SHORT PAPER

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Chemical reactivity of 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones towards nitrogen nucleophiles. Part 1. One-pot ring conversion of 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones into 4-amino-2-aryl-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones†

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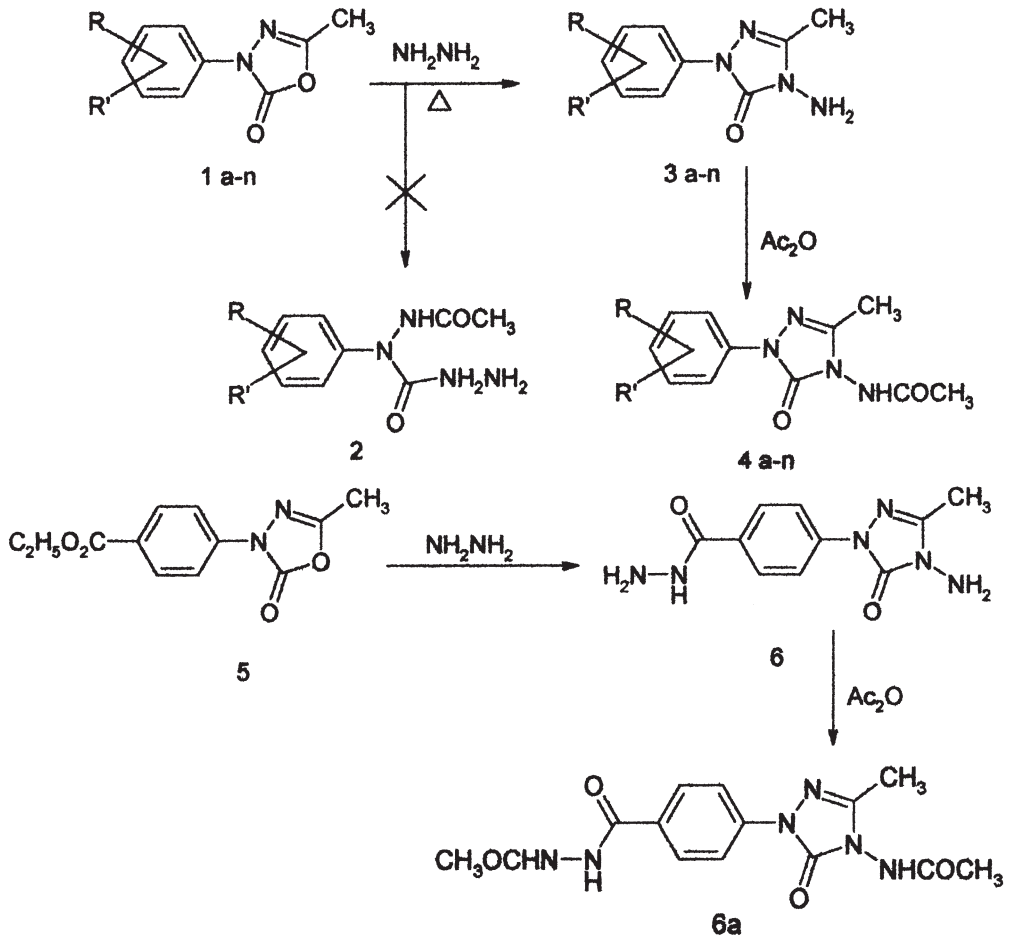
The ring transformation of 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones **1a–n** into 4-amino-2-aryl-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones **3a–n**, by reaction with hydrazine hydrate, is described. The products were screened for biological activity, and were found to be active against fungal strains.

Keywords: 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones, nitrogen nucleophiles

In continuation of our studies on the synthetic utility of sydnones,[1,2] we have recently reported[3] the facile synthesis of some new 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones (**1**) in excellent yield, by one-pot ring transformation of 3-arylsydnones.[4] Very few of these heterocycles have been reported to be prepared from phenyl hydrazines, with difficulty and in very low yields.[5] The physical and chemical properties of compounds **1** have therefore hitherto not been studied, and the first documentation of their spectral and antimicrobial studies came from our laboratory only.[3] Therefore, we felt it of interest to study the chemical reactivity of these heterocycles.



Scheme 1

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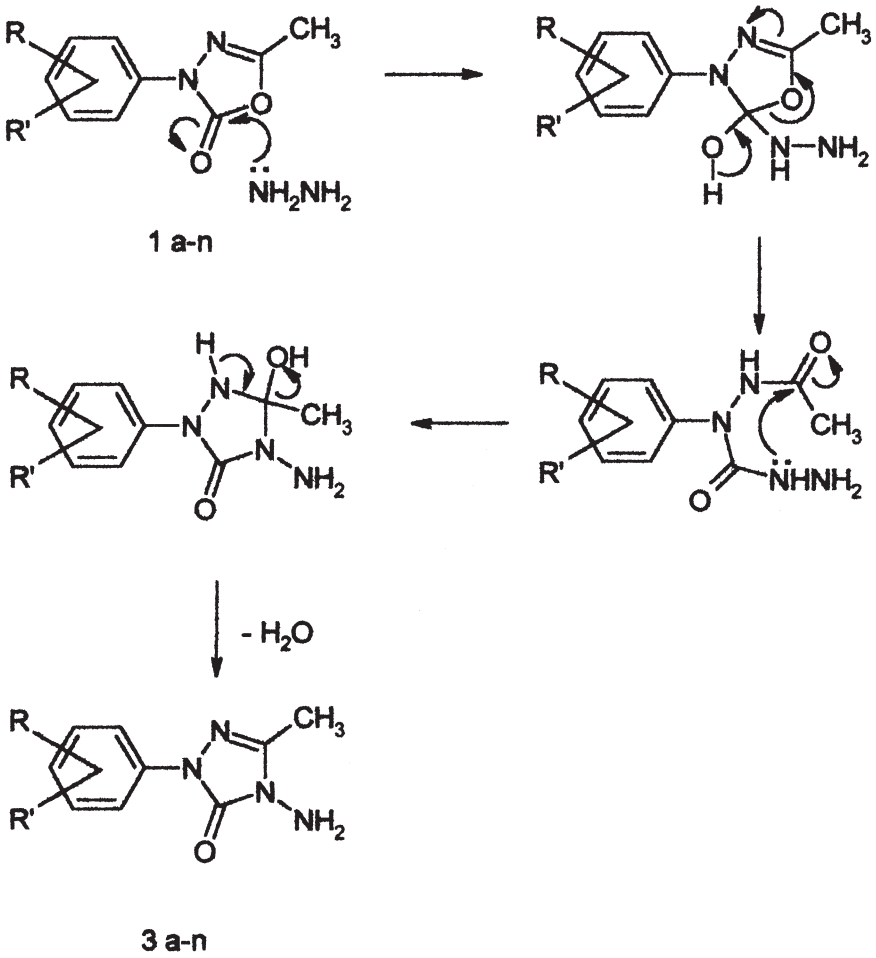
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 2

Compounds **1** can be expected to be reactive towards nucleophilic reagents on account of the presence of the carbonyl group. So, in order to study the susceptibility of these 1,3,4-oxadiazolin-2-ones **1a–n** towards nitrogen nucleophiles, we initially treated these compounds with hydrazine hydrate. We expected that the ring fission would yield the N^1-acetamido-N^1-aryl-N^2-carbohydrazides **2.** However, compounds **1a–n** underwent ready ring conversion into the so far unknown amino functionalised derivatives 4-amino-2-aryl-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones **3a-n.** (Scheme 1)

Surveying the literature[6,7] for the known synthetic procedures for such amino functionalised triazolinone derivatives, we concluded that such compounds would be difficult to synthesise or even inaccessible by the reported methods. These novel compounds would be versatile precursors with numerous synthetic applications and also interesting for biological and pharmacological studies. In this paper we report our synthetic strategy for a simple and useful approach to the synthesis of compounds **3a–n** from 3-arylsydnones, by sequential one-pot ring conversions. The 3-arylsydnones[4] are readily prepared from the corresponding primary amines.

A probable mechanism (Scheme 2) involves initial attack of the nucleophile on C-2, which is the most reactive site in the 1,3,4-oxadiazolin-2-one ring. This adduct formation would be followed by ring opening, breaking the O(1)- C(2) bond, resulting in the formation of the open chain intermediates **2** (not isolated)**.** Subsequent ring closure by an internal S_N2 attack results in the formation of the title compounds **3.** This mechanism, which involves the addition of a nucleophile, ring opening and then ring closure of an open chain intermediate by intramolecular nucleophilic attack, may be described as an ANRORC type of ring conversion. [8] The title compounds (**3a–n**) were obtained by heating the 3-aryl-5-methyl-1,3,4-oxadiazolin-2-ones (**1a–n**) with hydrazine hydrate in ethanol. The presence of the primary amino group was also confirmed by spectral data and by acetylation. In the 3-(*p*-carbethoxyphenyl)sydnone (**5**) the carbethoxy group was found to be equally susceptible to attack by hydrazine hydrate and afforded the 4-amino-2-(*p*-hydrazinocarbonylphenyl)-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**6**).

The structures of all these compounds were assigned on the basis of elemental analysis, IR, NMR (^{1}H, ^{13}C) and mass spectral data. The IR spectra of compounds **3a–n** were characterised by the presence of two bands at 3333 and 3215 cm^{-1} for the ν_{NH_2} and a band at 1709 cm^{-1} for the $\nu_{C=O}$ (flanked by two nitrogens). The latter appeared at a considerably lower frequency than that of the $\nu_{C=O}$ in the precursor compound **1**[3] (lactone-lactam 1775 cm^{-1}) and this is consistent with the replacement of the oxygen atom by nitrogen.

The ^{1}H-NMR of all these compounds showed a singlet at δ 2.37 for the ring methyl protons and another singlet at δ 4.33 for the NH_2 protons (D_2O-exchanged). The up-field chemical shifts of the NH_2 protons and the IR absorption frequencies for the NH_2 and CO groups indicate the absence of H-bonding between these groups. The ^{1}H-NOE experiment for the CH_3 and NH_2 did not show any enhancement, hence these groups are not in close proximity with each other.

Table 1 4-Amino-2-aryl-5-methyl-2,4-dihydro-3*H*-triazol-3-ones (**3a–n**, **6**) and 4-acetylamino—2-aryl-5-methyl-2,4-dihydro-1,2,4-triazol-3-ones (**4a–n**, **6a**)

No.	R	R′	Yield/%	M.p./°C	Molecular formula	Elemental analysis found/calc. (%)		
						C	H	N
3a	H	H	60	162–165	$C_9H_{10}N_4O$	56.51 56.84	5.18 5.26	29.25 29.27)
3b	H	4-CH_3	75	171–173	$C_{10}H_{12}N_4O$	58.40 58.82	5.65 5.88	29.20 27.42
3c	H	4-Cl	70	162–164	$C_9H_9ClN_4O$	48.02 48.12	3.85 4.00	25.02 25.25
3d	H	3-Cl	55	133–135	$C_9H_9ClN_4O$	48.02 48.12	3.80 4.00	25.00 25.25
3e	H	4-Br	71	185–187	$C_9H_9BrN_4O$	40.08 40.14	3.01 3.34	20.53 20.81
3f	H	2-OCH_3	76	170–173	$C_{10}H_{12}N_4O_2$	54.22 54.61	5.25 5.45	25.30 25.45
3g	H	4-OCH_3	65	174–176	$C_{10}H_{12}N_4O_2$	54.20 54.61	5.21 5.45	25.28 25.45
3h	H	4-CO_2H	55	180–183	$C_{10}H_{10}N_4O_3$	50.10 51.28	4.12 4.30	23.66 23.92
3i	H	2-CH_3	65	175–178	$C_{10}H_{12}N_4O$	58.80 58.81	5.65 5.92	27.36 27.43
3j	3-Cl	4-CH_3	70	176–178	$C_{10}H_{11}ClN_4O$	50.12 50.42	4.24 4.61	23.11 23.52
3k	2-Cl	5-OCH_3	74	162-164	$C_{10}H_{11}ClN_4O_2$	47.01 47.21	4.00 4.32	21.85 22.03
3l	2-OCH_3	5-OCH_3	68	148–150	$C_{11}H_{14}N_4O_3$	52.60 52.79	5.38 5.60	22.00 22.39
3m	3-NO_2	4-Cl	69	162–164	$C_9H_8ClN_5O_3$	40.21 40.51	2.60 2.97	25.82 26.01
3n	2-Cl	5-Cl	71	150–152	$C_9H_8Cl_2N_4O$	41.52 41.74	2.94 3.08	21.42 21.64
4a	H	H	60	180–182	$C_{11}H_{12}N_4O_2$	56.55 56.96	5.01 5.19	23.95 24.16
4b	H	4-CH_3	60	201–203	$C_{12}H_{14}N_4O_2$	58.35 58.59	5.40 5.69	22.60 22.78
4c	H	4-Cl	58	195–197	$C_{11}H_{11}ClN_4O_2$	49.30 49.59	3.80 4.12	20.83 21.03
4d	H	3-Cl	55	200–203	$C_{11}H_{11}ClN_4O_2$	49.25 49.59	3.85 4.12	20.90 21.03
4e	H	4-Br	58	210–212	$C_{11}H_{11}BrN_4O_2$	42.25 42.49	3.20 3.53	17.80 18.02
4f	H	2-OCH_3	50	188–190	$C_{12}H_{14}N_4O_3$	54.85 55.04	5.22 5.34	21.15 21.40
4g	H	4-OCH_3	60	192–194	$C_{12}H_{14}N_4O_3$	54.80 55.04	5.12 5.34	21.20 21.40
4h	H	4-CO_2H	55	200–202	$C_{12}H_{12}N_4O_4$	52.10 52.27	4.10 4.35	20.01 20.32
4i	H	2-CH_3	51	185–187	$C_{12}H_{14}N_4O_2$	58.35 58.59	5.35 5.69	22.50 22.78
4j	3-Cl	4-CH_3	57	200–202	$C_{12}H_{13}ClN_4O_2$	51.03 51.39	4.25 4.63	19.85 19.98
4k	2-Cl	5-OCH_3	55	182–184	$C_{12}H_{13}ClN_4O_3$	48.44 48.64	4.20 4.38	18.65 18.91
4l	2-OCH_3	5-OCH_3	51	182–185	$C_{13}H_{16}N_4O_4$	53.21 53.51	5.20 5.48	18.90 19.09
4m	3-NO_2	4-Cl	50	175–177	$C_{11}H_{10}ClN_5O_4$	42.22 42.45	2.95 3.21	22.30 22.51
4n	2-Cl	5-Cl	50	205–207	$C_{11}H_{10}Cl_2N_4O_2$	43.65 43.91	3.03 3.32	18.54 18.62
6	H	4-$CONHNH_2$	85	220–223	$C_{10}H_{12}N_6O_2$	48.01 48.38	4.45 4.87	33.60 33.85
6a	H	4-CONHNHAc	80	250–255	$C_{14}H_{16}N_6O_4$	50.35 50.60	4.55 4.85	25.00 25.29

The ^{13}C-NMR of a typical compound (**3c**) showed four weak signals at δ 119, 128, 136 and 154 which are assignable to the quaternary carbons of the aromatic ring at C-4, C-1, C-5 of triazolinone and the carbonyl carbon respectively. The other aromatic carbons appeared as strong signals at δ 117 (C-3/5), and at 130 (C-2/6). The methyl carbon was observed at δ 11.0.

The electron –impact mass spectrum of the 4-methylphenyl derivative (**3b**) showed the molecular ion at m/e 204, which agrees with the molecular formula of the compound.

The acetyl derivatives **4** showed IR bands at 3296 (ν_{NH}), 1727 ($\nu_{C=O}$ of triazolinone) and 1690 cm^{-1} (amide $\nu_{C=O}$). The presence of an acetyl group was also evidenced in the ^{1}H NMR spectrum of these compounds, which showed singlets for two methyl groups at δ 2.20 ($COCH_3$) and 2.26 (ring CH_3). The amide NH proton was observed at δ 10.0 (D_2O exchanged). The ^{1}H-NMR spectrum of compound **6** showed the absence of the signals for the ethyl group and two signals appeared at δ 4.33 and 4.44 for the two NH_2 (of 4-amino and $NHNH_2$) protons respectively, while the NH (CONH) proton was observed at δ 7.26 (all are D_2O-exchanged).

Similar reactions with other nitrogen nucleophiles are now in progress in our laboratory.

Biological activity

All the compounds were screened for their antimicrobial activity by the cup-plate method at 100μg/ml concentration in DMF against the Gram-negative *Escherichia coli* and Gram-positive *Bacillus bacilli* bacteria, and also against *Pencillium lanosum* and *Aspergillus candida* fungi, using norfloxacin and griseofulvin as the reference drugs respectively. All these compounds were inactive against the bacterial strains, but some of them showed selective fungal inhibitory activity, higher even than the reference drug griseofulvin. Compounds **3g**, **i**, **j**, and **l** exhibited considerably higher activity than griseofulvin only against *P. lanosum*, while compounds **4g**, **h**, **k** and **m** exhibited higher antifungal activity only against *A. candida*. The acetyl derivatives **4** were also inactive against the bacterial strains but all the compounds were more active against both the fungi.

Experimental

Melting points are uncorrected. IR spectra were recorded on a Nicolet Impact 410 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker AC-300 F, 300MHz spectrometer in $CDCl_3$/DMSO-d_6 with TMS as internal standard. The mass spectra were recorded on an MI ver 14 UIC 002002 spectrometer.

4-Amino-2-aryl-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-ones (**3a–n**, **6**)**.** *General procedure:* To a suspension of compound **1** or **5** (0.01 mol) in dry alcohol (15 ml) was added hydrazine hydrate (1.5 ml) and the mixture was refluxed on a water-bath for 8 hours. The reaction mixture was then diluted with water and the solid obtained after filtration was crystallised from ethanol to give light brown crystals. (Table 1)

4-Acetylamino-2-aryl-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-ones (**4a–n**, **6a**). *General procedure:* A mixture of compound **3** or **6** (0.01 mol) and acetic anhydride (10 ml) was refluxed on an oil-bath for 2–3 hours. The reaction mixture was then diluted with water and the white solid was filtered and crystallised from alcohol (Table 1).

The analytical data of all the compounds are given in Table 1 and the ^{1}H-NMR of selected compounds is given below.

4-Amino-2-phenyl-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**3a**): δ 2.36 (3H, s, CH_3), 4.30 (2H, s, NH_2, D_2O exchanged), 7.00–7.60 (5H,m, Ar–H).

4-Amino-2-(4-methylphenyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**3b**): δ 2.35 (3H, s, 4-CH_3), 2.37 (3H, s, CH_3), 4.30 (2H, s, NH_2, D_2O exchanged), 7.69–7.71 (2H, d, *J* = 8.4, Ar–H), 7.78–7.81 (2H, d, *J* = 8.4, Ar–H); MS: m/z 204 (M^+,100%), 190, 105, 91.

4-Amino-2-(4-chlorophenyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**3c**): δ 2.37 (3H, s, CH_3), 4.30 (2H, s, NH_2, D_2O exchanged), 7.38–7.41 (2H, d, *J* = 8.7, Ar–H), 7.86–7.88 (2H, d, *J* = 8.7, Ar–H).

4-Amino-2-(4-bromophenyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**3e**): δ 2.37 (3H, s, CH_3), 4.30 (2H, s, NH_2, D_2O exchanged), 7.42–7.45 (2H, d, *J* = 7.4, Ar–H), 7.88–7.90 (2H, d, *J* = 7.4, Ar–H).

4-Amino-2-(4-methoxyphenyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**3g**): δ 2.37 (3H, s, CH_3), 3.50 (3H, s, OCH_3), 4.30 (2H, s, NH_2, D_2O exchanged), 7.39–7.41 (2H, d, *J* = 7.4, Ar–H), 7.62–7.64 (2H, d, *J* = 7.4, Ar–H).

4-Amino-2-(2,5-dimethoxyphenyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**3l**): δ 2.37 (3H, s, CH_3), 3.50 (6H, s, OCH_3), 4.3 (2H, s, NH_2, D_2O exchanged), 7.35–7.70 (3H, m, Ar–H).

4-Acetylamino-2-phenyl-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**4a**): δ 2.20 (3H, s, $COCH_3$), 2.27 (3H, s, CH_3), 7.1–7.5 (5H, m, Ar–H), 9.9 (1H, s, CONH, D_2O exchanged).

4-Acetylamino-2-(4-methylphenyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**4b**): δ 2.20 (3H, s, $COCH_3$), 2.26 (3H, s, 4–CH_3), 2.67 (3H, s, CH_3), 7.23–7.42 (2H, d, *J* = 8.7, Ar–H), 7.44–7.72 (2H, d, *J* = 8.7, Ar–H), 9.90 (1H, s, CONH, D_2O exchanged).

4-Acetylamino-2-(4-carboxyphenyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one **(4h)**: δ 2.20 (3H, s, $COCH_3$), 2.26 (3H, s, CH_3), 7.36–7.65 (2H, d, *J* = 8.7,Ar–H), 7.49–7.78 (2H, d, *J* = 8.7, Ar–H), 9.9 (IH, s, CONH, D_2O exchanged), 11.9 (1H, s, COOH).

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