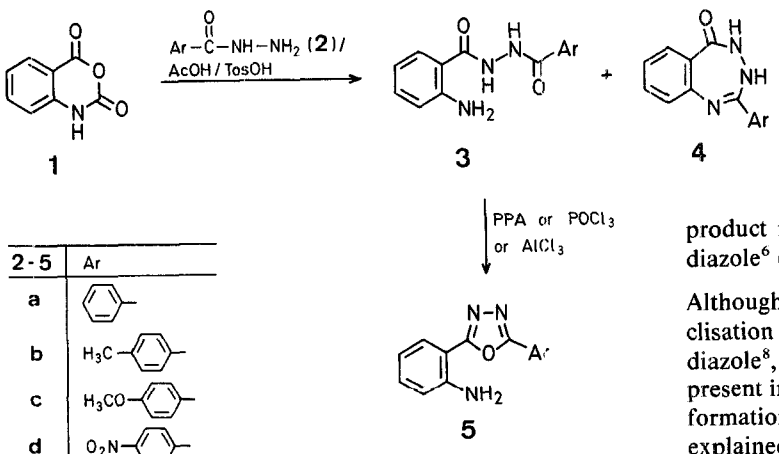
A Facile Synthesis of 2-Aryl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones

Ch. K. REDDY, P. S. N. REDDY, C. V. RATNAM*

Department of Chemistry, Osmania University, Hyderabad 500007, India

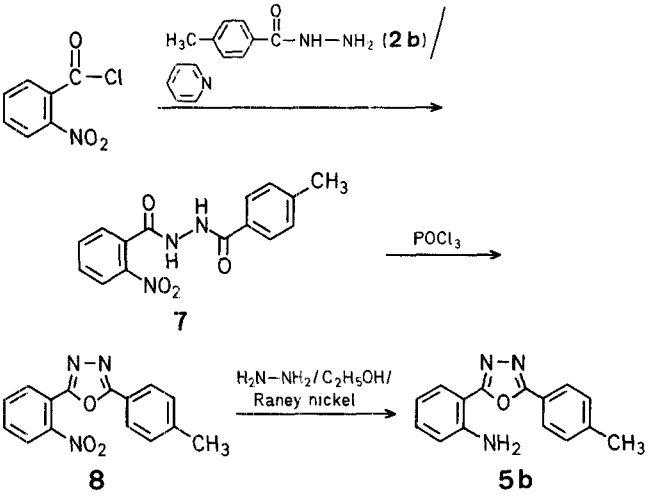
We report here a one-step synthesis of hitherto unknown 2-aryl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones **(4)**. Isatoic anhydride[1] **(1)**, on reaction with benzoylhydrazine **(2a)**[2] in a mixture of acetic acid and *p*-toluenesulphonic acid yielded 2-phenyl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one **(4a)**. Similarly, substituted hydrazines **2b–d**[3,4,5] reacted to give benzotriazepinones **4b–d** in 40–50% yield. However, hydrazines **3b–d** were also formed as products (Scheme **A**, see Table 1). The possibility that 2-(2-aminophenyl)-5-aryl-1,3,4-oxadiazole **(5)** had formed instead of **4** was eliminated by comparing **4b** with an authentic sample of the oxadiazole **5b** prepared by an alternative and unambiguous route as described below.



2-5	Ar
a	C6H5–
b	H3C–C6H4–
c	H3CO–C6H4–
d	O2N–C6H4–

Scheme **A**

The hydrazine **7** prepared by the reaction of *o*-nitrobenzoyl chloride with *p*-methylbenzoylhydrazine **(2b)** in pyridine was cyclised to the nitrophenyloxadiazole **8** by refluxing with phosphoryl chloride. Reduction of **8** with hydrazine hydrate in the presence of Raney nickel gave the aminophenyloxadiazole **5b** (Scheme **B**).

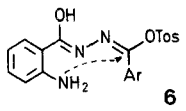


Scheme **B**

The difference in mass spectral fragmentation between the benzotriazepinones **4** and the isomeric oxadiazoles **5** are in agreement with the reported observations[6]. Moreover, we find also characteristic differences in the U.V. and I.R. spectra. Compounds **4** show prominent I.R. absorptions for the carbonyl group at 1670 cm^{-1} which are absent in **5**. In the U.V. spectra, oxadiazoles **5** have an intense peak at 350 nm due to the amino-induced bathochromic shift of the n-π^* transition, which is not present in **4**.

When the isatoic anhydride/acid hydrazide reactions were carried out in acetic acid in the absence of *p*-toluenesulphonic acid, only products **3** were formed. The hydrazines **3** were converted to **4** by prolonged refluxing in acetic acid/*p*-toluenesulphonic acid, suggesting the intermediacy of **3** in the main reaction. Attempts to cyclise the hydrazines **3** to the benzotriazepinones **4** using polyphosphoric acid, phosphoryl chloride, or aluminum chloride resulted in the exclusive formation of oxadiazole **5** (Table 2). An earlier report[7] on the cyclisation of 1-(2-aminobenzoyl)-2-(2-pyridoyl)-hydrazine (**3**; Ar = 2-pyridyl) to give 1,3,4-benzotriazepinone (**4**; Ar = 2-pyridyl) in polyphosphoric acid has been corrected and the product is, in fact 2-(2-aminophenyl)-5-(2-pyridyl)-1,3,4-oxadiazole[6] (**5**; Ar = 2-pyridyl).

Although *p*-toluenesulphonic acid was used earlier in the cyclisation of 1,2-dibenzoylhydrazine to 2,5-diphenyl-1,3,4-oxadiazole[8], our results show that, when a free amino group is present in the *ortho*-position of one of the benzoyl groups, the formation of benzotriazepinone **4** is preferred. This could be explained through the detosylative cyclisation of the intermediate tosylate ester **6** by the attack of the more nucleophilic amino group.



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1-(2-Aminobenzoyl)-2-aroylhydrazines (3b–d); General Procedure:
A mixture of isatoic anhydride (**1**; 1.63 g, 10 mmol) and aroylhydrazine **2b–d** (10 mmol) in glacial acetic acid (5 ml) is heated under reflux for 30 min resulting in a clear solution. On cooling, products **3b–d** are deposited as crystalline solids which are filtered and recrystallised from benzene (Table 1).

2-Aryl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (4a–d); General Procedure:

Method A: To a mixture of isatoic anhydride (**1**; 1.63 g, 10 mmol) and *p*-toluenesulphonic acid (20 mg) in acetic acid (10 ml), the appropriate aroylhydrazine **2a–d** (10 mmol) is added and the mixture is heated under reflux for 9 h. The solution is cooled, added slowly to cold water (250 ml), and extracted with chloroform (3 × 50 ml). The chloroform layer is dried with anhydrous sodium sulphate and the solvent removed in vacuo to yield a gummy substance which is chromatographed over a column of neutral alumina (120–200 mesh) using petroleum ether (60–80 °C) and benzene as eluents. Products **4a–d** are obtained from the petroleum ether/benzene fractions (1 : 1, 5 × 20 ml), while the benzene fractions (5 × 20 ml) give **3b–d** (Table 1).

Method B: A mixture of the appropriate 1-(1-aminobenzoyl)-2-aroylhydrazine **3b–d** (1 g, 6.6–5.3 mmol), *p*-toluenesulphonic acid (20 mg), and acetic acid (10 ml) is refluxed continuously for 9 h and worked up as specified in Method A to yield **4b–d.**

Table 1. 1-(2-Aminobenzoyl)-2-aroyl Hydrazides (**3**) and 2-Aryl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (**4**)

Product No.	Yield[a] [%]	m.p. [°C][b] (solvent)	Molecular Formula[c]	M.S. *m/e* [M$^+$][d]	U.V. (Methanol)[e] λ_{max} [nm] (logε)	I.R. (KBr) [cm^{-1}][f] ν_{NH}	$\nu_{C=O}$	$\nu_{C=N}$	^{1}H-N.M.R. ($CDCl_3$)[g,h] δ [ppm]
3b	90	198° (C_6H_6)	$C_{15}H_{15}N_3O_2$ (269.3)	269	240 (4.12), 245 (4.13), 260 (4.17), 270 (4.13)	3400, 3300, 3250	1670, 1630	—	2.31 (s, 3H, CH_3); 6.6 (br. s, 2H, NH_2); 7.5 (m, 8H_{arom}); 10.2 (br. s, 2H, 2CONH)
3c	89	200° (C_6H_6)	$C_{15}H_{15}N_3O_3$ (285.3)	285	242 (4.11), 250 (4.16), 258 (4.13), 270 (4.13)	3400, 3250, 3200	1670, 1630	—	3.82 (s, 3H, OCH_3); 6.6 (br. s, 2H, NH_2); 7.8 (m, 8H_{arom}); 10.2 (br. s, 2H, 2CONH)
3d	87	238° (C_6H_6)	$C_{14}H_{12}N_4O_4$ (300.3)	300	239 (4.14), 250 (4.13), 258 (4.16), 270 (4.14)	3350, 3300, 3200	1670, 1630	—	—[i]
4a	50	179° (C_6H_6/PE)[j]	$C_{14}H_{11}N_3O$ (237.3)	237	280 (4.14)	3180, 3280	1670	1610	5.0 (br. s, 2H, 2NH); 7.9 (m, 9H_{arom})
4b	36	152° (C_6H_6/PE)[j]	$C_{15}H_{13}N_3O$ (251.3)	251	245 (4.19), 252 (4.17), 275 (4.11)	3180, 3280	1670	1610	2.31 (s, 3H, CH_3); 5.0 (br. s, 2H, 2NH); 7.85 (m, 8H_{arom})
4c	37	182° (C_6H_6/PE)[j]	$C_{15}H_{13}N_3O_2$ (267.3)	267	244 (4.15), 255 (4.17), 290 (4.18)	3180, 3280	1670	1610	3.81 (s, 3H, OCH_3); 5.0 (br. s, 2H, 2NH); 7.9 (m, 8H_{arom})
4d	40	242° (C_6H_6/PE)[j]	$C_{14}H_{10}N_4O_3$ (282.3)	282	260 (4.18), 295 (4.13)	3180, 3280	1670	1610	—[i]

[a] Yield of the recrystallised product.
[b] Melting points are uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.40, H ±0.02, N ±0.03.
[d] Mass spectra were recorded on MS-30 instrument with D-55 data system.
[e] Recorded on Shimadzu UV-240 Graphicord Spectrophotometer.
[f] Recorded on Perkin-Elmer Infracord 337 spectrophotometer.
[g] Recorded on Hitachi Perkin-Elmer 100 MHz instrument.
[h] NH-Protons are exchangable with deuterium.
[i] ^{1}H-N.M.R. could not be recorded due to poor solutility in usual solvents.
[j] PE = Petroleum ether (60–80 °C).

Table 2. 2-(2-Aminophenyl)-5-aryl-1,3,4-oxadiazoles **5** prepared

Product No.	Method	Yield [%]	m.p. [°C]	Molecular formula[a,b]	U.V. (methanol) λ [nm] (logε)	M.S. *m/e* (%)
5a	A	54	151°	$C_{14}H_{11}N_3O$ (237.3)	258 (4.06), 281 (4.19), 352 (4.09)	237 (M$^+$, 100), 208 (7), 180 (10), 120 (60), 119 (42), 92 (21), 91 (20)
	B	50				
	C	42				
5b	A	62	181°	$C_{15}H_{13}N_3O$ (251.3)	258 (4.14), 282 (4.21), 295 (4.15), 353 (4.12)	251 (M$^+$, 100), 220 (10), 208 (5), 194 (25), 180 (16), 125 (13), 120 (70), 119 (50), 92 (23), 91 (20)
	B	63				
	C	40				
5c	A	60	146°	$C_{15}H_{13}N_3O_2$ (267.3)	258 (4.05), 285 (4.08), 352 (4.04)	267 (M$^+$, 100), 238 (6), 210 (12), 135 (45), 120 (40)
	B	61				
	C	39				
5d	A	65	261°	$C_{14}H_{10}N_4O_3$ (282.3)	258 (4.12), 282 (4.19), 353 (4.11)	282 (M$^+$, 100), 252 (5), 120 (92), 104 (8), 92 (20)
	B	60				
	C	41				

[a] Satisfactory microanalyses obtained: C ±0.12, H ±0.02, N ±0.03.
[b] **5a–d**, I.R. (KBr): ν_{NH_2} = 3320–3420, $\nu_{C=N}$ = 1610 cm^{-1}.

2-(2-Aminophenyl)-5-aryl-1,3,4-oxadiazoles 5b–d; General Procedure:

Method A, using polyphosphoric acid: The appropriate hydrazine **3** (1 g, 6.6–5.3 mmol) is added to freshly prepared polyphosphoric acid (10 g of phosphorus pentoxide in 6 ml of phosphoric acid)[9] and the mixture is heated for 3 h on a steam bath. The resulting clear solution is cooled, poured on crushed ice (500 g), and neutralised with aqueous ammonia (60 ml). The precipitated products are filtered and recrystallised from petroleum ether (60–80 °C).

Method B, using phosphoryl chloride: A mixture of the appropriate hydrazine **3** (1 g, 6.6–5.3 mmol) and phosphoryl chloride (5 ml) is refluxed for 3 h. The resulting solution is poured on crushed ice (500 g) and neutralised with aqueous ammonia (60 ml). The precipitated products **5b–d** are purified as described in Method A.

Method C, using aluminium chloride: To a solution of the appropriate hydrazine **3** (1 g, 6.6–5.3 mmol) in chloroform (10 ml), anhydrous aluminium chloride (3 g) is added and the mixture is refluxed on a steam bath for 2 h. The solvent is removed under reduced pressure and the residue is poured into ice-cold water (10 ml) to yield **5b–d.** These are purified as described in Method A.

Compound **5a** is obtained by the direct reaction of isatoic anhydride (**1**: 1.63 g, 10 mmol) with benzoylhydrazine (**2a**; 1.36 g, 10 mmol) in polyphosphoric acid as described in Method A.

2-(2-Aminophenyl)-5-(4-methylphenyl)-1,3,4-oxadiazole (5b):

1-(2-Nitrobenzoyl)-2-(4-methylbenzoyl)-hydrazine **(7):** To a solution of *o*-nitrobenzoyl chloride (1.85 g, 10 mmol) in pyridine (3 ml), *p*-methylbenzoylhydrazine (**2b**; 1.5 g, 10 mmol) is added and the mixture is left aside for a few minutes at room temperature. The crystalline compound that separates is filtered and recrystallised from methanol; yield: 2.21 g (74%); m.p. 256 °C.

$C_{15}H_{13}N_3O_4$	calc.	C 60.20	H 4.38	N 14.04
(299.3)	found	59.92	4.34	14.13

I.R. (KBr): ν = 3200–3150 (NH), 1680, 1640 (C=O), 1530, 1350 cm^{-1} (NO_2).

2-(2-Nitrophenyl)-5-(4-methylphenyl)-1,3,4-oxadiazole **(8):** A mixture of **7** (1 g, 3.34 mmol) and phosphoryl chloride (5 ml) is refluxed for 3 h. The resulting solution is poured on crushed ice (500 g) and neutralised with aqueous ammonia (60 ml). The precipitated product **8** is filtered and recrystallised from ethanol; yield: 0.68 g (52%); m.p. 119 °C.

$C_{15}H_{11}N_3O_3$	calc.	C 64.05	H 3.94	N 14.94
(281.3)	found	64.25	3.91	14.86

I.R. (KBr): ν = 1610 (C=N), 1530, 1350 cm^{-1} (NO_2).

Conversion of **8** *to* **5b:** To a solution of **8** (1 g, 3.56 mmol) in ethanol (20 ml) and hydrazine hydrate (80% v/v, 10 ml), freshly prepared Raney nickel[10] (500 mg) is added. The heterogeneous mixture is refluxed on a steam bath till the yellow colour of the solution has disappeared (~ 1 h). After cooling, the catalyst is removed by filtration, the solvent evaporated from the filtrate, and the residue is crystallised from petroleum ether (60–80 °C) to give **5b**; yield: 0.53 g (55%); m.p. 181 °C.

The mixture melting point of the sample **5b** prepared as above and a sample of **5b** obtained from the cyclisation of **3b** in phosphoryl chloride or polyphosphoric acid or aluminium chloride is undepressed. Spectral data (U.V., I.R., ^{1}H-N.M.R., and mass) of these two samples show them to be identical.

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