A Convenient Synthesis of 1-Aryl-3-methyl-1,2,4-triazolin-5-ones From the Reaction Between Acetone Arylhydrazones and Acetyl Isocyanate

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The reaction of acetone arylhydrazones with acetyl isocyanate gave the corresponding 4-acetyl-1-aryl-3,3-dimethyl-1,2,4-triazolidin-5-ones which eliminated acetone upon acidic hydrolysis to give 1-aryl-3-methyl-1,2,-4-triazolin-5-ones. The above transformation can be achieved in one pot by a simple solvent swap.

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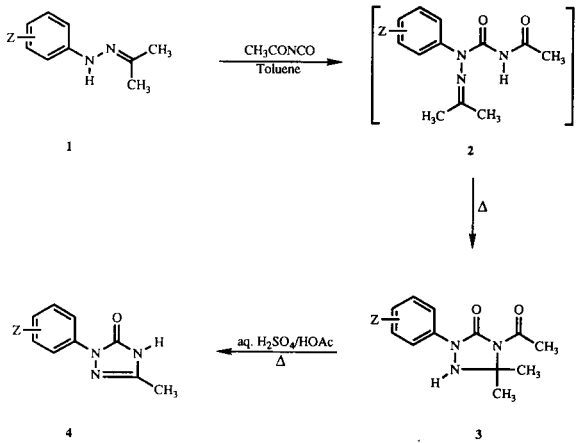
There are a variety of methods available for the synthesis of 1,3-disubstituted-1,2,4-triazolin-5-ones [1-2]. Among these, is the reaction of benzoyl isocyanate with acetone arylhydrazones to give 4-benzoly-1-aryl-3,3-dimethyl-1,2,4-triazolidin-5-ones. Acidic hydrolysis of these intermediates gives the corresponding 1,3-diaryl-1,2,4-triazolin-5-ones [3-4]. A similar reaction sequence using alkanoyl isocyanates should, in principle, provide 1-aryl-3-alkyl-1,2,4-triazolin-5-ones. A vast number of 1-aryl-4-haloalkyl-3-methyl-1,2,4-triazolin-5-ones have been described in the patent literature as having potentially useful herbicidal properties [5]. The 4-haloalkyl substituent in the above compounds are typically introduced *via* alkylation of the appropriate 1-aryl-3-methyl-1,2,4-triazolin-5-ones **4** in the presence of a base [5b-e]. As part of our program to develop synthetic routes to these triazolinones we became interested in new and general methods for the preparation of the heterocycle **4** allowing for variation of the aryl substituents.

We envisioned that the reaction between an acetone arylhydrazone **1** and acetyl isocyanate would, provide the intermediate **2** which should cyclize to give the appropriate 1-aryl-3,3-dimethyl-1,2,4-triazolidin-5-one **3**. The acid catalyzed hydrolysis of these intermediates, with the elimination of acetone, should give the desired heterocycle, 1-aryl-3-methyl-1,2,4-triazolin-5-ones **4** (Scheme 1). We wish to report our results on this synthetic methodology. Thus, for example, when acetyl isocyanate was allowed to react with acetone 4-chloro-3-nitrophenylhydrazone (**1i**) in toluene at room temperature for three hours, a 3:1 mixture of the adduct **2i** and the heterocycle **3i** was isolated. Heating this mixture in toluene at reflux led to the complete conversion of **2i** to **3i**. The acetylated intermediate was isolated in 85% yield. The acid catalyzed hydrolysis of **3i**, with the elimination of acetone, to give the desire triazolinone **4i** was achieved in 95% yield from the treatment of **3i** with a mixture of aqueous acetic and sulfuric acids at 90-100° for ten minutes. To explore the generality of this procedure, a variety of acetone (substituted-phenyl)hydrazone derivatives were allowed to react with acetyl isocyanate in an analogous fashion to give the corresponding 1-(substituted-phenyl)-3,3-dimethyl-1,2,4-triazolidin-5-ones (**3**). These were further converted to the triazolinones **4** on acidic hydrolysis. These results are summarized in the Table.

Scheme 1



1 2 3 4

Table

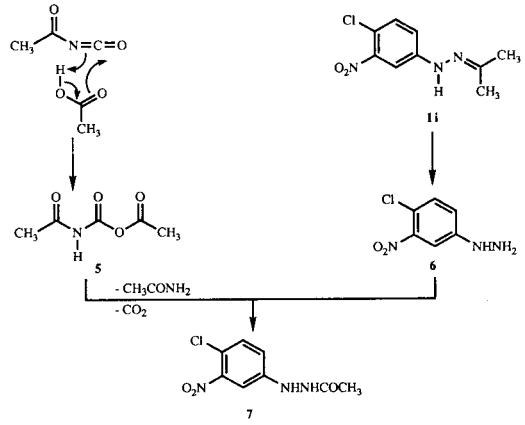
Percentage Yields and Melting Points of Isolated Products

		3		**4**	
	Z	% Yield[*]	mp (°C)	% Yield	mp (°C) (lit mp)
a	H	85	107-108	96	164-165
b	4-Cl	72*	125-126	95	(165-166)[2] 136-137
c	4-F	41*	85-86	94	123-124
d	4-OCH_3	57	93-94	97	166-167
e	2-Cl	54	120-121	91	(165-166)[2] 172-173
f	2,4-diCl	50	129-131	96	190-192
g	2-F,4-Cl	39*	88-90	94	196-198
h	3,4-diCl	92	140-141	95	249-250
i	3-NO_2,4-Cl	85	141-142	95	207-208

[*] Isolated yield after column chromatography.

We also examined the possibility of combining the above two steps into a one pot procedure. Acetic acid was the obvious choice as solvent. Thus, when acetyl isocyanate was added to a mixture of the hydrazone **1i** in acetic acid, an exotherm was observed (a similar exotherm was also noted on mixing acetyl isocyanate in neat acetic acid). Work up of this reaction, after stirring at room temperature for a few hours gave, the acetylated phenylhydrazine **7** as the only isolated product. Thus, it appears that acetyl isocyanate reacts with acetic acid to form the intermediate **5** which then serves as an acetylating agent and reacts with 4-chloro-3-nitrophenylhydrazine **6** (which results from the hydrolysis of the corresponding acetone hydrazone **1i**) to give 1-acetyl-2-phenylhydrazine **7** (Scheme 2). A one pot conversion of **1i** to the triazolinone **4i** was, however, easily

Scheme 2



acheived by a simple solvent swap. Thus, after heating **1i** and acetyl isocyanate together in toluene for two hours, the solvent was removed by distillation under reduced pressure and replaced with a mixture of acetic and aqueous sulfuric acids and the mixture heated at reflux to give the desired heterocycle **4i** in 85% yield without isolation of the intermediate **3i**.

EXPERIMENTAL

Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are uncorrected. The ^{1}H nmr data were obtained with a General Electric QE300 (300 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Column chromatography was performed on Merck silica gel 60 (240-400) mesh; silica gel plates were routinely used for tlc determinations. Elemental analyses were preformed at FMC Corporation, Analytical Services Department. Acetyl isocyanate was prepared by a literature method from the reaction of acetyl chloride with silver cyanate in dimethyl ether [6]. The acetone arylhydrazones **1a-1h** were prepared from the corresponding commercially available arylhydrazines or their hydrochloride salts with acetone in water. The hydrazones were used immediately without further purification.

General Procedure for the Preparation of 4-Acetyl-1-aryl-3,3-dimethyl-1,2,4-triazolidin-5-ones **3a-3i**.

Under a dry nitrogen atmosphere, a solution of acetyl isocyanate (0.011 mole) in toluene (10 ml) was added dropwise to a stirred solution or suspension of the acetone arylhydrazone (**1**, 0.01 mole) in toluene (20 ml). The mixture was stirred at room temperature for 15 minutes and then heated at gentle reflux for 3 hours. The solvent was removed under reduced pressure and the residue worked up further as described below.

4-Acetyl-1-phenyl-3,3-dimethyl-1,2,4-triazolidin-5-one (**3a**).

The residue was triturated with diethyl ether and the resulting solid was collected by filtration at the pump and dried *in vacuo* to give a colorless solid (85% yield), mp 107-108°; ^{1}H nmr (DMSO-d_6): δ 1.52 (s, 6H), 2.40 (s, 3H), 6.14 (s, 1H), 7.12 (m, 1H), 7.39 (m, 1H), 7.7 (d, J = 8 Hz, 1H); ir (potassium bromide): 3380 (w), 3220, 1725, 1695 cm^{-1}.

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.80; H, 6.43; N, 18.02. Found: C, 61.77; H, 6.31; N, 17.99.

4-Acetyl-1-(4-chlorophenyl)-3,3-dimethyl-1,2,4-triazolidin-5-one (**3b**).

The residue was chromatographed on silica gel eluting with 1% methanol in methylene chloride. The fractions containing the pure product were combined and the solvent was removed *in vacuo* to give a colorless solid (72% yield), mp 125-126°; ^{1}H nmr (DMSO-d_6): δ 1.53 (s, 6H), 2.40 (s, 3H), 6.44 (s, 1H), 7.45 (d, J = 8 Hz, 2H), 7.72 (d, J = 8 Hz, 2H); ir (potassium bromide): 3380 (w), 3220, 1730, 1695 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}ClN_3O_2$: C, 53.83; H, 5.23; N, 15.70; Cl, 13.27. Found: C, 54.10; H, 5.09; N, 15.57; Cl, 13.09.

4-Acetyl-1-(4-fluorophenyl)-3,3-dimethyl-1,2,4-triazolidin-5-one (**3c**).

The residue was chromatographed on silica gel eluting with 1% methanol in methylene chloride. The fractions containing the pure product were combined and the solvent removed *in vacuo*. The oily residue was triturated with hexanes and the resulting solid was collected by filtration at the pump to give a colorless microcrystalline powder (41% yield), mp 85-86°; ^{1}H nmr (DMSO-d_6): δ 1.52 (s, 6H), 2.40 (s, 3H), 6.43 (s, 1H), 7.23 (m, 2H), 7.70 (m, 2H); ir (potassium bromide): 3380 (w), 3220, 1710 (br) cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}FN_3O_2$: C, 57.37; H, 5.57; N, 16.73. Found: C, 57.47; H, 5.50; N, 16.52.

4-Acetyl-1-(4-methoxyphenyl)-3,3-dimethyl-1,2,4-triazolidin-5-one (**3d**).

The residue was triturated with diethyl ether and resulting solid was collected by filtration at the pump and dried *in vacuo* to give a cream colored microcrystalline powder (57% yield), mp 93-94°; ^{1}H nmr (DMSO-d_6); δ 1.52 (s, 6H), 2.40 (s, 3H), 3.37 (s, 3H), 6.38 (s, 1H), 6.97 (d, J = 8 Hz, 2H), 7.60 (d, J = 8 Hz, 2H); ir (potassium bromide): 3460 (w), 3380, 3220, 1735, 1685 cm^{-1}.

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.31; H, 6.46; N, 15.97. Found: C, 59.37; H, 6.39; N, 15.88.

4-Acetyl-1-(2-chlorophenyl)-3,3-dimethyl-1,2,4-triazolidin-5-one (**3e**).

The residue was triturated with a small amount of diethyl ether and the resulting solid was collected by filtration at the pump and dried *in vacuo* to give a colorless solid (54% yield), mp

120-121°; ^{1}H nmr (DMSO-d_6): δ 1.6 (s, 6H), 2.39 (s, 3H), 6.46 (s, 1H), 7.42 (m, 2H), 7.6 (m, 2H); ir (potassium bromide): 3440 (w), 3350, 3210, 1710 (br) cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}ClN_3O_2$: C, 53.83; H, 5.23; N, 15.70; Cl, 13.27. Found: C, 53.97; H, 5.14; N, 15.47; Cl, 12.97.

4-Acetyl-1-(2,4-dichlorophenyl)-3,3-dimethyl-1,2,4-triazolidin-5-one (**3f**).

The residue was triturated with diethyl ether and the resulting solid was collected by filtration at the pump and dried *in vacuo* to give a colorless microcrystalline powder (50% yield), mp 129-131°; ^{1}H nmr (DMSO-d_6): δ 1.60 (s, 6H), 2.38 (s, 3H), 6.45 (s, 1H), 7.54-7.80 (m, 3H); ir (potassium bromide): 3460 (w), 3370, 3220, 1735, 1700 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}Cl_2N_3O_2$: C, 47.68; H, 4.30; N, 13.90; Cl, 23.50. Found: C, 47.54; H, 4.13; N, 13.67; Cl, 23.27.

4-Acetyl-1-(4-chloro-2-fluorophenyl)-3,3-dimethyl-1,2,4-triazolidin-5-one (**3g**).

The residue was chromatographed on silica gel eluting with 1% methanol in methylene chloride. The fractions containing the pure product were combined and the solvent was removed *in vacuo* to give a colorless solid (39% yield), mp 88-90°; ^{1}H nmr (DMSO-d_6): δ 1.58 (s, 6H), 2.39 (s, 3H), 6.60 (s, 1H), 7.4 (m, 1H), 7.55 (m, 2H); ir (potassium bromide): 3380 (w), 3340 (w), 3200, 1735, 1680 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}ClFN_3O_2$: C, 50.04; H, 4.55; N, 14.71; Cl, 12.43; F, 6.66. Found: C, 50.08; H, 4.37; N, 14.65; Cl, 12.39; F, 6.98.

4-Acetyl-1-(3,4-dichlorophenyl)-3,3-dimethyl-1,2,4-triazolidin-5-one (**3h**).

The residue was triturated with diethyl ether and the resulting solid was collected by filtration at the pump and dried *in vacuo* to give a colorless microcrystalline powder (92% yield), mp 140-141°; ^{1}H nmr (DMSO-d_6): δ 1.53 (s, 6H), 2.40 (s, 3H), 6.46 (s, 1H), 7.65 (m, 2H), 7.90 (s, 1H); ir (potassium bromide); 3460 (w), 3380, 3230, 1735, 1680 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}Cl_2N_3O_2$: C, 47.68; H, 4.30; N, 13.90; Cl, 23.50. Found: C, 47.96; H, 4.20; N, 13.68; Cl, 23.24.

4-Acetyl-1-(4-chloro-3-nitrophenyl)-3,3-dimethyl-1,2,4-triazolidin-5-one (**3i**).

The residue was recrystallized from absolute ethanol to give colorless needles (85% yield). A second recrystallization from ethanol gave an analytical sample: mp 140-141°; ^{1}H nmr (DMSO-d_6): δ 1.54 (s, 6H), 2.40 (s, 3H), 6.58 (s, 1H), 7.8 (d, J = 8 Hz, 1H), 7.98 (m, 1H), 8.3 (d, J = 2 Hz, 1H); ir (potassium bromide): 3370 (w), 3220, 1730, 1700 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}ClN_4O_4$: C, 46.08; H, 4.16; N, 17.92; Cl, 11.36. Found: C, 46.28; H, 3.96; N, 17.68; Cl, 11.34.

General Procedure for the Preparation of 1-Aryl-3-methyl-1,2,4-triazolin-3-ones **4a-4i**.

A mixture of the 4-acetyl-1-aryl-3,3-dimethyl-1,2,4-triazolidin-3-one (**3**, 2.0 mmoles), acetic acid (10 ml), concentrated sulfuric acid (0.2 ml) and water (1 ml) was heated between 90-100° for 10 minutes. The solvent was removed under reduced pressure and the residue was triturated with water and the resulting solid was collected by filtration at the pump, washed well with water and dried *in vacuo* at 80°.

3-Methyl-1-phenyl-1,2,4-triazolin-5-one (**4a**).

A colorless solid was obtained (96% yield), mp 164-165° (lit mp 165-166° [2]); ^{1}H nmr (DMSO-d_6): δ 2.19 (s, 3H), 7.18 (m, 1H), 7.42 (m, 2H), 7.90 (m, 2H), 11.8 (br, 1H); ir (potassium bromide): 1700 cm^{-1}.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.71; H, 5.14; N, 24.00. Found: C, 61.65; H, 5.04; N, 23.77.

1-(4-Chlorophenyl)-3-methyl-1,2,4-triazolin-5-one (**4b**).

A colorless solid was obtained (95% yield), mp 136-137°; ^{1}H nmr (DMSO-d_6): δ 2.18 (s, 3H), 7.64 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H), 11.9 (br, 1H); ir (potassium bromide): 1700 cm^{-1}.

Anal. Calcd. for $C_9H_8ClN_3O$: C, 51.55; H, 3.82; N, 20.05; Cl, 16.95. Found: C, 51.60; H, 3.63; N, 19.90; Cl, 16.82.

1-(4-Fluorophenyl)-3-methyl-1,2,4-triazolin-5-one (**4c**).

A colorless solid was obtained (94% yield). Recrystallization from ethanol gave an analytical sample, mp 123-124°; ^{1}H nmr (DMSO-d_6): δ 2.19 (s, 3H), 7.25 (m, 2H), 7.86 (m, 2H), 11.85 (br, 1H); ir (potassium bromide): 1700 cm^{-1}.

Anal. Calcd. for $C_9H_8FN_3O$: C, 55.96; H, 4.15; N, 21.76; F, 9.84. Found: C, 55.72; H, 3.86; N, 21.53; F, 9.75.

1-(4-Methoxyphenyl)-3-methyl-1,2,4-triazolin-5-one (**4d**).

A colorless solid was obtained (97% yield). Recrystallization from ethnol gave an analytical sample, mp 166-167° (lit mp 165-166° [2]); ^{1}H nmr (DMSO-d_6): δ 2.18 (s, 3H), 3.76 (s, 3H), 6.98 (d, J = 8 Hz, 2H), 7.76 (d, J = 8 Hz, 2H), 11.74 (br, 1H); ir (potassium bromide): 1700 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.36; N, 20.49. Found: C, 58.26; H, 5.33; N, 20.33.

1-(2-Chlorophenyl)-3-methyl-1,2,4-triazolin-5-one (**4e**).

A colorless solid was obtained (91% yield), mp 172-173°; ^{1}H nmr DMSO-d_6): δ 2.18 (s, 3H), 7.42-7.52 (m, 3H), 7.58-7.64 (m, 1H), 11.7 (br, 1H); ir (potassium bromide): 1700 cm^{-1}.

Anal. Calcd. for $C_9H_8ClN_3O$: C, 51.55; H, 3.82; N, 20.05; Cl, 16.95. Found: C, 51.60; H, 3.58; N, 19.98; Cl, 17.05.

1-(2,4-Dichlorophenyl)-3-methyl-1,2,4-triazolin-5-one (**4f**).

A colorless solid was obtained (96% yield), mp 190-192°; ^{1}H nmr (DMSO-d_6): δ 2.17 (s, 3H), 7.54 (s, 2H), 7.81 (s, 1H), 11.72 (br, 1H); ir (potassium bromide): 1700 cm^{-1}.

Anal. Calcd. for $C_9H_7Cl_2N_3O$: C, 44.26; H, 2.87; N, 17.21; Cl, 29.10. Found: C, 44.48; H, 2.77; N, 17.00; Cl, 29.10.

1-(4-Chloro-2-fluorophenyl)-3-methyl-1,2,4-triazolin-5-one (**4g**).

A colorless solid was obtained (94% yield), mp 196-198°; ^{1}H nmr (DMSO-d_6): δ 2.18 (s, 3H), 7.38 (m, 1H), 7.5-7.68 (m, 2H), 11.8 (br, 1H); ir (potassium bromide): 1700 cm^{-1}.

Anal. Calcd. for $C_9H_7ClFN_3O$: C, 47.47; H, 3.08; N, 18.46; Cl, 15.69; F, 8.35. Found: C, 47.47; H, 2.92; N, 18.68; Cl, 15.65; F, 8.23.

1-(3,4-Dichlorophenyl)-3-methyl-1,2,4-triazolin-5-one (**4h**).

A colorless solid was obtained (95% yield), mp 249-250°; ^{1}H nmr (DMSO-d_6): δ 2.19 (s, 3H), 7.64 (d, J = 8 Hz, 1H), 7.83 (m, 1H), 8.10 (s, 1H), 12.0 (br, 1H); ir (potassium bromide): 1700 cm^{-1}.

Anal. Calcd. for $C_9H_7Cl_2N_3O$: C, 44.26; H, 2.87; N, 17.21; Cl, 29.10. Found: C, 44.02; H, 2.57; N, 17.14; Cl, 29.15.

1-(4-Chloro-3-nitrophenyl)-3-methyl-1,2,4-triazolin-5-one (**4i**).

A colorless solid was obtained (95% yield), mp 207-208°; ^{1}H nmr (DMSO-d_6): δ 2.20 (s, 3H), 7.82 (d, J = 8 Hz, 1H), 8.17 (m, 1H), 8.52 (s, 1H), 11.90 (br, 1H); ir (potassium bromide): 1700 cm^{-1}.

Anal. Calcd. for $C_9H_6ClFN_4O_3$: C, 42.44; H, 2.75; N, 22.00; Cl, 13.95. Found: C, 42.81; H, 2.37; N, 21.79; Cl, 14.32.

Acetone 4-Chloro-3-nitrophenylhydrazone (**1i**).

A 2 l three necked round-bottomed flask equipped with a mechanical stirrer, a thermometer and an addition funnel was charged with 4-chloro-3-nitroaniline (27 g, 0.1564 mole), galical acetic acid (100 ml) and concentrated hydrochloric acid (36.5-38%, 500 ml). The mixture was heated to 50° for 30 minutes and then cooled to −10°. A solution of sodium nitrite (11.0 g, 0.1594 mole) in water (50 ml) was added to the stirred mixture over a period of 20 minutes keeping the temperature between −5 to −10°. The solution was held at −5° for an additional 30 minutes. A solution of stannous chloride dihydrate (81 g, 0.359 mole) in concentrated hydrochloric acid (70 ml) was added over a 30 minute period, keeping the temperature below 27°. The reaction mixture was stirred for 2 hours. A mixture of acetone (40 ml, 0.5447 mole) and water (100 ml) was added to the stirred reaction mixture over a 15 minute period. The mixture was stirred for a further 2 hours. The solid was collected by filtration at the pump and washed thoroughly with water and dried *in vacuo* at 40° to give a bright orange solid (30.2 g, 85%), mp 120-122°; ^{1}H nmr (DMSO-d_6): δ 1.89 (s, 3H), 1.97 (s, 3H), 7.25 (m, 1H), 7.47 (d, J = 8 Hz, 1H), 7.59 (s, 1H), 9.32 (s, 1H); ir (potassium bromide): 3350, 1610 cm^{-1}. This material was used without further purification.

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