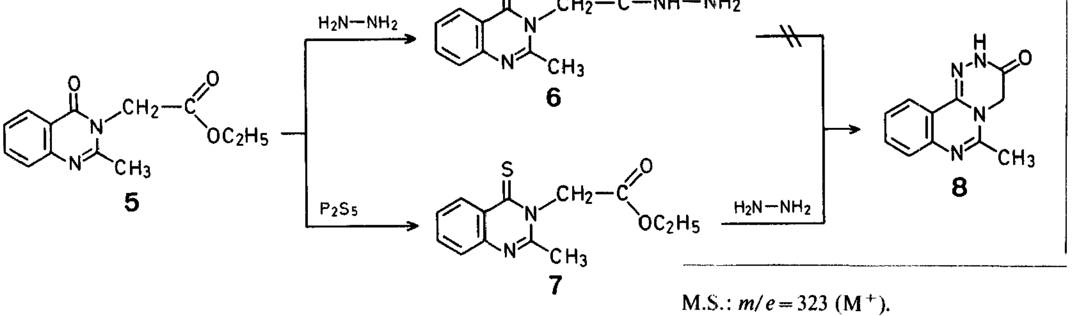
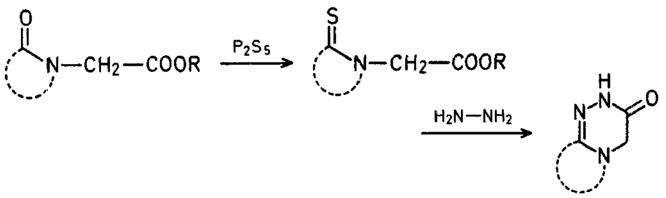
We were interested in the synthesis of heterocyclic-fused 1,2,4-triazine derivatives. A convenient general method for their preparation has hitherto not been reported. Ethyl 3-benzylidene-1-oxo-2,3-dihydroisoindole-2-acetates[1] (**1**) and ethyl 2-methyl-4-oxo-3,4-dihydroquinazoline-3-acetate[2] (**5**) have attracted considerable interest as potential building blocks for the preparation of some heterocyclic systems.

A recently reported synthesis[3] of fused 1,2,4-triazine derivatives is tedious and gives only low yields. In an attempt to find an alternative synthesis of heterocyclic-fused 1,2,4-triazines, we tried to cyclize the hydrazides **2a**, **2b**, and **6** using various cyclizing agents such as phosphoryl chloride, phosphorus pentoxide, polyphosphoric acid, etc. The hydrazides were obtained from the carboxylic esters **1a**, **1b**, and **5**, respectively, and hydrazine hydrate. However, compounds **2a**, **2b**, and **6** failed to cyclize because of the insufficient positive character of their lactam carbonyl C-atom. We finally found that the fused 1,2,4-triazine derivatives **4a**, **4b**, and **8** can be conveniently prepared from the lactam-*N*-acetic esters **1a**, **1b**, and **5** via sulfurization with phosphorus(V) sulfide and reaction of the resultant thiolactam-*N*-acetic esters **3a**, **3b**, and **7**, respectively, with hydrazine hydrate. The sequence was performed with the isolated (*E*)- and (*Z*)-isomers of **1a** and **1b**. The increased positive character of the thiocarbonyl C-atom in the thiolactams **3a**, **3b**, and **7** favors cyclization.





From the results obtained it can be seen that our method for the synthesis of heterocyclic fused 1,2,4-triazine derivatives is efficient and general and compares favorably with earlier methods[4,5].



(*E*) and (*Z*) Ethyl 3-Benzylidene-1-oxo-2,3-dihydroisoindole-2-acetates (1a and 1b):

Either (*E*)- or (*Z*)-3-benzylidene-1-oxo-2,3-dihydroisoindole-2-acetic acid is heated under reflux for 4 h in excess ethanol containing a few drops of conc. sulfuric acid. The ethanol is then evaporated and the residue taken up in ether. The ethereal solution is washed with aqueous 5% sodium hydrogen carbonate and with water, dried with anhydrous sodium sulfate, and evaporated to give compounds **1a** or **1b**, respectively.

(*E*) and (*Z*) Ethyl 3-Benzylidene-1-thioxo-2,3-dihydroisoindole-2-acetates (3a and 3b):

A mixture of compound **1a** or **1b** (3.07 g, 0.01 mol) and phosphorus(V) sulfide (4.5 g) in dry pyridine (45 ml) is heated under reflux for 5 h. Pyridine is removed in vacuo and the residue is extracted with chloroform (3 × 40 ml). Evaporation of chloroform gives the crude product which is chromatographed (silica gel, benzene) to afford product **3a** or **3b**. The product recrystallized from benzene/petroleum ether; yield: 2.8 g (87%).

(*E*)-Isomer **3a**; m.p. 123–124 °C.

$C_{19}H_{17}NO_2S$	calc.	C 70.56	H 5.30	N 4.33	S 9.91
(323.4)	found	70.50	5.37	4.35	9.89

M.S.: $m/e = 323$ (M^+).

I.R. (KBr): $\nu = 1775$ cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): $\delta = 1.27$ (t, 3H, —CH$_2$—C**H**$_3$); 4.25 (q, 2H, —C**H**$_2$—CH$_3$); 5.20 (s, 2H, —C**H**$_2$); 6.60 (s, 1H, =C**H**—); 7.3–7.5 (m, 8H$_{arom}$); 7.9–8.2 ppm (m, 1H, C$_7$**H**).

(*Z*)-Isomer **3b**; m.p. 113–115 °C.

$C_{19}H_{17}NO_2S$	calc.	C 70.56	H 5.30	N 4.33	S 9.91
(323.4)	found	70.52	5.33	4.28	9.93

M.S.: $m/e = 323$ (M^+).

I.R. (KBr): $\nu = 1750$ cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): $\delta = 1.27$ (t, 3H, —CH$_2$—C**H**$_3$); 4.22 (q, 2H, —C**H**$_2$—CH$_3$); 5.13 (s, 2H, —C**H**$_2$); 6.53 (s, 1H, =C**H**—); 7.2–7.4 (m, 8H$_{arom}$); 7.8–8.0 ppm (m, 1H, C$_7$**H**).

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(*E*)- and (*Z*)-6-Benzylidene-3-oxo-2,3,4,6-tetrahydro[1,2,4]triazino[3,4-*a*]indoles (4a and 4b):

A mixture of compound **3a** or **3b** (3.23 g, 0.01 mol) and hydrazine hydrate (4 ml) in ethanol is heated under reflux for 2.5 h (a crystalline solid begins to separate after 30 min). The mixture is then cooled, the solid product isolated by suction, and recrystallized from methanol/dichloromethane (1/1) to give pure **4a** or **4b**; yield: 2.15 g (78%).

(*E*)-Isomer **4a**; m.p. 257-258 °C.

$C_{17}H_{13}N_3O$	calc.	C 74.17	H 4.76	N 15.26
(275.3)	found	74.21	4.74	15.28

M.S.: $m/e = 275$ (M^+).

I.R. (KBr): $\nu = 3300\text{-}2900, 1675\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/DMSO\text{-}d_6/TMS_{int}$): $\delta = 4.33$ (s, 2H, $-C\underline{H}_2$); 6.17 (s, 1H, $=C\underline{H}-$); 7.35-7.55 (m, 8H_{arom}); 7.7-7.9 (m, 1H, $C_{10}\underline{H}$); 10.83 ppm (br s, 1H, N$\underline{H}$).

(*Z*)-Isomer **4b**; m.p. 253-254 °C.

$C_{17}H_{13}N_3O$	calc.	C 74.17	H 4.76	N 15.26
(275.3)	found	74.19	4.79	15.29

M.S.: $m/e = 275$ (M^+).

I.R. (KBr): $\nu = 3230\text{-}1665\ cm^{-1}$.

^{1}H-N.M.R. ($DMSO\text{-}d_6/CF_3COOD/TMS_{int}$): $\delta = 4.33$ (s, 2H, $C\underline{H}_2$); 6.23 (s, 1H, $=C\underline{H}-$); 7.3-7.6 (m, 8H_{arom}); 7.6-7.8 (m, 1H, $C_{10}\underline{H}$); 10.80 ppm (br s, 1H, N$\underline{H}$).

Ethyl 2-Methyl-4-oxo-3,4-dihydroquinazoline-3-acetate (7):

A mixture of ethyl 2-methyl-4-oxo-3,4-dihydroquinazoline-3-acetate (**5**; 2.46 g, 0.01 mol) and phosphorus(V) sulfide (5.0 g) in dioxan (60 ml) is heated under reflux for 15 h. The solvent is removed in vacuo and the crude product is chromatographed (silica gel, benzene) to afford **7**. Product **7** is recrystallized from benzene/petroleum ether to give yellow needles of **7**; yield: 1.72 g (66%); m.p. 154-155 °C.

$C_{13}H_{14}N_2O_2S$	calc.	C 59.52	H 5.38	N 10.68	S 12.22
(262.3)	found	59.56	5.39	10.65	12.25

M.S.: $m/e = 262$ (M^+).

I.R. (KBr): $\nu = 1730\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.28$ (t, 3H, $-CH_2-C\underline{H}_3$); 2.63 (s, 3H, $C\underline{H}_3$); 4.23 (q, 2H, $-C\underline{H}_2-CH_3$); 5.38 (s, 2H, $C\underline{H}_2$); 7.2-7.6 (m, 3H_{arom}); 8.8-9.1 ppm (m, 1H, $C_5\underline{H}$).

6-Methyl-3-oxo-3,4-dihydro-2*H*-[1,2,4]triazino[4,3-*c*]quinazoline (8):

A mixture of compound **7** (2.62 g, 0.01 mol) and hydrazine hydrate (10 ml) in ethanol (50 ml) is heated under reflux for 2 h. The precipitated solid is isolated by suction, washed with ethanol, and recrystallized from ethanol/dichloromethane (1/1) to give pure **8**; yield: 1.5 g (70%); m.p. 298-300 °C.

$C_{11}H_{10}N_4O$	calc.	C 61.67	H 4.71	N 26.15
(214.2)	found	61.65	4.69	26.19

M.S.: $m/e = 214$ (M^+).

I.R. (KBr): $\nu = 3100\text{-}2700, 1675\ cm^{-1}$.

^{1}H-N.M.R. ($DMSO\text{-}d_6/TMS_{int}$): $\delta = 2.43$ (s, 3H, CH_3); 4.68 (s, 2H, $C\underline{H}_2$); 7.2-7.7 (m, 3H_{arom}); 7.9-8.1 (m, 1H, $C_{11}\underline{H}$); 11.05 ppm (s, 1H, N$\underline{H}$).

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[1] V. Scartoni et al., *J. Chem. Soc. Perkin Trans. 1* **1979**, 1547.

[2] J. P. Barthwal et al., *J. Pharm. Sci.* **62**, 613 (1973).

[3] S. Chaloupka, J. H. Bieri, H. Heimgartner, *Helv. Chim. Acta* **63**, 1797 (1980).

[4] R. Metze, P. Schreiber, *Chem. Ber.* **89**, 2466 (1956).

[5] A. Bischler, *Ber. Dtsch. Chem. Ges.* **22**, 2801 (1889).

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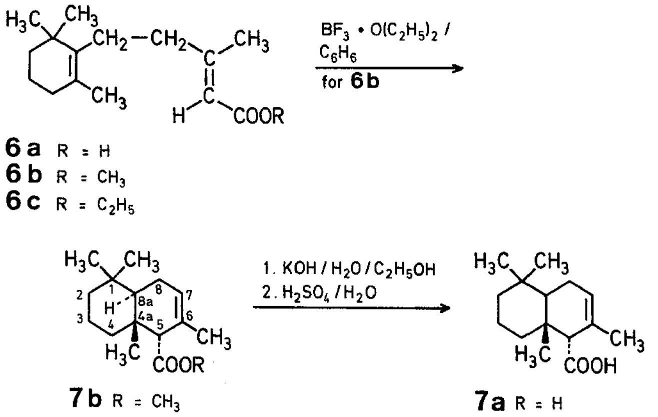
C. Schmidt, N. H. Chishti, T. Breining, *Synthesis* **1982** (5), 391-393:
The formula scheme for the reaction **6**→**7** (p. 391) should be:



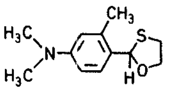
B. A. Arbuzov, N. N. Zobova, *Synthesis* **1982** (6), 433-450:
The correct name for compound **15** (p. 436) is *N*′-benzoyl-*N*,*N*-dimethyl-2-phenyl-2-butenamidine and for compound **30b** (p. 439) is 4-trifluoroacetylimino-2-trifluoromethyl-4*H*, 9a*H*-pyrido[2,1-*b*]-1,3,5-oxadiazine.

Chen-Chu Chan, Xian Huang, *Synthesis* **1982** (6), 452-454:
The last sentence on page 452 should read: However, under the normal conditions [20% aqueous sodium hydroxide in the presence of benzyltriethylammonium chloride (TEBA)] the ring underwent cleavage and the main product was dimethylmalonic acid in the case of methylation.

P. Molina, A. Arques, A. Ferao, *Synthesis* **1982** (8), 645-647:
Compounds **3**,**4**, and **6** are substituted pyrido[2,1-*b*][1,3,4]thiadiazinium salts.

Abstract 6431, *Synthesis* **1982** (9), 801
The correct name for the title compounds **3** is 2-oxoalkanehydroximic chlorides.

B. Burczyk, Z. Kortylewicz, *Synthesis* **1982** (10), 831-832:
In Table 1 (p. 832) the b.p. of product **6a** should be 113-114°C/0.3 torr; the structure and molecular formula of product **7d** should be



and $C_{12}H_{17}NOS$ (223.2); the b.p. and n_D^{20} of product **8a** should be 114-116°C/60 torr and 1.5346, respectively. In Table 2 (p. 832) the second term in the ^{1}H-N.M.R. spectrum of product **7b** should be 1.90 (s, 3H, CH_3).

K. D. Deodhar, A. D. D'Sa, S. R. Pednekar, D. S. Kanekar, *Synthesis* **1982** (10), 853-854:
The correct name for compounds **4a**,**b** (p. 854) is (*E*)- and (*Z*)-6-benzylidene-3-oxo-2,3,4,6-tetrahydro[1,2,4]triazino[3,4-*a*]isoindoles.

L. Lepage, Y. Lepage, *Synthesis* **1982** (10), 882-884:
The correct name for compound **10** (p. 884) is 2-acetyl-1,4-diphenyl-1,2,3,4-tetrahydro-1,4-epithiopentacene-7,12-quinone.

R. R. Schmidt, A. Wagner, *Synthesis* **1982** (11), 958-962:
It should be noted that the numbers in the products **5**-**16c** in Table 1 refer only to the ^{1}H-N.M.R. data in Table 2 and are not identical with the numbering used for the systematic nomenclature of the products.

T. Takajo, S. Kambe, W. Ando, *Synthesis* **1982** (12), 1080-1081:
The compounds **7** should be named 2,4,6,12-tetraaryl-2,5,6,7-tetrahydro-4*H*-3,6a-methanoindeno[1,2-*f*][1,3,5]triazocines.