SYNTHESIS of 1,2,4-TRIAZINES; XIII [1] REGIOSELECTIVE SYNTHESIS of TRIALKYL-1,2,4-TRIAZINES

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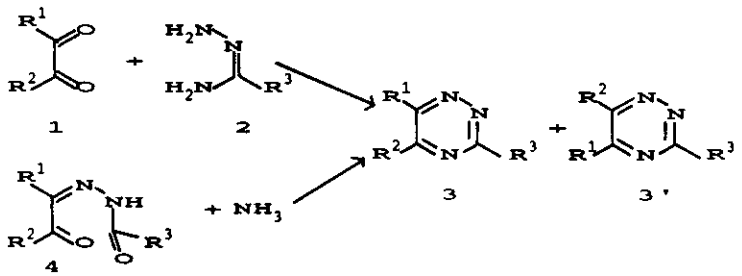
Abstract - Trialkyl-1,2,4-triazines (3) were prepared by heating α-oxoacylhydrazones (4) or N,N-dimethylaminomethylene hydrazones (19) with ammonium acetate at 100°C. The solvent plays an important role in the regioselectivity of these reactions.

Dedicated to Professor Dr. M. Hamana on the occasion of his 75th birthday

In the previous paper[1] we described the regioselective synthesis of ethyl 3,5-disubstituted 1,2,4-triazine-6-carboxylates by using 2,3-dioxocarboxylate 2-hydrazones as key intermediates. The high regioselectivity of this procedure prompted us to study a new regioselective synthesis of trialkyl-1,2,4-triazines.

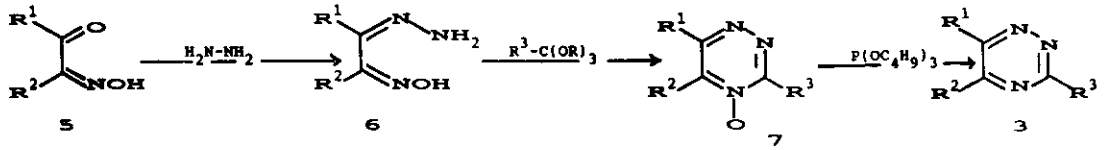
Trialkyl-1,2,4-triazines (3) have been prepared by the reaction of 1,2-dioxo compounds (1) with amidrazones (2)[2,3] or by cyclization of α-ketoacylhydrazones (4) with ethanolic ammonia in a sealed tube.[4] (Scheme 1)



Scheme 1

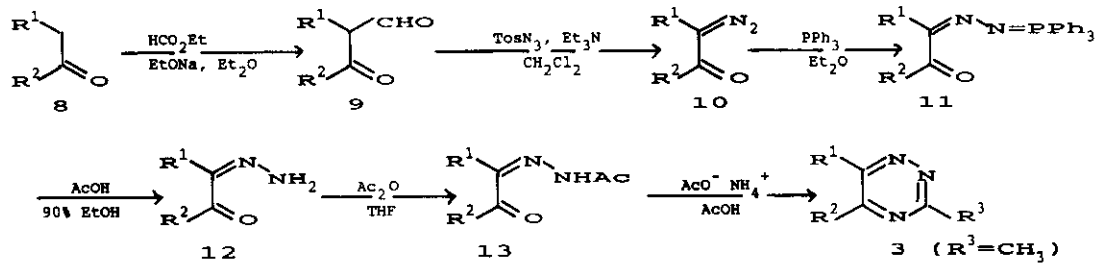
These procedures, however, often lead to a mixture of isomeric 1,2,4-tria-

zines (3) and (3'), when R^1 and R^2 are different.[5-7] This problem can be solved to some extent by starting with α-keto oximes (5) and using the reaction sequence shown in Scheme 2.[8] Another method is reported by S. Konno et al.[9]



Scheme 2

But there is still some difficulty in the selective introduction of different alkyl substituents into the 5- and 6-positions of 1,2,4-triazines. Here we would like to report a new regioselective synthesis of trialkyl-1,2,4-triazines (3) by using α-oxo hydrazones (12). (Scheme 3)

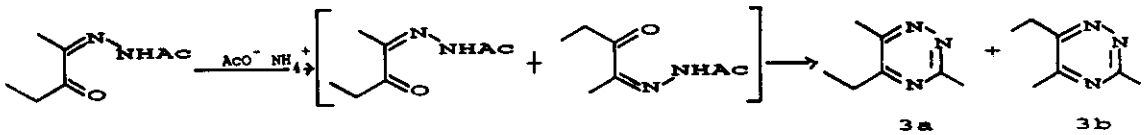


Scheme 3

Ketones (8) were formylated by reaction with ethyl formate in the presence of sodium ethoxide.[10] The obtained α-formyl ketones (9) were treated with *p*-toluenesulfonyl azide to give α-diazo ketones (10),[11] which were then mixed with triphenylphosphine to form the phosphazines (11). Hydrolysis of the phosphazines (11) in 90% ethanol in the presence of acetic acid gave α-oxo hydrazones (12). After acetylation of the hydrazones (12), (R^1=CH_3, R^2=C_2H_5), cyclization was carried out by heating (13) with ammonium acetate in acetic acid at 100°C. Nmr analysis, however, showed the presence of regioisomers in the product, which suggested that isomerization of the acetylhydrazones (13) occurred under these reaction conditions.

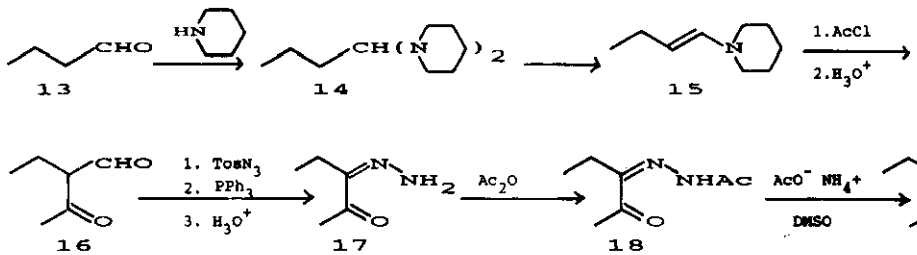
The cyclization was then studied in different solvents. The results obtained are summarized in Table 1.

Table 1: Solvent Effect on the Cyclization of 2,3-Pentanedione 2-Acetylhydrazone



Solvent	Yield (%)	Isomer ratio 3a	:	3b
acetic acid	67	7	:	3
N,N -dimethylformamide	78	9	:	1
dimethyl sulfoxide	88	10	:	0

These results show a remarkable solvent effect for the isomer ratio; no isomerization of the acetylhydrazone was observed in dimethylsulfoxide, providing a selective route to 5-ethyl-3,6-dimethyl-1,2,4-triazine (3a). On the other hand, 6-ethyl-3,5-dimethyl-1,2,4-triazine (3b) could be prepared as shown in Scheme 4.



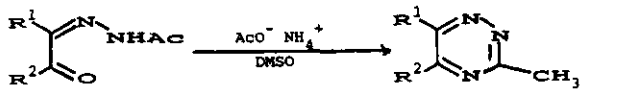
Scheme 4

Butyraldehyde (13) was converted to the aminal (14) which was then heated under reduced pressure to give the enamine (15).[12] The enamine (15) was treated with acetyl chloride and hydrolyzed producing the α-formyl ketone (16).[13] The formyl ketone (16) was subjected to the same reactions as shown in Scheme 3 to give 6-ethyl-3,5-dimethyl-1,2,4-triazine (3b).

6-Ethyl-3-methyl-5-propyl-1,2,4-triazine (3c) was also prepared in the si-

milar manner, starting with 3,4-heptanedione 3-acetylhydrazone. The results are summarized in Table 2.

Table 2: Synthesis of Trialkyl-1,2,4-triazines via Acetylhydrazones



4 3 (R^3=CH_3)

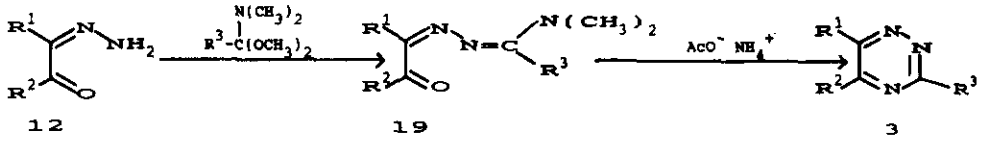
Compound	R^1	R^2	Yield (%)
3a	CH_3	C_2H_5	88
3b	C_2H_5	CH_3	74
3c	C_2H_5	C_3H_7	97

As shown in Table 2, trialkyl-1,2,4-triazines with different alkyl groups at the 5- and 6-position can be obtained in good yields. High regioselectivity was confirmed by nmr studies in all products. α-Oxo-N,N-dimethylaminomethylenhydrazones (19), which can be very easily obtained from α-oxohydrazones (12) and N,N-dimethylformamide or N,N-dimethylacetamide dimethylacetal, can also be supposed to be promising intermediates for trialkyl-1,2,4-triazines (3). Cyclization of (19) was carried out by heating with ammonium acetate in acetic acid at 100°C.

The results obtained are summarized in Table 3.

Not only trialkyl-1,2,4-triazines but also 5,6-dialkyl-1,2,4-triazines could be prepared in fairly good yields. The reaction proceeded without isomerization in acetic acid, which is in contrast with the results obtained for the cyclization of 2,3-pentanedione 2-acetylhydrazones (Table 1). Thus these new methods provide a general route to 1,2,4-triazines bearing various alkyl groups in the 3-, 5- and/or 6-positions.

Table 3: Synthesis of Trialkyl- and Dialkyl-1,2,4-triazines via N,N-Dimethylaminomethylenehydrazones (19)



12 19 3

Compound	R^1	R^2	R^3	Yield (%)
3a	CH_3	C_2H_5	CH_3	54
3b	C_2H_5	CH_3	CH_3	65
3c	C_2H_5	n-C_3H_7	CH_3	60
3d	CH_3	C_2H_5	H	65
3e	C_2H_5	CH_3	H	67
3f	C_2H_5	n-C_3H_7	H	63

EXPERIMENTAL

General: ^{1}H-Nmr spectra were recorded with a Varian EM 60 (60 MHz) or Brucker PC 300 (300 MHz) spectrometer with tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer 297. Melting points were taken on a Reichert melting point apparatus and are uncorrected. For column chromatography Macherey & Nagel silica gel 60 (70-230 mesh ASTM) was used.

α-Oxophosphazines (11)

General Procedure: To a solution of the α-formyl ketones (9) (50 mmol) and triethylamine (9.19 g, 91 mmol) in methylene chloride (100 ml) was added a solution of p-toluenesulfonyl azide (8.93 g, 45.3 mmol) in methylene chloride (30 ml) with stirring below 5°C. After stirring at room temperature for 2 h, the reaction mixture was washed with cold 5% KOH (110 ml) and with water (30 ml). The organic phase was dried over anhydrous Na_2SO_4 and evaporated at 30°C under reduced pressure. The residue was dissolved in ether

(30 ml) and mixed with a solution of triphenylphosphine (9.43 g, 36 mmol) in ether (50 ml). After standing over night at 0°C, the reaction mixture was filtered to give the α-oxophosphazines (11) as yellow crystalls.
The compounds prepared are listed below with their physical data.

2,3-Pentanedione 2-Triphenylphosphazine (11a): yield: 33%; mp 115-123°C; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 0.94 (3H, t, J=7 Hz), 2.15 (3H, s), 2.63 (2H, q, J=7 Hz), 7.20-8.00 (15H, m); ir (nujol) 2940, 1650, 1530, 1460, 1440, 1090, 920, 740, 720, 690 cm^{-1}; Anal. Calcd for $C_{23}H_{23}N_2OP$: C 73.78; H 6.19; N 7.48; Found: C 73.89; H 5.84; N 6.89.

2,3-Pentanedione 3-Triphenylphosphazine (11b): This compound could not be isolated. Column chromatography of the reaction mixture on silica gel eluting with n-hexane/ethyl acetate (1:1) gave 2,3-pentanedione 3-hydrazone 12b.

3,4-Heptanedione 3-Triphenylphosphazine (11c): yield: 48%; mp 113-117°C; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 0.74 (3H, t, J=7 Hz), 1.10-1.90 (2H, m), 2.50 (2H, q, J=7 Hz), 2.82 (2H, q, J=7 Hz), 7.20 (15H, m); ir (nujol) 2940, 1650, 1460, 1440, 1120, 1090, 1060, 1000, 960, 910, 730, 700 cm^{-1}; Anal. Calcd for $C_{25}H_{27}N_2OP$: C 74.61; H 6.76; N 6.96; Found: C 74.68; H 6.54; N 6.77.

α-Oxohydrazones (12):

General Procedure: The α-oxophosphazines (11) (10 mmol) were suspended in 90% ethanol (20 ml) containing acetic acid (0.1 ml). The mixture was refluxed for 2 h and evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with n-hexane/ethyl acetate (1:1) to give the α-oxohydrazones (12).
The compounds prepared are listed below with their physical data.

2,3-Pentanedione 2-Hydrazone (12a): yield: 78%; mp 52-53°C; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 1.08 (3H, t, J=7 Hz), 1.85 (3H, s), 2.81 (2H, q, J=7 Hz), 5.60-6.40 (2H, b rd); ir (nujol) 3400, 3300, 3230, 2950, 1660, 1560, 1300, 1260,

1180, 1090, 1040, 920, 800 cm^{-1}; Anal. Cacld for $C_5H_{10}N_2O$: C 52.61; H 8.83; N 24.54; Found: C 52.72; H 8.51; N 24.40.

2,3-Pentanedione 3-Hydrazone (12b): yield: 40%; oil; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 0.97 (3H, t, J=7 Hz), 2.32 (3H, s), 2.43 (2H, q, J=7 Hz), 5.70-6.40 (2H, br d); ir (neat) 3420, 3320, 3260, 2960, 1720, 1660, 1560, 1460, 1360, 1340, 1250, 1180, 1120, 920 cm^{-1}; Anal. Calcd for $C_5H_{10}N_2O$: C 52.61; H 8.83 N 24.52; Found: C 52.48; H 8.56; N 24.26.

3,4-Heptanedione 3-Hydrazone (12c): yield: 83%; mp 46-47°C; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 0.92 (3H, t, J=7 Hz), 0.98 (3H, t, J=7 Hz), 1.60 (2H, sext, J= 7 Hz), 2.43 (2H, q, J=7 Hz), 2.68 (2H, q, J=7 Hz), 5.60-6.40 (2H, br d); ir (nujol) 3400, 3320, 3200, 2960, 1660, 1630, 1220, 1200, 1120, 1060, 890 cm^{-1}; Anal. Calcd for $C_7H_{14}N_2O$: C 59.13; H 9.92; N 19.70; Found: C 59.26; H 10.04; N 19.70.

α-Oxoacetylhydrazones (4):

General Procedure: To a solution of the α-oxohydrazones (12) (10 mmol) in tetrahydrofuran (10 ml) was added acetic anhydride (3.10 g, 30 mmol) at room temperature. The resulting solution was stirred 2 days at room temperature and then evaporated. The residue was chromatographed on silica gel eluting with n-hexane/ethyl acetate (1:1) to give the α-oxoacetylhydrazones (4). The compounds prepared are listed below with their physical data.

2,3-Pentanedione 2-Acetylhydrazone (4a): yield: 59%; mp 126-132°C; ^{1}H-nmr ($CDCl_3$, 60 MHz), δ 1.13 (3H, t, J=7 Hz), 2.05 (3H, s), 2.38 (3H, s), 2.89 (2H, q, J=7 Hz), 9.30-9.70 (1H, br d); ir (nujol) 3180, 3120, 2960, 1680, 1600, 1320, 1240, 1160, 1090, 1040, 1020, 930 cm^{-1}; Anal. Calcd for $C_7H_{12}N_2O_2$: C 53.83; H 7.74; N 17.94; Found: C 54.16; H 8.04; N 18.02.

2,3-Pentanedione 3-Acetylhydrazone (4b): yield: 68%; mp 85-87°C; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 1.01 (3H, t, J=7 Hz), 2.41 (3H, s), 2.44 (3H, s), 2.55 (2H, q, J=7 Hz), 9.30-9.80 (1H, br d); ir (nujol) 3180, 3100, 2960, 1680,

1600, 1310, 1240, 1160, 1130, 1010 cm^{-1}; Anal. Calcd for $C_7H_{12}N_2O_2$: C 53.83 H 7.74; N 17.94; Found: C 53.72; H 7.42; N 18.02.

3,4-Heptanedione 3-Acetylhydrazone (4c): yield: 82%; mp 63-64°C; ^{1}H-nmr ($CDCl_3$; 60 MHz), δ 0.93 (3H, t, J=7 Hz), 1.01 (3H, t, J=7 Hz), 1.67 (2H, sext, J=7 Hz), 2.40 (3H, s), 2.54 (2H, q, J=7 Hz), 2.82 (2H, t, J=7 Hz), 9.20-9.80 (1H, br d); ir (nujol) 3180, 3140, 2960, 1680, 1600, 1420, 1330, 1240, 1160, 1090, 1020, 930 cm^{-1}; Anal. Calcd for $C_9H_{16}N_2O_2$: C 58.67; H 8.75; N 15.20; Found: C 58.30; H 8.88; N 14.71.

Solvent Effect on the Cyclization of 2,3-Pentandione 2-Acetylhydrazone (4a)

Acetic Acid: To 2,3-pentanedione 2-acetylhydrazone (4a) (0.30 g, 1.9 mmol) in acetic acid (10 ml) was added ammonium acetate (0.44 g, 5.7 mmol). The mixture was stirred at 100°C for 4 h. The resulting solution was neutralized with 2 N sodium bicarbonate solution and extracted with ethyl acetate (2x50 ml). The extracts were washed with water (30 ml) and evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with n-hexane/ethyl acetate (1:1) to give a mixture of 3a and 3b.
The ratio of 3a and 3b was determined by integration of the signals for the methyl groups at the 6-position of 3a (2.68, s) and the 5-position of 3b (2.54, s) in their nmr spectra.

N,N-Dimethylformamide: To a solution of 4a (0.30 g, 1.9 mmol) in N,N-dimethylformamide (10 ml) was added ammonium acetate (0.44 g, 5.7 mmol). The mixture was stirred at 100°C for 4 h. The resulting solution was mixed with water (60 ml) and extracted with ethyl acetate (2x50 ml). The extracts were washed with water (30 ml) and evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with n-hexane/ethyl acetate (1:1) to give a mixture of 3a and 3b.
The ratio of 3a and 3b was determined as described for acetic acid.

Dimethyl Sulfoxide: To a solution of 4a (0.30 g, 1.9 mmol) in dimethyl sulfoxide (10 ml) was added ammonium acetate (0.44 g, 5.7 mmol). The mixture

was stirred at 100°C for 4 h. The solution was mixed with water (60 ml) and extracted with ethyl acetate (2x50 ml). The extracts were washed with water (30 ml) and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate to give 3a.

Trialkyl-1,2,4-triazines (3, R^3 = CH_3):

General Procedure A: To a solution of the α-oxoacetylhydrazones 4 (2.0 mmol) in dimethyl sulfoxide (10 ml) was added ammonium acetate (0.46 g, 6.0 mmol). After stirring for 4 h at 100°C the resulting solution was pured into water (60 ml) and extracted with ethyl acetate (2x50 ml). The extracts were washed with water (30 ml) and evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate to give the trialkyl-1,2,4-triazines (3) (R^3 = CH_3).

General Procedure B: A solution of the α-oxohydrazones (12) (3.0 mmol) and N,N-dimethylacetamide dimethyl acetal (0.44 g, 3.3 mmol) in tetrahydrofuran (10 ml) was refluxed for 3 h. The resulting solution was evaporated and heated with ammonium acetate (0.69 g, 9.0 mmol) in acetic acid (10 ml) for 3 h at 100°C. The reaction mixture was neutralized with 2 N sodium bicarbonate solution and extracted with ethyl acetate (2x50 ml). The extracts were washed with water (30 ml) and evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate to give the trialkyl-1,2,4-triazines (3) (R^3 = CH_3).

The compounds prepared are listed below with their physical data.

5-Ethyl-3,6-dimethyl-1,2,4-triazine (3a): mp 42-43°C; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 1.30 (3H, t, J=7 Hz), 2.68 (3H, s), 2.78 (2H, q, J=7 Hz), 2.80 (3H, s); ir (neat) 2980, 2940, 1730, 1410, 1380, 1360, 1350, 1160, 1090, 1040, 1010, 970, 930 cm^{-1}; Anal. Calcd for $C_7H_{11}N_3$: C 61.29; H 8.08; N 30.63; Found: C 60.91; H 7.80; N 31.03.

6-Ethyl-3,5-dimethyl-1,2,4-triazine (3b): oil; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 1.37 (3H, t, J=7 Hz), 2.54 (3H, s), 2.79 (3H, s), 2.98 (2H, q, J=7 Hz); ir

(neat) 2970, 2930, 1740, 1720, 1520, 1420, 1400, 1380, 1320, 1180, 1150, 1080, 1060, 1040, 1020, 1010, 970 cm^{-1}; Anal. Calcd for $C_7H_{11}N_3$: C 61.29 H 8.08; N 30.63; Found: C 61.09; H 8.03; N 30.40.

6-Ethyl-3-methyl-5-n-propyl-1,2,4-triazine (3c): oil; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ 1.04 (3H, t, J=7.4 Hz), 1.38 (3H, t, J=7.4 Hz), 1.79 (2H, sext, J=7.4 Hz), 2.74 (2H, t, J=7.4 Hz), 2.79 (3H, s), 2.99 (2H, q, J=7.4 Hz); ir (neat) 2980, 2930, 2870, 1770, 1740, 1520, 1450, 1400, 1370, 1320, 1240, 1160, 1040 cm^{-1}; Anal. Calcd for $C_9H_{15}N_3$: C 65.42; H 9.15; N 25.43; Found: C 65.40; H 9.20; N 25.08.

5,6-Dialkyl-1,2,4-triazines (3, R^3 = H):

General Procedure: A solution of the α-oxohydrazones (12) (3.0 mmol) and N,N-dimethylformamide dimethyl acetal (0.39 g, 3.3 mmol) in tetrahydrofuran (10 ml) was refluxed for 3 h. The resulting solution was evaporated and heated with ammonium acetate (0.69 g, 9.0 mmol) in acetic acid for 3 h at 100°C. The reaction mixture was neutralized with 2 N sodium bicarbonate solution and extracted with ethyl acetate (2x50 ml). The extracts were washed with water (30 ml) and evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate to give 5,6-dialkyl-1,2,4-triazines (3) (R^3 = H).

The compounds prepared are listed below with their physical data.

5-Ethyl-6-methyl-1,2,4-triazine (3d): oil; ^{1}H-nmr ($CDCl_3$, 60 MHz), δ 1.33 (3H, t, J=7 Hz), 2.77 (3H, s), 2.84 (2H, q, J=7 Hz), 9.40 (1H, s); ir (neat) 2990, 2950, 1720, 1710, 1530, 1510, 1380, 1320, 1200, 1160, 1020, 880, 810 cm^{-1}; Anal. Calcd for $C_6H_9N_3$: C 58.52; H 7.66; N 34.12; Found: C 58.39, H 7.29; N 33.70.

6-Ethyl-5-methyl-1,2,4-triazine (3e): oil; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 1.38 (3H, t, J=7 Hz), 2.55 (3H, s), 3.00 (2H, q, J=7 Hz), 9.40 (1H, s); ir (neat) 2980, 2930, 1760, 1730, 1620, 1520, 1460, 1420, 1370, 1340, 1320, 1260, 1160, 1030, 960, 930 cm^{-1}; Anal. Calcd for $C_6H_9N_3$: C 58.52; H 7.66; N 34.12

Found: C 58.18; H 7.30; N 33.81.

6-Ethyl-5-n-propyl-1,2,4-triazine (3f): oil; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ 1.04 (3H, t, J=7.4 Hz), 1.38 (3H, t, J=7.4 Hz), 1.83 (2H, sext, J=7.4 Hz), 2.80 (2H, t, J=7.4 Hz), 3.03 (2H, q, J=7.4 Hz), 9.41 (1H, s); ir (neat) 2960, 2940, 2870, 1770, 1730, 1520, 1460, 1410, 1300, 1240, 1170, 1020, 960 cm^{-1}; Anal. Calcd for $C_8H_{13}N_3$: C 63.55; H 8.67; N 27.78; Found: C 62.81; H 8.54; N 27.37.

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