A Facile Synthesis of 4-Diarylmethyl-1-(2*H*)phthalazinones from 2,2-Diaryl-1,3-indanediones

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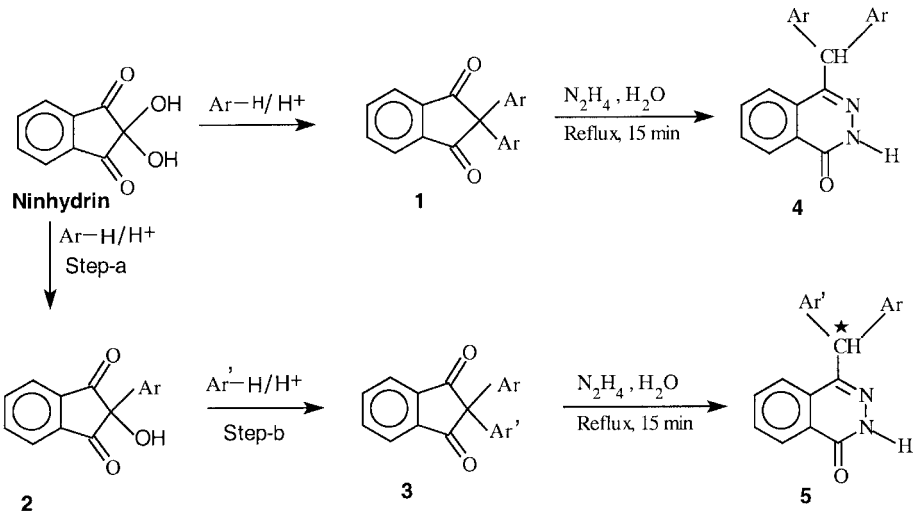
Received 15 March 2002

Abstract: Refluxing of 2,2-diaryl-1,3-indanediones in hydrazine hydrate for a brief period affords 4-diarylmethyl-1-(2*H*)phthalazinones in very high yield.

Key words: 2,2-diaryl-1,3-indanediones, 4-diarylmethyl-1-(2*H*)-phthalazinones, arylation, heterocycles, nucleophilic additions

It has been reported that various functional derivatives of 4-substituted alkyl-1-(2*H*) phthalazinone-2-acetates, such as corresponding acids, amides, and hydrazides have variety of biological activities like hyphotic,[1] anticonvulsive,[1] antibacterial,[2] antifungal,[2] antianaphilactic,[3] nootropic[3] and inhibition of aldose reductase[4] etc. Very few methods are known in literature for the synthesis of 4-phenyl- and 4-substituted alkyl-1-(2*H*) phthalazinones and their 2-acetates derivatives.[5–11] The most well known one is the reaction of 2-acylbenzoic acids with hydrazine to give 4-alkyl-1-(2*H*)phthalazinones. However, this method is not suitable for the preparation of compounds like 4-diarylmethyl-1-(2*H*)phthalazinones, as corresponding starting materials *viz*., 2-substituted benzoic acids are not easily available. Therefore, it becomes quite pertinent to develop suitable and efficient routes to prepare such potentially bioactive 4-diarylmethyl-1-(2*H*) phthalazinones from readily available starting materials.

Keeping this in view, we wish to report a very convenient method for the preparation of 4-diarylmethyl-1-(2*H*)-phthalazinones starting from easily prepared 2,2-diaryl-1,3-indanediones[12] such as **1** and **3** (Scheme 1). It was found that 2,2-diaryl-1,3-indanediones (Scheme 1) react



1 and **4**

a: Ar = Ph
b: Ar = *p*-MeC_6H_4
c: Ar = *p*-ClC_6H_4
d: Ar = *p*-BrC_6H_4
e: Ar = *p*-IC_6H_4
f: Ar = *p*-$OMeC_6H_4$
g: Ar = 2,4-di-$OMeC_6H_3$

2, **3** and **5**

a: Ar = 2,3,4-tri-$OMeC_6H_2$, Ar' = *p*-$OMeC_6H_4$
b: Ar = 2,4-di-$OMeC_6H_3$, Ar' = *p*-$OMeC_6H_4$
c: Ar = 2,4-di-C_6H_3, Ar' = *p*-ClC_6H_4

Scheme 1

Synlett 2002, No. 5, 03 05 2002. Article Identifier:
1437-2096,E;2002,0,05,0823,0825,ftx,en;D26301ST.pdf.

ISSN 0936-5214

with hydrazine hydrate (99%) under refluxing conditions for about 15 minutes to give 4-diarylmethyl-1-(2*H*)phthalazinones **4** and **5** in very high yields.[13]

The experimental results are presented in the Table. With same aryl substituents phthalazinones **4,** as expected, are achiral, whereas for the presence of two different aryl units on C-α the phthalazinones **5** formed are potentially resolvable racemic mixture. A proposed mechanism for the reaction is depicted in Scheme 2. The nucleophilic attack of hydrazine to either of the carbonyl groups of 2,2-diaryl-1,3-indanediones produced the open chain hydrazides **6**, which undergo a subsequent intramolecular nucleophilic attack on the other CO, followed by dehydration to give the final products 4-diarylmethyl-1-(2*H*)phthalazinones, **4** and **5**.

Table 4-Diarylmethyl-1-(2*H*)phathalazinones from 2,2-Diaryl-1,3-indanediones

Entry	Substrates	Products	Yields[a] (%)	mp (°C)[b]
a	**1a**	**4a**	92	220
b	**1b**	**4b**	93	230
c	**1c**	**4c**	94	228
d	**1d**	**4d**	93	254
e	**1e**	**4e**	91	279
f	**1f**	**4f**	92	226
g	**1g**	**4g**	90	222
h	**3a**	**5a**	75	271
i	**3b**	**5b**	80	289
j	**3c**	**5c**	85	254

[a] Yields refer to pure isolated products.
[b] Mps are uncorrected.

The substrates **1a**–**1g** were derived from ninhydrin following the reported procedure.[12] The compounds **3a**–**3c** were prepared following a slightly modified technique.[14] All the substrates and products were thoroughly characterized by ^{1}H (300.13 MHz) and ^{13}C (75.47 MHz) NMR studies in $CDCl_3$ and confirmed for **4c** by two dimensional ^{13}C-^{1}H correlation studies optimised for one-bond and long range couplings.[15]

We are also presently engaged in the synthesis of various *N*(2) substituted derivatives of 4-diarylmethyl-1-(2*H*)-phthalazinones and in the exploration of potential biological activities of the compounds prepared.

Acknowledgement

The authors are grateful to UGC, New Delhi and the University of Calcutta for providing financial support.

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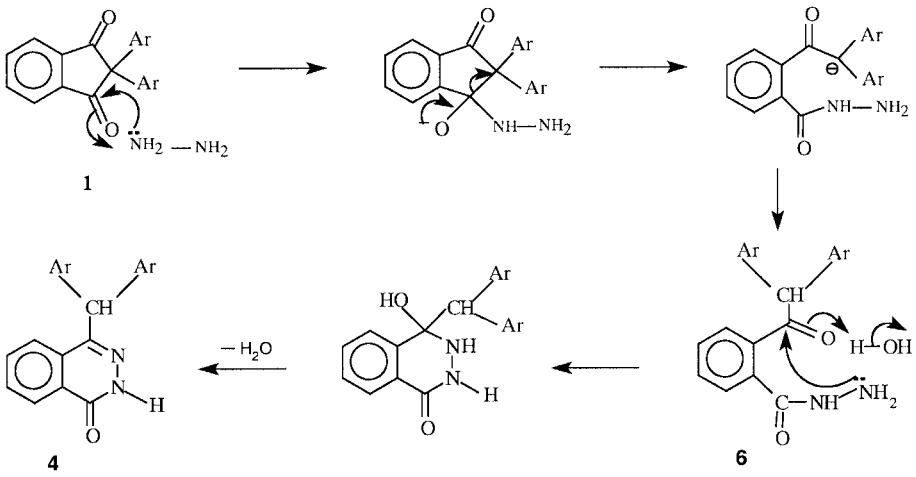

Scheme 2

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(13) ***General Procedure for Preparation of 4a–4g, 5a–5c:*** The appropriate substrate **1a**–**1g, 3a**–**3c** (1.4 mmol) was added to hydrazine hydrate (10mL, 99%) and the mixture refluxed for about 15 minutes. The cooled reaction mixture was acidified with 6 N HCl to pH 6. The solid product separated was extracted with $CHCl_3$ and worked up as usual. The residue from the $CHCl_3$ layer was purified by column chromatography over silica gel and $CHCl_3$ eluate fractions afforded pure solid products **4a**–**4g, 5a**–**5c** which were crystallised from $CHCl_3$ –light-petroleum.
(14) 2,2′- Diaryl-1,3-indanediones **3a**–**3c** were synthesized following step-a and step-b (Scheme 1). Initially the monoarylated ninhydrin adducts, **2a**–**2c** were synthesised by stirring ninhydrin (1.4 mmol) and the appropriate hydrocarbon Ar-H (4.2 mmol) in a mixture of acetic acid (10 mL) and concd H_2SO_4 (1.0 mL) for about 0.5 h at room temperature. The solid product separated was filtered out and washed thoroughly with acetic acid and then with water. The product was purified by silica-gel column chromatography using acetone as the eluent (yield ~85%).
For the 2nd arylation of **2a**–**2c**, the appropriate hydrocarbon Ar′-H (4.2 mmol) was added to a solution of monoarylated ninhydrin **2a**–**2c** (1.4 mmol) in a mixture of acetic acid (10 ml) and concd H_2SO_4 (3–4 mL). The mixture was stirred at 25 °C for 6 h and then poured over ice. The product was extracted into $CHCl_3$ and the organic phase was washed twice with water, twice with brine, further washed with water, dried over Na_2SO_4, and concentrated in vacuo. The resulting solid was further purified by recrystallisation from $CHCl_3$ (yield ~70%).
(15) Spectral data for **4c**: IR (KBr): (cm^{-1}) 1659 (CO), 3170 (NH); ^{1}H NMR (δ): 10.8 (1 H, *s*, N*H*), 8.46 (1 H, *m*, H-8), 7.73 (3 H, *m*, H-5, H-6, H-7), 7.28 (4 H, *apparent d*, *J* = 8.6 Hz, H-3′, H-3″, H-5′, H-5″), 7.13 (4 H, *apparent d*, *J* = 8.6 Hz, H-2′, H-2″, H-6′, H- 6″), 5.90 (1 H, *s*, H-α); ^{13}C NMR (δ): 159.9 (C-1), 147.2 (C-4), 139.1 (C-1′, C-1″), 133.6 (C-6), 133.2 (C-4′, C-4″), 131.5 (C-7), 130.6 (C-2′, C-2″, C-6′, C-6″), 129.7 (C-9 or C-10), 128.9 (C-3′, C-3″, C- 5′, C-5″), 128.5 (C-10 or C-9), 127.3 (C-8), 124.8 (C-5), 52.0 (C-α). Anal. Calcd for $C_{21}H_{14}Cl_2N_2O$: C 66.15; H 3.70; Cl 18.60; N 7.35. Found: C 66.06; H 3.78; Cl 18.52; N 7.29%.
Spectral data for **4f**: IR (KBr): (cm^{-1}) 1667 (CO), 3176 (NH); ^{1}H NMR (δ): 10.4 (1 H, *br*, N*H*), 8.45 (1 H, *m*, H-8), 7.79 (1 H, *m*, H-6), 7.71 (2 H, *m*, *J* = 8.6 Hz, H-5, H-7), 7.12 (4 H, *apparent d*, *J* = 8.7 Hz, H-2′, H-2″, H-6′, H-6″), 6.84 (4 H, *apparent d*, *J* = 8.7 Hz, H-3′, H-3″, H-5′, H-5″), 5.88 (1 H, *s*, H-α), 3.77 (6 H, *s*, 2 × OCH_3); ^{13}C NMR (δ): 159.9 (C-1), 158.6 (C-4′, C-4″), 148.6 (C-4), 133.4 (C-6), 133.3 (C-1′, C-1″), 131.1 (C-7), 130.2 (C-2′, C-2″, C-6′, C-6″), 130.1 (C-9 or C-10), 128.5 (C-10 or C-9), 127.1 (C-8), 125.2 (C-5), 114.1 (C-3′, C-3″, C-5′, C-5″), 55.2 (2 × OCH_3), 51.7 (C-α). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C 74.17; H 5.41; N 7.52. Found: C 74.14; H 5.37; N 7.48%.