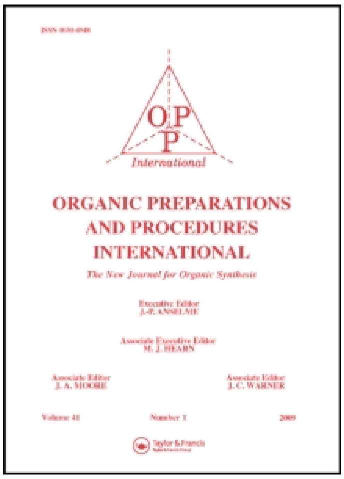

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SYNTHESIS OF 2-ARYL-4,5,6,7-TETRAHYDRO-6,6-DIMETHYL-2 H-BENZO[D][1,2,3]TRIAZOL-4-ONES

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SYNTHESIS OF
2-ARYL-4,5,6,7-TETRAHYDRO-6,6-DIMETHYL-2 H-BENZO[d][1,2,3]TRIAZOL-4-ONES

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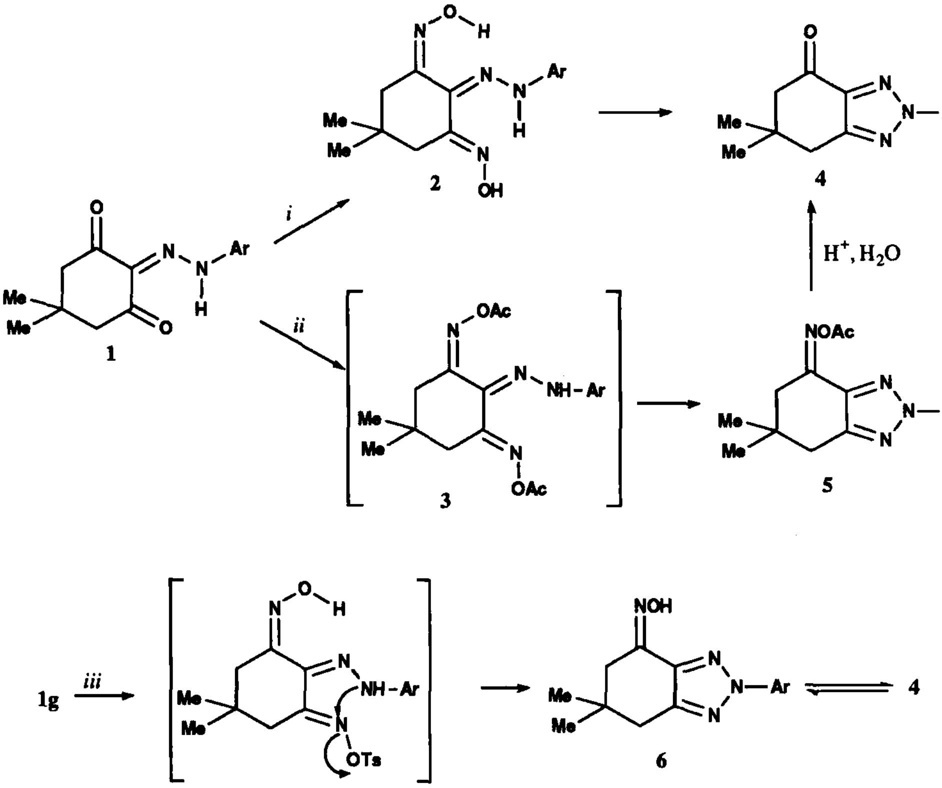
The Boulton-Katritzky rearrangement[1] of (Z)4,5,6,7-tetrahydro-6,6-dimethyl-2H-benzo[c][1,2,5]oxadiazol-4-one arylhydrazones[2] to the corresponding 2-aryl-4,5,6,7-tetrahydro-6,6-dimethyl-2H-benzo[d][1,2,3]triazol-4-one oximes **6** has been achieved under basic conditions or by photochemical transformation.[3] Analogous rearrangement in the reverse direction was unsuccessful, apparently due to the thermodynamic stability of the triazole ring[3,4] rather than to an unfavored geometry of the condensed ring system. This prompted us to investigate the synthesis of 2-aryl-4,5,6,7-tetrahydro-6,6-dimethyl-2H-benzo[d][1,2,3]triazol-4-ones and the potential of the 2-arylhydrazones **1** as precursors for heterocyclic synthesis.

Sequential reaction of 5,5-dimethylcyclohexan-1,2,3-trione 2-phenylhydrazone (**1a**) with hydroxylamine and then acetic anhydride gave **4a** and neither **6a** nor **5a**. The reaction could be extended to various derivatives of **4**. A possible explanation is that the initially formed dioxime **2** was converted to the acetyl derivative **3** which intramolecular nucleophilic attack of the hydrazono-nitrogen could give the triazole **5**. Subsequent conversion to the ketone **4** may be due to the presence of acetic acid, formed as a result of the dehydration process. In order to confirm such an assumption, the reaction was repeated in the presence of pyridine as the acid scavenger. Thus, the reaction of **1g** with hydroxylamine hydrochloride in pyridine followed by acetic anhydride afforded **5g**. Alternatively, the dehydrative cyclization of the mixed hydrazone oxime from **1g** could be effected by *p*-toluenesulfonyl chloride to give **6**. These data confirmed that the dehydration takes place between the hydrazone and oxime residues when the latter group is transformed to an oxime derivative having a suitable leaving character.

Triazoles may be synthesized by the action of lead tetraacetate[5] or cupric chloride[6-8] on bishydrazones. The action of the latter on trisarylhydrazones **7** was studied in order to examine the influence of an extra adjacent hydrazono group on the bishydrazone system. The unsymmetrically substituted trisarylhydrazones **7**[9-11] were prepared by the reaction of phenylhydrazine with the substituted hydrazones **1**. Attempted reaction of **1** with a molar equivalent of phenylhydrazine in order to obtain a mixed bishydrazone failed; compound **7** was the predominant product. An exception was the

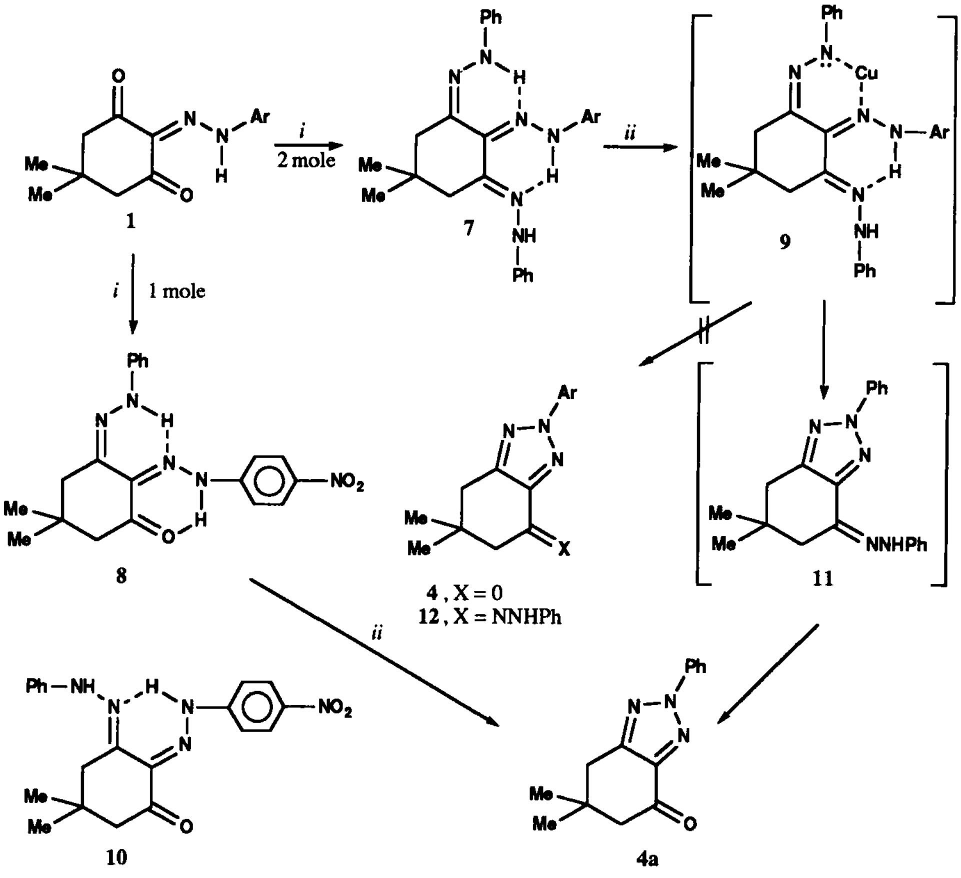


i) $NH_2OH{\bullet}HCl$, AcONa *ii*) $NH_2OH{\bullet}HCl$, Pyridine, then Ac_2O *iii*) $NH_2OH{\bullet}HCl$, Pyridine, then TosCl
a) Ar = C_6H_5 b) Ar = p-BrC_6H_4 c) Ar = o-ClC_6H_4 d) Ar = p-ClC_6H_4 e) Ar = o-MeC_6H_4
f) Ar = m-MeC_6H_4 g) Ar = p-MeC_6H_4 h) Ar = p-$NO_2C_6H_4$

Scheme 1

p-nitrophenyl derivative **1h** which gave the mixed bishydrazone **8**. This may be attributed to the high insolubility of **8** which led to its separation as soon as it was formed. The *p*-nitro derivative **7h** was obtained by the reaction of **8** with phenylhydrazine. When the bishydrazone **8** and trishydrazones **7** were treated with an ethanolic solution of cupric chloride, the same product **4a** (not **12**) was obtained in each case. Apparently the aniline residue lost was that carrying the substituent whether or not the latter was electron-donating or electron-withdrawing. The reaction may occur by initial complexation to copper to form **9** followed by expulsion of the aromatic amine moiety and subsequent cleavage of the hydrazone residue by HCl resulting from the complexation to give **4a** (Scheme 2). A similar cleavage took place when furan 2,3,4-trione-3,4-bis-(phenylhydrazone) was treated with cupric chloride to give the corresponding 3-phenylhydrazone.[6]

The IR spectra of compounds **2** showed bands at 1611-1594 (C=N), 3140-3100 (NH), and 3439-3378 cm^{-1} (NOH). Conversion of **2** to **4** led to the appearance of a band in the range 1700-1690 cm^{-1} (CO) indicating the cleavage of the hydroxyimino group, whereas the spectrum of **5** showed a



i) $PhNHNH_2$, AcOH ii) $CuCl_2$

a) Ar = C_6H_5 b) Ar = p-BrC_6H_4 c) Ar = o-ClC_6H_4 d) Ar = p-ClC_6H_4 e) Ar = o-MeC_6H_4
f) Ar = m-MeC_6H_4 g) Ar = p-MeC_6H_4 h) Ar = p-$NO_2C_6H_4$

Scheme 2

TABLE 1. ^1H NMR Spectral Data Chemical Shifts (δ)

Cpd	Solvent	Me	CH_2	Ar-H	NH and OH
2d	DMSO-d_6	0.90(s)	2.50(s), 2.46(s)	7.24(m)	12.90{s), 11.76(s), 11.00(bs)
4h	$CDCl_3$	1.20(s)	2.93(s), 2.60(s)	8.36(s)	
7b	$CDCl_3$	1.07(s)	2.45(s), 2.17(s)	7.10(m)	13.57(s), 12.57(s)
7b	DMSO-d_6	1.07(s)	2.53(s)	7.35(m)	13.83(s), 12.60(s), 9.83(s)
7h	DMSO-d_6	1.07(s)	2.48(d)	8.82(d) 7.25(m)	14.07(s), 12.57(s), 9.82(s)

band at 1622 cm^{-1} (C=N) in addition to a band at 1778 cm^{-1} (NOAc), indicating the presence of the oxime group. The presence of a carbonyl absorption (1724 cm^{-1}) in **8** and the absence of such absorption in **7** supported the assigned structures. The ^1H NMR spectra of **2**, **4** and **7** showed the two methyl groups as a singlet in the range δ1.12-0.90 and two resonances for the two CH_2 groups indicating their non-equivalence. The NMR spectra confirmed the previously reported[12-16] intramolecular H-bonding in hydrazones. The ^1H NMR of **7b** in DMSO-d_6 showed the presence of three signals for the three NH groups at δ 13.83, 12.60 and 9.83. The first two signals indicated the presence of two hydrogen bonded NH groups whereas the third one could be due to the involvement of the NH in hydrogen bonding with DMSO-d_6. There was no change in the position of the NH signals with time when the spectra were measured after a week. The spectra of the trishydrazones **7** in $CDCl_3$ have been reported[5] to show two signals in the region δ 12.90-12.78 and 13.88-13.62 due to one and two NH groups respectively. In our hands, the spectrum of **7a** measured in $CDCl_3$ showed two signals in the same downfield regions (δ 13.57 and 12.57), but each was due to a single proton. The third NH peak was hidden under the signals of the aromatic region. The ^1H NMR spectrum of the dioxime **2d** in DMSO-d_6 showed the presence of three signals at δ 12.90, 11.76 and 11.00 for the NH and 2 NOH groups.

In summary, reaction of 5,5-dimethylcyclohexan-1,2,3-trione-2-arylhydrazones **1** with hydroxylamine gave the respective dioximes **2** whose dehydrative cyclization with acetic anhydride afforded **4** as a result of an additional cleavage of the oxime residue. The presence of an acid scavenger prohibited this process. The action of cupric chloride on 5,5-dimethylcyclohexan-1,2,3-trione-2-arylhydrazone-1,3-bis-(phenylhydrazone) **7** caused a cyclization of two of the hydrazone residues and cleavage of the third one to give 4,5,6,7-tetrahydro-6,6-dimethyl-2-phenyl-2H-benzo[d][1,2,3]triazol-4-one **4a** regardless of the substituent on the aryl group of **7**.

EXPERIMENTAL

Mps were determined with a Meltemp apparatus and are uncorrected. IR spectra were recorded with a Unicam SP 1025 spectrometer and ^1H NMR spectra were determined with an EM- 390 spectrometer using TMS as a reference and are reported in chemical shifts (ppm). Microanalyses were obtained at the Unit of Microanalysis, Faculty of Science, Cairo University.

5.5-Dimethylcyclohexan-1,2,3-trione-2-arylhydrazone-1,3-dioximes (2) (Table 2).- A solution of **1** (10 mmol) in ethanol (50 mL) was treated with hydroxylamine hydrochloride (1.7 g, 24 mmol) and sodium acetate (0.82 g, 10 mmol). The reaction mixture was boiled under reflux for 5 hrs. The mixture was concentrated under reduced pressure, and the product was collected, washed repeatedly with water, and dried. It was crystallized from ethanol as yellow needles.

2-Aryl-4,5,6,7-tetrahydro-6,6-dimethyl-2H-benzo[d][1,2,3]triazol-4-ones (4).- A suspension of compound **2** (10 mmol) in acetic anhydride (15 mL) was heated under reflux for 1 hr. The reaction mixture was then cooled and poured onto crushed ice. The product was collected, successively washed with water and ethanol and dried. It was crystallized from ethanol to provide colorless plates.

4,5,6,7-Tetrahydro-6,6-dimethyl-2-phenyl-2H-benzo[d][1,2,3]triazol-4-one (4 a), mp. 117-118° (lit.[5] mp. 116-118°); 52% yield, IR: 1692 cm^{-1} (C=O).

4,5,6,7-Tetrahydro-6,6-dimethyl-2-(4-tolyl)-2H-benzo[d][1,2,3]triazol-4-one (4g), mp. 156°, (lit.[5] mp. 153-155°);52% yield, IR: 1690 (C=O), 1618 cm^{-1} (C= N).

TABLE 2. Elemental Analysis and IR of 5,5-Dimethylcyclohexan-1,2,3-trione-2-(arylhydrazone)-1,3-dioximes

Cpd No.	Yield %	mp. (°C)	Anal. (Calcd)			IR (cm^{-1})	
			C	H	N	OH & NH	C=N
2a	85	221.-223	61.2 (61.3)	6.5 (6.6)	20.5 (20.4)	3439,3140	1602
2d	81	220	62.6 (62.5)	6.9 (7.0)	19.0 (19.4)	3434,3128	1594
2g	80	253-255	54.8 (54.5)	5.5 (5.6)	18.5 (18.2)	3378,3129	3611
2h	76	225-227	52.8 (52.7)	5.5 (5.4)	21.8 (21.9)	3414,3100	1596

4,5,6,7-Tetrahydro-6,6-dimethyl-2-(4-nitrophenyl)-2H-benzo[d][1,2,3]triazol-4-one (4h), mp. 282°; 41% yield, IR: 1700 (C=O), 1596 cm^{-1} (C=N).

Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.7; H, 4.9; N, 19.6. Found: C, 58.8; H, 4.8; N, 19.7

4,5,6,7-Tetrahydro-6,6-dimethyl-2-(4-tolyl)-2H-benzo[d][1,2,3]triazol-4-one Acetyl Oxime (5g).- A mixture of **1g** (2.6 g, 10 mmol) and hydroxylamine hydrochloride (1.7 g, 24 mmol) in pyridine (10 mL) was heated under reflux for 1 hr, and acetic anhydride (10 mL) was added. Heating was continued for another 1 hr. The mixture was cooled and poured onto crushed ice. The product was filtered off, washed with water and dried. It was crystallized from ethanol as pale yellow crystals (2.5 g, 58% yield); mp 172-174°; IR: 1778 (NOAc), 1622 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$): δ 8.00 and 7.20 (2d, 4 H, Ar-H), 2.75 (s, 4 H, 2 CH_2), 2.37 (s, 3 H, Me), 2.28 (s, 3 H, OAc) and 1.12 (s, 6 H, 2 Me).

Anal. Calcd for $C_{17}H_{20}N_4O_2$: C, 65.4; H, 6.5; N, 17.9. Found: C, 65.3; H, 6.4; N, 18.1

5,5-Dimethylcyclohexan-1,2,3-trione-2-arylhydrazone-1,3-bis-(phenylhydrazone) (7) (Table 3).- A stirred solution of **1** (10 mmol) in ethanol (50 mL) was treated with phenylhydrazine (3.24 g, 30 mmol) and 2 drops of acetic acid. The reaction mixture was kept at room temperature for 1 hr. The product was collected, washed with ethanol and dried. It was crystallized from *n*-butanol to afford orange- red plates.

5,5.Dimethylcyclohexan-1,2,3-trione-2-(4-nitrophenylhydrazone)-1-phenylhydrazone (8).- A stirred solution of **1h** (2.9 g, 10 mmol) in ethanol (60 mL) was treated with phenylhydrazine (1.62 g, 15 mmol) and 2 drops of acetic acid. The reaction mixture was kept at room temperature for 1 hr. The product was collected, washed with ethanol and dried. It was crystallized from chloroform-ethanol as brown plates (5.0 g, 81% yield); mp. 245°; IR: 3499, 3429 (NH), 1724 (C=O), 1596 cm^{-1} (C=N).

Anal. Calcd for $C_{20}H_{21}N_5O_3$: C, 63.3; H, 5.6; N, 18.5. Found: C, 63.1; H, 5.5; N, 18.2

4,5,6,7-Tetrahydro-6,6-dimethyl-2-phenyl-2H-benzo[d][1,2,3]triazol-4-one (4a).- A solution of **7** (10 mmol) in ethanol (20 mL) was treated with cupric chloride (1.57 g, 12 mmol). The reaction mixture was heated under reflux for 30 min. The solution was concentrated under reduced pressure, and hot water was added to incipient turbidity. The product was filtered off, washed with water, dried and crystallized from ethanol as a colorless product (2.4 g, 46% yield); mp 116°. The product was identical with an authentic sample of **4a**.

TABLE 3. Elemental Analysis and IR of 5,5-Dimethylcyclohexan-1,2,3-trione-2-arylhydrazone-1,3-bis-(phenylhydrazone)

Cpd. No.	Yield (%)	mp. (°C) (lit. mp.)		Anal. (Calcd)		IR (cm^{-1})	
			C	H	N	NH	C=N
7a	87	196 (195-197)				3332, 3192	1602
7b	81	201-202	62.1 (62.0)	5.2 (5.4)	16.4 (16.7)	3344, 3191	1599
7c	75	216-218	67.8 (68.0)	5.5 (5.9)	18.5 (18.3)	3350, 3198	1601
7d	79	213 (211-212)				3349, 3188	1601
7e	69	210	74.3 (73.9)	7.1 (6.9)	19.0 (19.2)	3335, 3150	1600
7f	74	196-198	74.2 (73.9)	6.8 (6.9)	19.2 (19.2)	3352, 3183	1601
7g	86	203-204 (202-203)				3350, 3200	1600
7h	82	245-246	66.3 (66.5)	5.6 (5.8)	21.2 (20.9)	3321, 3200	1600

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