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SYNTHESIS OF 1,2,4-TRIAZINES, XII

NEW SYNTHESIS OF 1,2,4-TRIAZINES WITH A FUNCTIONAL GROUP IN THE 6-POSITION

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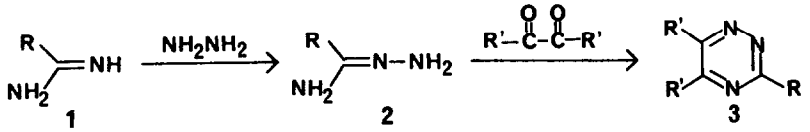
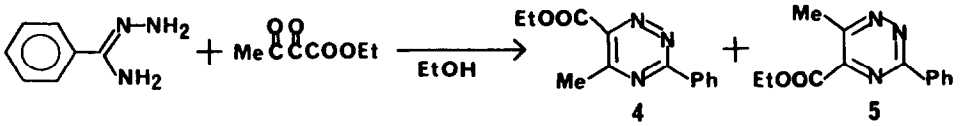
ABSTRACT: *6-Acyl- (15, 17) and 6-ethoxycarbonyl-5-substituted 1,2,4-triazines (11) were prepared by refluxing acylhydrazones (10, 14) or N,N-dimethylaminomethylenehydrazones (16) with ammonium acetate in acetic acid. NMR-studies confirmed the high regio selectivity of this procedure.*

Amidrazones (**2**) which can be easily prepared by the reaction of amidines (1) with hydrazine are versatile intermediates for the synthesis of heterocycles [1-5]. Due to their facile preparation a great number of 1,2,4-triazines (**3**) have been prepared by the reaction of **2** with 1,2-dioxo compounds [6-8] (Scheme 1).



Scheme 1

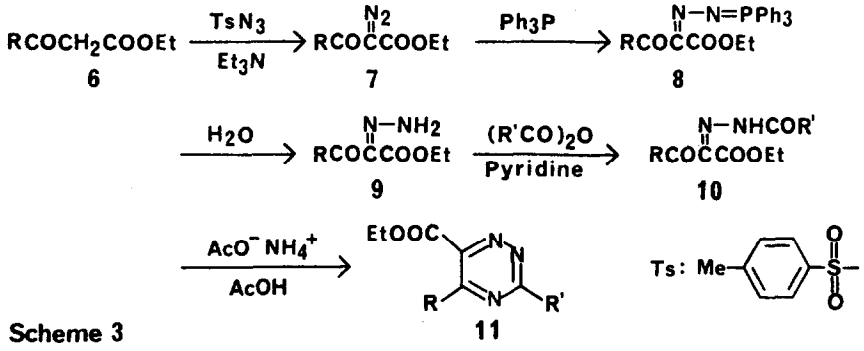
During our studies on 1,2,4-triazines we had to prepare 1,2,4-triazine-6-carboxylates (**4**). Above mentioned reaction, however, required some improvement, because we obtained a mixture of the two isomers **4** and **5**, as shown in Scheme 2[9].



Scheme 2

The α-hydrazones (9) which can be easily prepared from ethyl ß-oxocarboxylates (6), as shown in Scheme 3, attracted almost no attention as synthetic intermediates. But their multifunctionality can be regarded as a useful synthetic tool for the synthesis of heterocycles. This prompted us to check if these intermediates can be used for the synthesis of 1,2,4-triazines with an ethoxycarbonyl or acyl group in the 6-position. Here we would like to report the results of our studies.

Ethyl ß-oxocarboxylates (6) were treated with p-toluenesulfonyl azide and triethylamine to give the α-diazo compounds (7), which were mixed with triphenylphosphine to form the phosphazines (8)[10]. The phosphazines (8) were hydrolyzed in aqueous ethanol to give the hydrazones (9), as described by Bestmann[11,12]. The hydrazones (9) were acylated in the presence of pyridine and the obtained acylhydrazones (10) were heated with ammoniumacetate in acetic acid under reflux [13].



Scheme 3

Results were summarized in Table 1.

Table 1:

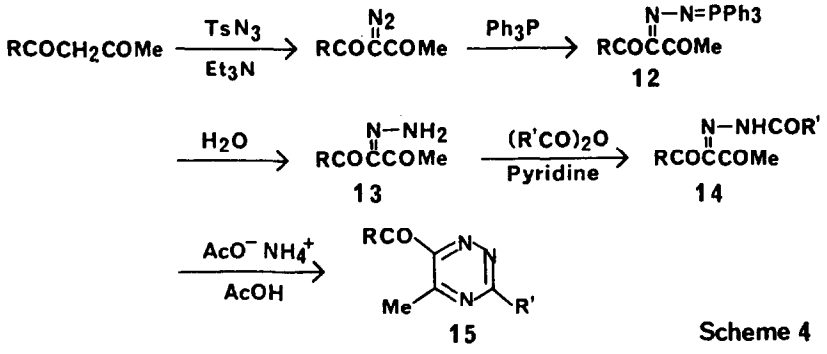
Synthesis of acylhydrazones 10 and 1,2,4-triazine-6-carboxylates 11

	R	R'	yield 10	yield 11
a	Me	Me	79%	91%
b	Et	Me	68%	80%
c	i-Pr	Me	66%	86%
d	i-Pr	Ph	46%	85%
e	Ph	Me	85%	77%
f	Me	Ph	53%	81%
g	Me	Et	52%	93%
h	Me	i-Pr	84%	91%
i	Me	t-Bu	85%	98%

As shown in Table 1, ethyl 1,2,4-triazine-6-carboxylates (11) can be prepared in fairly good yields. Bulky groups such as i-propyl and t-butyl groups can easily be introduced into the 3- and/or 5-position. The absence of their regio isomers was confirmed by ^{1}H-NMR analysis. For example, the methyl groups at the 5 position of 4 and at the 6-position of 5 appear at δ = 2.89 and 2.79 as singlets in their ^{1}H-NMR spectra, respectively[9]. Since we observe only one singlet in the ^{1}H-NMR specta of 11f this procedure proves to be a good method for the synthesis of 5-substituted 1,2,4-triazine-6-carboxylates.

This method was then successfully applied to the synthesis of 6-acyl-1,2,4-triazines (15) via the 1,2,3-triketone 2-hydrazones (13).

1,2,3-Triketone-2-triphenylphosphazines (12) were prepared from acetylacetone and benzoylacetone according to the method described by Regitz[10]. He reports that the hydrolysis of the phosphazine 12a in 90% ethanol in the presence of catalytic amounts of 6N HCl yields the phosphazine-hydrate. The desired 2,3,4-pentanetrione 3-hydrazone (13a) could be prepared according to the procedure described by Bestmann[12]. Thus obtained hydrazones 13 were acylated in pyridine and then cyclized by reaction with ammonium acetate in acetic acid to give 3-substituted-5-methyl-6-acyl-1,2,4-triazines (15) (Scheme 4).
Results are summarized in Table 2.



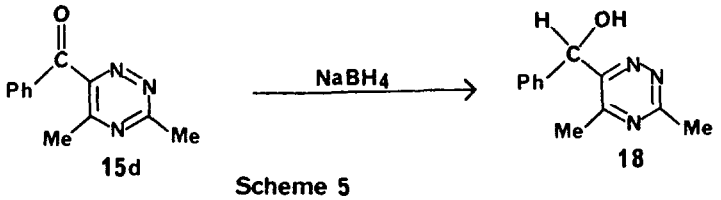
Scheme 4

Table 2:
Synthesis of acylhydrazones 14 and 1,2,4-triazines 15 and 17

	R	R'	yield 14	yield 15
a	Me	Me	43%	86%
b	Me	Et	67%	99%
c	Me	Ph	35%	76%
d	Ph	Me	100%	92%

	R	R'	yield 17
a	Me	Me	53%
b	Me	OEt	25%
c	Et	OEt	31%
d	i-Pr	OEt	25%
e	Ph	OEt	26%

The desired products were obtained in good yields. Their regio isomers could not be detected by ^{1}H-NMR analysis. The structure of **15d** was determined by reduction with sodium borohydride, which gave the 6-(1-hydroxybenzyl)-3,5-dimethyl-1,2,4-triazine (**18**) as the single product. It is noteworthy that the acyl group can easily be introduced in the 6-position of 1,2,4-triazines by this method.

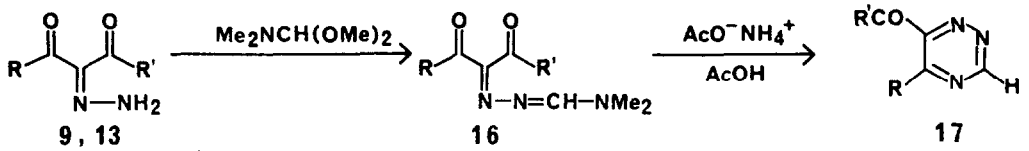


15d 18

Scheme 5

Introduction of a hydrogen at the 3-position of 1,2,4-triazines may be achieved by using ethyl 2,3-dioxocarboxylate 2-formylhydrazones and 1,2,3-triketone 2-formylhydrazones as starting materials. However both compounds could not be prepared by refluxing the hydrazones **9** and **13** in ethyl formate. **9** and **13** were therefore treated with N,N-dimethylformamide dimethyl acetal to give the N,N-dimethylaminomethylenehydrazones (**16**), which were refluxed without isolation with ammonium acetate in acetic acid.

Results are summarized in Table 2.



9, 13 16 17

Scheme 6

The desired 1,2,4-triazines with a hydrogen at the 3-position could be prepared in moderate yields without their regio isomers. Thus the hydrazones **9** and **13** proved to be versatile intermediates for the selective synthesis of 6-acyl- and 6-ethoxycarbonyl-5-substituted 1,2,4-triazines. Other utilization of these promising intermediates is under investigation.

Experimental

General methods: ^{1}H-NMR spectra were recorded with a Varian EM 360 spectrometer (60 MHz) in deuteriochloroform solutions, tetramethylsilane as internal standard. – Infrared spectra were recorded with a Perkin-Elmer infrared spectrometer 297. – Melting points were taken on a Reichert melting point apparatus and are uncorrected. – Column chromatography was performed with Macherey-Nagel silica gel 60 (70 – 230 mesh).

Ethyl 2,3-dioxocarboxylate 2-hydrazones (**9**):

These compounds are prepared in the similar manner as described by Bestmann[12]. The prepared hydrazones are listed below with their physical data.

Ethyl 2,3-dioxobutanoate 2-hydrazone (**9**, R=Me): Yield 84%; m.p. 85–90°C (Lit.[12] 85–93°C); ^{1}H-NMR ($CDCl_3$) δ 1.35 (3H, t, J=7Hz), 2.33, 2.53 (total 3H, each s), 4.30 (2H, q, J=7Hz), 8.70–9.40 (2H, brd).

Ethyl 2,3-dioxopentanoate 2-hydrazone (**9**, R=Et): Yield 62%; m.p. 45–50°C; ^{1}H-NMR ($CDCl_3$) δ 1.34 (6H, t, J=7Hz), 2.77, 2.95 (total 2H, each q, J=7Hz), 4.30 (2H, q, J=7Hz), 8.70–9.40 (2H, brd); IR (Nujol) 3330, 3170, 2930, 1720, 1660, 1300, 1260, 1180, 1160, 1120, 1070, 1020, 970, 930 cm^{-1}; Anal. Calcd. for $C_7H_{12}N_2O_3$: C 48.83; H 7.02; N 16.27%. Found: C 48.76; H 7.07; N 16.41%.

Ethyl 2,3-dioxo-4-methylpentanoate 2-hydrazone (**9**, R=i-Pr): Yield 100%; oil; ^{1}H-NMR ($CDCl_3$) δ 1.10 (6H, d, J=7Hz), 1.35 (3H, t, J=7Hz), 3.51 (1H, sept, J=7Hz), 4.29 (2H, q, J=7Hz), 8.70–9.30 (2H, brd); IR (Nujol) 3330, 3170, 2930, 1660, 1580, 1560, 1300, 1220, 1180, 1160, 1100, 1030, 950 cm^{-1}; Anal. Calcd. for $C_8H_{14}N_2O_3$: C 51.60; H 7.58; N 15.04%. Found: C 51.45; H 7.59; N 14.81%.

Ethyl 2,3-dioxo-3-phenylpropanoate 2-hydrazone (**9**, R=Ph): Yield 62%; m.p. 57–61°C (Lit.[12] 59–62°C); ^{1}H-NMR ($CDCl_3$) δ 1.27 (3H, t, J=7Hz), 4.28 (2H, q, J=7Hz), 7.20–7.60 (3H, m), 7.70–8.00 (2H, m), 8.70–9.50 (2H, brd).

2,3,4-Pentanetrione 3-hydrazone (**13**, R=Me):

2,3,4-Pentanetrione-3-triphenylphosphazine[10] (8.00 g, 20.6 mmol) is suspended in 90% ethanol (50 ml). The resulting mixture is stirred for two days to give a clear solution. The solution is concentrated under reduced pressure and diluted with ether. After stirring with powdered anhydrous $ZnCl_2$ (14g) for 30 min, the ether solution is filtered. The filtrate is washed with sodium bicarbonate solution (200 ml) and dried over anhydrous $MgSO_4$. The solvent is evaporated under reduced pressure to give crude crystals, which are triturated with n-hexane-ether (10 ml, 10:1) to give white crystals. Yield 81%; m.p. 107–108°C; ^{1}H-NMR ($CDCl_3$) δ 2.33 (3H, s), 2.53 (3H, s), 9.20–10.10 (2H, brd); IR (Nujol) 3350, 3160, 2920, 1660, 1560, 1360, 1320, 1300, 1230, 1160, 1020, 970, 930 cm^{-1}; Anal. Calcd. for $C_5H_8N_2O_2$: C 46.87; H 6.29; N 21.86%. Found: C 46.86; H 6.39; N 22.13%.

1-Phenyl-1,2,3-butanetrione 2-hydrazone (**13**, R=Ph): This compound is prepared according to the method described by Regitz[10].

Ethyl 2,3-dioxobutanoate 2-acylhydrazones (**10**, R=Me):

General procedure: To a solution of the hydrazone **9** (R=Me, 1.90 mmol) and carboxylic acid anhydride (2.09 mmol) in tetrahydrofuran (5 ml) pyridine (0.17 g, 2.15 mmol) is added with stirring at room temperature. After stirring overnight, the resulting solution is diluted with ethyl acetate and washed with 0.1 N hydrochloric acid (20 ml) and water (30 ml). The organic phase is concentrated and chromatographed on silica gel (eluting with n-hexane-chloroform-tetrahydrofuran, 6:2:1) to give *ethyl 2,3-dioxobutanoate 2-acylhydrazones* (**10**, R=Me).

The compounds prepared are listed below with their physical data.

Ethyl 2,3-dioxobutanoate 2-acetylhydrazone (**10a**): m.p. 70–74°C; ^{1}H-NMR ($CDCl_3$) δ 1.38 (3H, t, J=7Hz), 2.41 (3H, s), 2.50 (3H, s), 4.38 (2H, q, J=7Hz), 11.20–11.50 (1H, brd); IR (Nujol) 3230, 3150, 2950, 1750, 1700, 1610, 1300, 1250, 1180, 1080, 1030 cm^{-1}; Anal. Calcd. for $C_8H_{12}N_2O_4$: C 48.00; H 6.04; N 13.99%. Found: C 47.79; H 5.89; N 14.04%.

Ethyl 2,3-dioxobutanoate 2-benzoylhydrazone (**10f**): m.p. 81–83°C; ^{1}H-NMR ($CDCl_3$) δ 1.40 (3H, t, J=7Hz), 2.57 (3H, s), 4.42 (2H, q, J=7Hz), 7.20–7.70 (3H, m), 7.70–8.00 (2H, m), 11.20–11.50 (1H, brd); IR (Nujol) 3230, 2950, 1700, 1660, 1530, 1370, 1290, 1250, 1230, 1170, 1150, 1020, 930, 750 cm^{-1}; Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C 59.54; H 5.38; N 10.68%. Found: C 59.38; H 5.21; N 10.81%.

Ethyl 2,3-dioxobutanoate 2-propionylhydrazone (**10g**): m.p. 67–68°C; ^{1}H-NMR ($CDCl_3$) δ 1.25 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 2.47 (3H, s), 2.75 (2H, q, J=7Hz), 4.38 (2H, q, J=7Hz), 11.00–11.50 (1H, brd); IR (Nujol) 3240, 3150, 2950, 1760, 1710, 1600, 1330, 1270, 1230, 1190 cm^{-1}; Anal. Calcd. for $C_9H_{14}N_2O_4$: C 50.46; H 6.59; N 13.08%. Found: C 50.26; H 6.69; N 13.56%.

Ethyl 2,3-dioxobutanoate 2-isobutyrylhydrazone (**10h**): m.p. 55–58°C; ^{1}H-NMR ($CDCl_3$) δ 1.25 (6H, d, J=7Hz), 1.37 (3H, t, J=7Hz), 2.47 (3H, s), 3.28 (1H, sept, J=7Hz), 4.37 (2H, q, J=7Hz), 11.00–12.00 (1H, brd); IR (Nujol) 3170, 2930 1740, 1700, 1590, 1520, 1360, 1300, 1240, 1140, 1050 cm^{-1}; Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C 52.62; H 7.07; N 12.27%. Found: C 52.88; H 6.82; N 12.95%.

Ethyl 2,3-dioxobutanoate 2-pivaloylhydrazone (**10i**): m.p. 88°C; ^{1}H-NMR ($CDCl_3$) δ 1.33 (9H, s), 1.37, (3H, t, J=7Hz), 2.50 (3H, s), 4.37 (2H, q, J=7Hz), 11.50–12.00 (1H, brd); IR (Nujol) 3230, 2950, 1700, 1660, 1530, 1370, 1290, 1250, 1230, 1170, 1150, 1020, 930 cm^{-1}; Anal. Calcd. for $C_{11}H_{18}N_2O_4$: C 54.53; H 7.49; N 11.56%. Found: C 54.53; H 7.36; N 11.59%.

Ethyl 2,3-dioxocarboxylate 2-acetylhydrazones (**10**, R'=Me) and *2-benzoylhydrazones* (**10**, R'=C_6H_5): *General procedure*: To a solution of the hydrazone **9** (1.90 mmol) in pyridine (3 ml) acetic anhydride (0.58g, 5.70 mmol) or benzoic anhydride (1.29 g, 5.70 mmol) is added with stirring at room temperature. After stirring overnight, the resulting solution is poured into cold 1N hydrochloric acid (60 ml) and extracted with ethyl acetate (2x50 ml). The extracts are washed with water (30 ml) and evaporated under reduced pressure. The residue is chromatographed on silica gel (eluting with n-hexane–chloroform–tetrahydrofuran, 6:2:1) to give *ethyl 2,3-dioxocarboxylate 2-acetylhydrazones* (**10**, R'=Me) and 2-benzoylhydrazones (**10**, R'=C_6H_5).

The compounds prepared are listed below with their physical data.

Ethyl 2,3-dioxopentanoate 2-acetylhydrazone (**10b**): m.p. 90–97°C; ^{1}H-NMR ($CDCl_3$) δ 1.15 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 2.38 (3H, s), 2.85 (2H, q, J=7Hz), 4.35 (2H, q, J=7Hz), 11.00–11.50 (1H, brd); IR (Nujol) 3170, 3100, 2900, 1740, 1680, 1590, 1320, 1290, 1190, 1160, 1020, 940 cm^{-1}; Anal. Calcd. for $C_9H_{14}N_2O_4$: C 50.46; H 6.59; N 13.08%. Found: C 50.44; H 6.73; N 13.30%.

Ethyl 2,3-dioxo-4-methylpentanoate 2-acetylhydrazone (**10c**): m.p. 78–80°C; ^{1}H-NMR ($CDCl_3$) δ 1.18 (6H, d, J=7Hz), 1.35 (3H, t, J=7Hz), 2.37 (3H, s), 3.78 (1H, sept, J=7Hz), 4.33 (2H, q, J=7Hz), 11.30–12.00 (1H, brd); IR (Nujol) 3170, 3090, 2900, 1730, 1680, 1590, 1320, 1280, 1260, 1200, 1150, 1010, 960 cm^{-1}; Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C 52.62; H 7.07; N 12.27%. Found: C 52.60; H 7.12; N 12.28.

Ethyl 2,3-dioxo-4-methylpentanoate 2-benzoylhydrazone (**10d**): m.p. 53–54°C; ^{1}H-NMR ($CDCl_3$) δ 1.20 (6H, d, J=7Hz), 1.39 (3H, t, J=7Hz), 3.63 (1H, sept. J=7Hz), 4.40 (2H, q, J=7Hz), 7.30–7.80 (3H, m), 7.80–8.10 (2H, m) 12.50–13.00 (1H, brd); IR (Nujol) 3180, 2930, 1740, 1660, 1600, 1530, 1260, 1210, 1120, 1110, 1010, 960, 920 cm^{-1}; Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C 62.06; H 6.25; N 9.65%. Found C 61.92; H 6.20; N 9.67%.

Ethyl 2.3-dioxo-3-phenylpropionate 2-acetylhydrazone (**10e**): ^{1}H-NMR ($CDCl_3$) δ 1.15, 1.26 (total 3H, each t, J=7Hz), 2.23, 2.37 (total 3H, each s), 4.23, 4.33 (total 2H, each q, J=7Hz), 7.20–8.00 (5H, m), 11.50–12.00 (1H, brd); IR (Nujol) 3250, 2920, 1720, 1700, 1660, 1320, 1260, 1210, 1150, 1030 cm^{-1}; Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C 59.54; H 5.38; N 10.68%. Found: C 59.75; H 5.41; N 10.76%.

2,3,4-Triketone 3-acylhydrazones (**14**):

These compounds are synthesized in the similar manner as described for the preparation of *ethyl 2,3-dioxocarboxylate 2-acetylhydrazones* (**10**, R'=Me).

The compounds prepared are listed below with their physical data.

2,3,4-Pentanetrione 3-acetylhydrazone (**14a**): oil; ^{1}H-NMR ($CDCl_3$) δ 2.40 (3H, s), 2.45 (3H, s), 2.57 (3H, s), 12.50–13.30 (1H, brd); IR (Nujol) 3160, 2900, 1710, 1680, 1650, 1520, 1360, 1290, 1250, 1150 cm^{-1}; Anal. Calcd. for $C_7H_{10}N_2O_3$: C 49.43; H 5.93; N 16.47%; Found: C 48.93; H 5.93; N 16.49%.

2,3,4-Pentanetrione 3-propionylhydrazone (**14b**): m.p. 53–54°C, ^{1}H-NMR ($CDCl_3$) δ 1.23 (3H, t, J=7Hz), 2.48 (3H, s), 2.58 (3H, s), 2.77 (2H, q, J=7Hz), 12.00–13.00 (1H, brd); IR (Nujol) 3220, 1730, 1710, 1680, 1540, 1310, 1230, 1160, 1090, 1060 cm^{-1}; Anal. Calcd. for $C_8H_{12}N_2O_3$: C 52.17; H 6.57; N 15.21% Found: C 52.02; H 6.60; N 15.23%

2,3,4-Pentanetrione 3-benzolhydrazone (**14c**): m.p. 118–119°C; ^{1}H-NMR ($CDCl_3$) δ 2.56 (3H, s), 2.64 (3H, s), 7.30–7.70 (3H, m), 7.70–8.00 (2H, m) 14.00–15.00 (1H, brd); IR (Nujol) 3200, 2980, 1700, 1520, 1360, 1300, 1240, 1160 cm^{-1}; Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C 62.06; H 5.21; N 12.06%. Found: C 62.06; H 5.07; N 12.21%.

1-Phenyl-1,2,3-butanetrione 2-acetylhydrazone (**14d**): m.p. 92–95°C; ^{1}H-NMR ($CDCl_3$) δ 2.24, 2.50 (total 3H, each s), 2.56 (3H, s), 7.20–8.10 (5H, m), 9.50–10.10 (1H, brd); IR (Nujol) 3200, 3120, 2910, 1710, 1690, 1680, 1660, 1600, 1280, 1240, 1160 cm^{-1}; Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C 62.06; H 5.21; 12.06%. Found: C 62.06; H 5.15; N 12.19%.

3,5-Disubstituted-6-acetyl(benzoyl or ethoxycarbonyl)-1,2,4-triazines (**11** or **15**):

General procedure: The acylhydrazones **10** or **14** (1.40 mmol) and ammonium acetate (216 mg, 2.80 mmol) are dissolved in acetic acid (10 ml). The resulting mixture is refluxed for 5 hr and neutralized with sodium bicarbonate solution. The resulting solution is extracted with ethyl acetate (2x40 ml). The extracts are washed with water (30 ml) and concentrated. The residue is chromatographed on silica gel (eluting with n-hexane–ethyl acetate, 1:1 for **15**, n-hexane–chloroform–tetrahydrofuran, 6:2:1 for **11**) to give *3,5-disubstituted-6-acetyl(benzoyl* or *ethoxycarbonyl)-1,2,4-triazines* (**11** or **15**).

The compounds prepared are listed below with their physical data.

Ethyl 3,5-dimethyl-1,2,4-triazine-6-carboxylate (**11a**): oil; ^{1}H-NMR ($CDCl_3$) δ 1.47 (3H, t, J=8Hz), 2.80 (3H, s), 2.93 (3H, s), 4.51 (2H, q, J=8Hz); IR (neat) 2980, 1730, 1530, 1440, 1380, 1270, 1120, 1090, 1030, 850 cm^{-1}; Anal. Calcd. for $C_8H_{11}N_3O_2$: C 53.03; H 6.12; N 23.19%. Found: C 52.76; H 6.14; N 23.47%.

Ethyl 3-methyl-5-ethyl-1,2,4-triazine-6-carboxylate (**11b**): oil; ^{1}H-NMR ($CDCl_3$) δ 1.33 (3H, t, J=7Hz), 1.47 (3H, t, J=7Hz), 2.91 (3H, s), 3.07 (2H, q, J=7Hz), 4.52 (2H, q, J=7Hz); IR (neat) 2980, 1730, 1520, 1410, 1370, 1270, 1240, 1090, 1030 cm^{-1}; Anal. Calcd. for $C_9H_{13}N_3O_2$: C 55.37; H 6.71; N 21.52%. Found: C 55.49; H 6.60; 21.44%.

Ethyl 3-methyl-5-isopropyl-1,2,4-triazine-6-carboxylate (**11c**): oil, ^{1}H-NMR ($CDCl_3$) δ 1.32 (6H, d, J=7Hz), 1.45 (3H, t, J=7Hz), 2.92 (3H, s), 3.57 (1H, sept, J=7Hz), 4.53 (2H, q, J=7Hz); IR (neat) 2980, 1730, 1530, 1420, 1250, 1090 cm^{-1}; Anal. Calcd. for $C_{10}H_{15}N_3O_2$: C 57.40; H 7.23; N 20.08%. Found: C 57.17; H 7.31; N 19.89%.

Ethyl 3-phenyl-5-isopropyl-1,2,4-triazine-6-carboxylate (**11d**): m.p. 48–50°C; ^{1}H-NMR ($CDCl_3$) δ 1.42 (6H, d, J=7Hz), 1.48 (3H, t, J=7Hz), 3.71 (1H, sept, J=7Hz), 4.54 (2H, q, J=7Hz), 7.30–7.70 (3H, m), 8.40–8.80 (2H, m); IR (Nujol) 2960, 1720, 1510, 1450, 1390, 1380, 1300, 1260, 1220, 1190, 1160 cm^{-1}; Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C 66.40; H 6.32; N 15.49%. Found: C 66.42; H 6.37; N 15.26%.

Ethyl 3-methyl-5-phenyl-1,2,4-triazine-6-carboxylate (**11e**): m.p. 76–77°C; ^{1}H-NMR ($CDCl_3$) δ 1.25 (3H, t, J=7Hz), 2.97 (3H, s), 4.37 (2H, q, J=7Hz), 7.20–7.80 (5H, m); IR (Nujol) 2960, 1740, 1500, 1460, 1440, 1370, 1350, 1280, 1260, 1240, 1160, 1140, 1070, 1050 cm^{-1}; Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C 64.19; H 5.39; N 17.27%. Found: C 63.86; H 5.27; N 17.33%.

Ethyl 3-phenyl-5-methyl-1,2,4-triazine-6-carboxylate (**11f**): m.p. 68–70°C; ^{1}H-NMR ($CDCl_3$) δ 1.48 (3H, t, J=7Hz), 2.89 (3H, s), 4.53 (2H, q, J=7Hz), 7.30–7.60 (3H, m), 8.40–8.70 (2H, m); IR (Nujol) 2980, 1720, 1510, 1460, 1370, 1260 cm^{-1}; Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C 64.19; H 5.39; N 17.27%. Found: C 64.10; H 5.19; N 17.47%.

Ethyl 3-ethyl-5-methyl-1,2,4-triazine-6-carboxylate (**11g**): oil; ^{1}H-NMR ($CDCl_3$) δ 1.44 (3H, t, J=7Hz), 1.48 (3H, t, J=7Hz), 2.83 (3H, s), 3.18, (2H, q, J=7Hz), 4.53 (2H, q, J=7Hz); IR (neat) 2980, 1720, 1520, 1420, 1380, 1260, 1110 cm^{-1}; Anal. Calcd. for $C_9H_{13}N_3O_2$: C 55.37; H 6.71; N 21.52%. Found: C 55.04; H 6.88; N 21.60%.

Ethyl 3-isopropyl-5-methyl-1,2,4-triazine-6-carboxylate (**11h**): oil; ^{1}H-NMR ($CDCl_3$) δ 1.47 (6H, d, J=7Hz), 1.47 (3H, t, J=7Hz), 2.85 (3H, s), 3.47 (1H, sept, J=7Hz), 4.52 (2H, q, J= 7Hz); IR (neat) 2980, 1720, 1520, 1380, 1260, 1110 cm^{-1}; Anal. Calcd. for $C_{10}H_{13}N_3O_2$: C 57.40; H 7.23; N 20.08%. Found: C 57.14; H 7.20; N 19.78%.

Ethyl 3-tert-butyl-5-methyl-1,2,4-triazine-6-carboxylate (**11i**): oil; ^{1}H-NMR ($CDCl_3$) δ 1.47 (3H, t, J=7Hz), 1.55 (9H, s), 2.82 (3H, s), 4.52 (2H, q, J=7Hz); IR (neat) 2980, 1720, 1510, 1380, 1270, 1250, 1220, 1170, 1110, 1060 cm^{-1}; Anal. Calcd. for $C_{11}H_{17}N_3O_2$: C 59.17; H 7.67; N 18.82%. Found: C 59.29; H 7.78; N 18.66%.

6-Acetyl-3,5-dimethyl-1,2,4-triazine (**15a**): oil; ^{1}H-NMR ($CDCl_3$) δ 2.80 (3H, s), 2.87 (3H, s) 2.91 (3H, s); IR (neat) 2930, 1700, 1520, 1420, 1360, 1230, 1100, 1070, 1030, 940 cm^{-1}; Anal. Calcd. for $C_7H_9N_3O$: C 55.62; H 6.00; N 27.80%. Found: C 55.44; H 6.23; N 27.42%.

6-Acetyl-3-ethyl-5-methyl-1,2,4-triazine (**15b**): oil; ^{1}H-NMR ($CDCl_3$) δ 1.42 (3H, t, H=7Hz), 2.82 (3H, s), 2.85 (3H, s), 3.12 (2H, q, J=7Hz); IR (neat) 2980, 1700, 1510, 1420, 1380, 1360, 1240, 1110, 1080, 950 cm^{-1}; Anal. Calcd. for $C_8H_{11}N_3O$: C 58.17; H 6.71; N 24.44%. Found: C 58.03; H 6.93; N 24.57%

6-Acetyl-5-methyl-3-phenyl-1,2,4-triazine (**15c**): m.p. 92-94°C; ^{1}H-NMR ($CDCl_3$) δ 2.93 (6H, s), 7.40-7.70 (3H, m), 8.50-8.70 (2H, m); IR (Nujol) 2960, 1690, 1510, 1460, 1440, 1380, 1360, 1240, 1100, 1030, 960 cm^{-1}; Anal. Calcd. for $C_{12}H_{11}N_3O$: C 67.59; H 5.20; N 19.71%; Found: C 67.77; H 5.21; N 19.59%.

6-Benzoyl-3,5-dimethyl-1,2,4-triazine (**15d**): oil; ^{1}H-NMR ($CDCl_3$) δ 2.67 (3H, s) 2.97 (3H, s), 7.50-7.70 (3H, m), 7.50-8.10 (2H, m); IR (neat) 3060, 2940, 1770, 1670, 1600, 1520, 1260, 900 cm^{-1}; Anal. Calcd. for $C_{12}H_{11}N_3O$: C 67.59; H 5.20; N 19.71%. Found: C 67.33; H 5.35; N 19.41%.

5-Substituted-6-acetyl(or ethoxycarbonyl)-1,2,4-triazines (**17**):

General procedure: To a solution of the hydrazone **9** or **13** (2.34 mmol) in tetrahydrofuran (5 ml) a solution of N,N-dimethylformamide dimethyl acetal (0.28 g, 2,34 mmol) in tetrahydrofuran (2 ml) is added with stirring at 0°C. After 3 hr, the resulting solution is concentrated and mixed with ammonium acetate (0.36 g, 4.7 mmol). The mixture is refluxed in acetic acid (10 ml) for 5 hr. The reaction mixture is neutralized with sodium bicarbonate solution and extracted with ethyl acetate (2x40 ml). The extracts are washed with water (30 ml) and concentrated. The residue is chromatographed on silica gel (eluting with n-hexane-ethyl acetate, 1:1) to give *5-substituted-6-acetyl-* or *6-ethoxycarbonyl-1,2,4-triazines* (**17**).

The compounds prepared are listed below with their physical data.

6-Acetyl-5-methyl-1,2,4-triazine (**17a**): oil; ^{1}H-NMR ($CDCl_3$) δ 2.88 (3H, s), 2.92 (3H, s), 9.63 (1H, s); IR (neat) 2920, 1700, 1510, 1420, 1360, 1230, 1140, 1090, 950 cm^{-1}; Anal. Calcd. for $C_6H_7N_3O$: C 52.55; H 5.15; N 30.64%. Found: C 52.87; H 5.43; N 30.38%.

Ethyl 5-methyl-1,2,4-triazine-6-carboxylate (**17b**): oil; ^{1}H-NMR ($CDCl_3$) 1.48 (3H, t, J=7Hz), 2.85 (3H, s), 4.55 (2H, q, J=7Hz), 9.60 (1H, s); IR (neat) 2980, 1720, 1510, 1420, 1370, 1330, 1270, 1250, 1230, 1140, 1100, 1030, 900, 860 cm^{-1}; Anal. Calcd. for $C_7H_9N_3O_2$: C 50.30; H 5.43; N 25.14 %. Found: C 50.38; H 5.53; N 25.10%

Ethyl 5-ethyl-1,2,4-triazine-6-carboxylate (**17c**): oil; ^{1}H-NMR ($CDCl_3$) δ 1.36 (3H, t, J=7Hz), 1.48 (3H, t, J=7Hz), 3.09 (2H, q, J=7Hz), 4.56 (2H, q, J=7Hz), 9.63 (1H, s); IR (neat) 2980, 1720, 1510, 1460, 1420, 1370, 1320, 1270, 1220, 1140, 1110, 1050, 890, 860 cm^{-1}; Anal. Calcd. for $C_8H_{11}N_3O_2$: C 53.03; H 6.12; N 23.19%. Found: C 53.33; H 6.26; N 23.36%.

Ethyl 5-isopropyl-1,2,4-triazine-6-carboxylate (**17d**); oil; ^{1}H-NMR ($CDCl_3$) δ 1.37 (6H, d, J=7Hz), 1.47 (3H, t, J=7Hz), 3.58 (1H, sept, J=7Hz), 4.55 (2H, q, J=7Hz), 9.67 (1H, s); IR (neat) 2980, 1730, 1530, 1510, 1450, 1370, 1330, 1220, 1160, 1100, 1020, 900, 860 cm^{-1}; Anal. Calcd. for $C_9H_{13}N_3O_2$: C 55.37; H 6.71; N 21.52; Found: C 55.32; H 7.01; N 21.07%.

Ethyl 5-phenyl-1,2,4-triazine-6-carboxylate (**17e**): oil; ^{1}H-NMR ($CDCl_3$) δ 1.25 (3H, t, J=7Hz), 4.42 (2H, q, J=7HZ), 7.30-8.00 (5H, m), 9.77 (1H, s); IR (neat) 3060, 2980, 2960, 1730, 1500, 1440, 1330, 1220, 1150, 1060, 1020 cm^{-1}; Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C 62.87; H 4.84; N 18.33%. Found: C 62.36; H 4.90; N 18.60%.

6-(1-Hydroxybenzyl)-3,5-dimethyl-1,2,4-triazine (**18**): To a stirred solution of **15d** (100 mg, 0.47 mmol) in tetrahydrofuran (5ml) sodium borohydride (20 mg, 0.47 mmol) is added at 0°C. After stirring at room temperature for 30 min, the reaction mixture is poured into water (25 ml) and extracted with ethyl acetate (2x50 ml). The extracts are washed with water (10 ml) and evaporated. The residue is chromatographed on silica gel (eluting with n-hexane-ethyl acetate, 1:1) to give 60 mg (60%) **18** as oil; ^{1}H-NMR ($CDCl_3$) δ 2.32 (3H, s), 2.85 (3H, s), 4.60-5.30 (1H, brd), 6.00 (1H, s), 7.36 (5H, s); Anal. Calcd. for $C_{12}H_{13}N_3O$: C 66.96; H 6.09; N 19.52%. Found: C 66.74; H 5.94; N 19.23%.

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