

SELECTIVE SYNTHESIS OF 2-SUBSTITUTED INDAZOLIN-3-ONES WITHOUT N-1 PROTECTION

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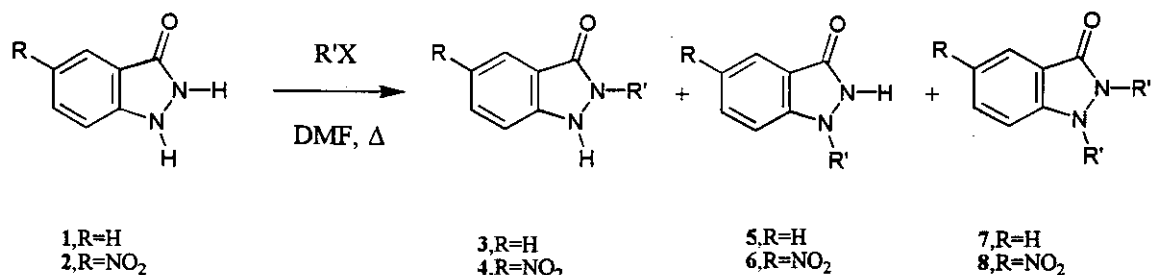
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Abstract - N-2-Alkylation of indazolin-3-ones was performed in neutral conditions. This method represents a direct and efficient entry to a class of compounds having interesting biological activities, avoiding the generally required N-1 protection.

Indazolin-3-one (or indazol-3-ol) derivatives have several biological activities. The analgesic and/or anti-inflammatory properties of benzydamine and benzadac (*O*-substituted 1-benzylindazolol derivatives) are well established,¹ and, on the other hand, the antihyperlipidemic activity² and the potential use as 5-lipoxygenase inhibitors³ of some 2-substituted indazolinones have been reported in recent years. A number of 1-substituted indazolols and 2-substituted indazolinones recently prepared⁴ as open-chain analogues of some cytostatic fused indazolinones⁵ have been found to display, in general, low activity values.

The chemistry of indazolols and indazolinones has been extensively reviewed by Baiocchi *et al.*¹ Whilst 1-substituted indazolols are easily available in high yields^{1,4} by direct alkylation of the parent indazolin-3-one in basic conditions, the preparation of 2-substituted indazolinones is not possible by direct alkylation¹ and requires either tedious N-1-protection/deprotection strategies or the cyclization from precursors

adequately functionalized (*N*-substituted *o*-nitrobenzamides). Therefore, only low to moderate yields can be obtained.^{1,4} We now present a simple and efficient method for the preparation of 2-substituted indazolin-3-ones as outlined in the Scheme 1.



R'X= a:benzyl bromide, b:butyl iodide, c:octyl iodide, d:hexadecyl iodide, e:3-picolyl chloride (as hydrochloride)

Scheme 1

RESULTS

Indazolin-3-ones (1) and (2) were chosen as the possible more active compounds in this series. Reactions of the indazol-3-ones (1) and (2) with alkyl halides in DMF⁶ and in the absence of any base produce 2-substituted indazolin-3-ones (3) and (4) in good yields (60 - 90 %) (Table 1). In all cases less than 20% of the corresponding 1-substituted 5 or 6 and/or 1,2-disubstituted 7 or 8 compounds were obtained.

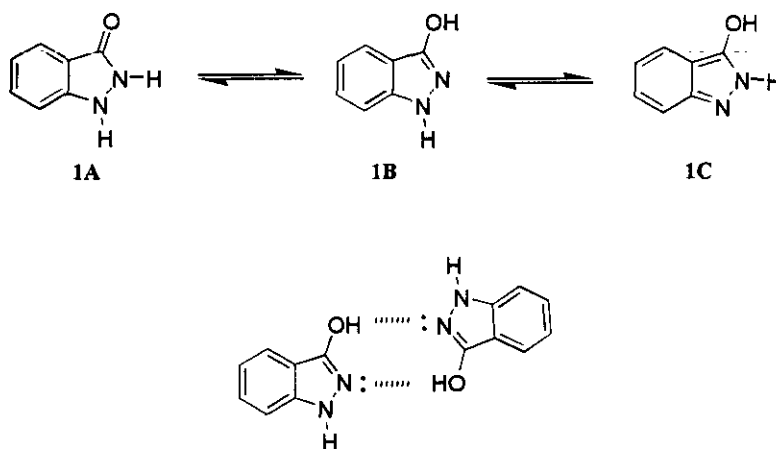
Table 1. Preparation of 2-substituted indazolin-3-ones

indazol-3-one 1 or 2	R'X	solvent	T (°C)	t (h)	1 or 2 / R'X molar ratio	3 or 4	yield 5 or 6	7 or 8
1	a	DMF	100	4	2 : 1	60	--	5
1	a	toluene	110	20	1 : 1	--	68	17
1	b	DMF	100	5	1 : 1	70	7	--
2	a	DMF	150	5	1 : 1	63	6	9
2	b	DMF	150	16	1 : 2	75	5	--
2	c	DMF	150	18	1 : 1.5	85	2	--
2	d	DMF	150	18	1 : 1.5	76	10	--
2	e	ODCB ⁶	150	3	1 : 1	90	--	--

The selectivity is influenced by the substitution on the indazolin-3-one and the nature of solvent.

In basic conditions alkylation is produced always by the more reactive N-1.¹ The results obtained suggest that in the absence of base the selectivity is not only controlled by the reactivity of both nitrogen atoms but also by the tautomeric equilibrium. Previous reports on the tautomeric equilibrium of indazolin-3-ones⁷ and on the existence of benzotriazol dimers⁸ in solution seem to support our results.

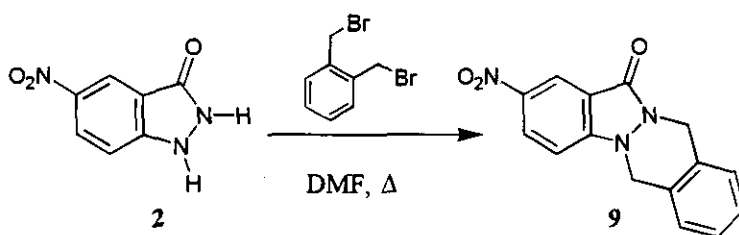
Indazolin-3-ones may exist in three tautomeric forms (1A-1C) (Scheme 2) but it has been shown that tautomers(1A) predominates in the solid phase and tautomers(1B) in solution. Thus, alkylation at N-2 must be favored in solution and in the absence of base. The presence of the electronwithdrawing nitro group diminishes the nucleophilicity of the indazolinone nucleus and the reaction requires higher temperatures (150 °C) than the corresponding indazolin-3-one (100 °C). However, N-2 selectivity is favored because conjugation of N-1 lone pair with 5-nitro group reduces its reactivity. Working at 150 °C 2-benzyl-5-nitroindazolin-3-one (4a) is obtained in 63% yield together with 6a (6% yield) and 8a (9% yield) as by-products, while benzylation of indazolin-3-one(1) affords 3a in a 33/67 ratio (from the nmr spectrum) together with 5a (7%) and 7a (60%) in the same reaction conditions (indazolin-3-one : halide molar ratio, 1:1).



Scheme 2

The nature of solvent has a strong influence on the selectivity. N-2 alkylation is observed with high selectivity in polar solvent. Thus, reaction of 1 with benzyl bromide in DMF affords a 92:8 mixture of 3a and 7a. However, 1-benzylindazolin-3-one (5a) is obtained with good selectivity in non polar solvents and a 80:20 mixture of 5a and 7a is obtained in refluxing toluene. Nevertheless, alkylation at N-1 is highly desactivated in compound (2) and after 5 days in refluxing toluene starting reactants are recovered. In non polar solvents, indazolin-3-one may exist as a dimer (Scheme 2), the nucleophilicity of N-2 is then reduced and it reacts by N-1, the only available nitrogen atom. In the presence of a polar solvent (DMF), indazolinone dimer dissociates and N-2-alkylation takes place.

Tetracyclic indazolinones with cytostatic activity against Hela cells⁵ can be easily synthesised in a "one pot" procedure. Thus, reaction of compound (2) with α,α' -dibromo-*o*-xylene in DMF at 150 °C for 5 hours in the absence of base affords the tetracyclic indazolinone (9) in 95 % yield. All methods previously reported⁵ require several steps: the synthesis either of *N,N'*-disubstituted 2-halogenohydrazines or (1,2,3,4-tetrahydrophthalaziny)benzoic acid followed by their cyclization. Alkylation with α,α' -dibromo-*o*-xylene in basic conditions gives the dimeric indazolol in poor yield.⁵



In conclusion, the selective N-2-alkylation of indazolin-3-one (1) and 5-nitroindazolin-3-one (2) can be efficiently achieved working in the absence of a base, avoiding the protection/deprotection methodology.

In the case of indazolin-3-one (1), selective N-1-alkylation is also possible by using toluene as solvent.

EXPERIMENTAL

Melting points were determined in capillary tubes on a Gallenkamp apparatus and are uncorrected.

Elemental analysis were performed on a Perkin Elmer PE 2400 CHN microanalyzer. ¹H Nmr and ¹³C nmr spectra were recorded on a Varian Unity 300 spectrometer operating at 299.890 and 75.415 MHz

respectively. Chemical shifts are expressed in parts per million (δ) relative to TMS in CDCl_3 except where specified. J values are expressed in Hz. Products were purified by flash chromatography on silica gel (Merck type 60 230-400 mesh) and/or by recrystallization. Reagents were purchased from commercial suppliers or prepared by literature methods.

2-Benzyl-1,2-dihydro-3H-indazol-3-one (3a). A stirred mixture of **1** (134 mg, 1 mmol), benzyl bromide (85.5 mg, 0.5 mmol) and DMF (3 ml) was heated at 100°C for 4 h. After addition of conc. hydrochloric acid/water (1:1 v/v mixture, 10 ml) the reaction was refluxed for one h. The hot solution was filtered to eliminate **7a** (^1H -nmr, δ , DMSO- d_6 , 5.06 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 7.05 - 7.65 (m, 14H). After cooling the pure product was collected by filtration as a white solid (135 mg, 60%); mp: $174\text{-}175^\circ\text{C}$ (from toluene). ^1H Nmr (300 MHz, DMSO- d_6): δ = 4.98 (s, 2H, CH_2), 7.10 (t, J = 7.2, 1H, H-5), 7.18-7.38 (m, 6H, H-7 and Ph), 7.49 (ddd, J = 8.3, 7.2 and 1.2, 1H, H-6), 7.67 (d, J = 7.8, 1H, H-4). ^{13}C Nmr (75 MHz, DMSO- d_6): δ = 46.75 (CH_2), 112.18 (C-7), 117.07 (C-3a), 120.86 (C-5), 123.01 (C-4), 127.44 (C-*para*), 127.57 (C-*ortho*), 128.48 (C-*meta*), 131.42 (C-6), 136.86 (C-*ipso*), 146.06 (C-7a), 160.76 (C-3). *Anal.* Calcd for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}$; C 73.92, H 5.25, N 13.26. Found; C 74.16, H 5.35, N 13.12.

2-Butyl-1,2-dihydro-3H-indazol-3-one (3b). A stirred mixture of **1** (134 mg, 1 mmol), butyl iodide (184 mg, 1 mmol) and DMF (2 ml) was heated at 100°C for 5 h. After addition of conc. hydrochloric acid/water (1:1 v/v mixture, 10 ml) the reaction was refluxed for one h. The product was extracted with methylene chloride (2x25 ml) and the organic layer was dried (MgSO_4). After evaporation of the solvent at reduced pressure, the residue was purified by flash chromatography (methylene chloride/methanol, 99:1) affording **3b** (133 mg, 70%) as an oil. ^1H Nmr (300 MHz): δ = 0.84 (t, J = 7.3, 3H, CH_3), 1.27 (sext, J = 7.3, 2H, $\text{CH}_2\text{-}3'$), 1.71 (quint, J = 7.3, 2H, $\text{CH}_2\text{-}2'$), 3.87 (t, J = 7.3, 2H, $\text{CH}_2\text{-}1'$), 7.09 (ddd, J = 7.8, 7.2 and 0.7, 1H, H-5), 7.20 (ddd, J = 8.3, 0.7 and 0.7, 1H, H-7), 7.44 (ddd, J = 8.3, 7.2 and 1.2, 1H, H-6), 7.72 (ddd, J = 7.8, 1.2 and 0.7, 1H, H-4). ^{13}C Nmr (75 MHz): δ = 13.52 (C-4'), 19.83 (C-3'), 30.31 (C-2'), 43.89 (C-2'), 112.09 (C-7), 118.29 (C-3a), 121.78 (C-5), 123.33 (C-4), 131.41 (C-6), 146.19 (C-7a), 161.86 (C-3). *Anal.* Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{O}$; C 67.77, H 7.39, N 15.81. Found; C 67.59, H 7.57, N 15.78.

2-Substituted 5-nitroindazolin-3-ones. (4a-d). General procedure. A mixture of **2**⁹ (179 mg, 1 mmol), the appropriate alkyl halide (1 to 2 mmol, see Table 1) and DMF (2 ml) was stirred and heated at 150 °C until the reaction was complete (tlc control) (5-18 h). Then a mixture of conc. hydrochloric acid/water (1:1, v/v, 10 ml) was added and refluxing for one h. After cooling the insoluble material was filtered off. Column chromatography (chloroform/methanol, 10:1) afforded the pure products.

2-Benzyl-5-nitro-1,2-dihydro-3H-indazol-3-one (4a). mp: 174 - 175 °C (from 2-propanol). ¹H Nmr (300 MHz, DMSO-*d*₆): δ = 5.08 (s, 2H, CH₂), 7.20-7.45 (m, 6H, H-7 and Ph), 8.25 (dd, *J* = 9 and 2, 1H, H-6), 8.50 (d, *J* = 2, 1H, H-4). ¹³C Nmr (75 MHz, DMSO-*d*₆): δ = 46.88 (CH₂), 111.95 (C-7), 114.29 (C-3a), 120.57 (C-4), 126.04 (C-6), 127.52 (C-*para*), 127.69 (C-*ortho*), 128.58 (C-*meta*), 136.06 (C-*ipso*), 140.40 (C-5), 145.80 (C-7a), 158.71 (C-3). *Anal.* Calcd for C₁₃H₁₀N₃O₃, C 60.94, H 3.93, N 16.40. Found C 60.85, H 4.04, N 16.32.

2-Butyl-5-nitro-1,2-dihydro-3H-indazol-3-one (4b). Isolated as an orange oil. ¹H Nmr (300 MHz): δ = 0.91 (t, *J* = 7.3, 3H, CH₃), 1.36 (sext, *J* = 7.3, 2H, CH₂-3'), 1.83 (quint, *J* = 7.3, 2H, CH₂-2'), 4.05 (t, *J* = 7.3, 2H, CH₂-1'), 7.30 (d, *J* = 9, 1H, H-7), 8.32 (dd, *J* = 9.1 and 2, 1H, H-6), 8.66 (d, *J* = 2, 1H, H-4). ¹³C Nmr (75 MHz): δ = 13.49 (C-4'), 19.83 (C-3'), 30.36 (C-2'), 44.36 (C-1'), 111.94 (C-7), 116.44 (C-3a), 120.98 (C-4), 126.59 (C-6), 142.21 (C-5), 146.84 (C-7a), 160.07 (C-3). *Anal.* Calcd for C₁₀H₁₂N₃O₃, C 53.81, H 5.87, N 18.82. Found; C 53.56, H 5.67, N 18.65.

5-Nitro-2-octyl-1,2-dihydro-3H-indazol-3-one (4c). Isolated as a pale yellow solid. mp: 124 - 125 °C (from ethyl acetate). ¹H Nmr (300 MHz): δ = 0.85 (t, *J* = 6.7, 3H, CH₃), 1.18 - 1.41 (m, 10H, 5xCH₂), 1.79 (quint, *J* = 7.3, 2H, CH₂-2'), 3.96 (t, *J* = 7.3, 2H, CH₂-1'), 7.30 (d, *J* = 9.1, 1H, H-7), 8.37 (dd, *J* = 8.9 and 1.9, 1H, H-6), 8.75 (d, *J* = 1.9, 1H, H-4). ¹³C Nmr (75 MHz): δ = 14.02 (C-8'), 22.57 (C-7'), 26.67 (C-2'), 28.25 (C-3'), 29.08 (C-4' and C-5'), 31.70 (C-6'), 44.70 (C-1'), 112.22 (C-7), 118.37 (C-3a), 121.20 (C-4), 126.83 (C-6), 143.09 (C-5), 148.02 (C-7a), 160.58 (C-3). *Anal.* Calcd for C₁₄H₂₁N₃O₃, C 60.20, H 7.58, N 15.04. Found; C 60.40, H 7.39, N 15.07.

2-Hexadecyl-5-nitro-1,2-dihydro-3H-indazol-3-one (4d). Isolated as pale yellow needles. mp: 127 - 128

°C (decomp.) (from toluene). ^1H Nmr (300 MHz, DMSO- d_6): δ = 0.83 (t, J = 6.7, 3H, CH_3), 1.18 - 1.25 (m, 26H, $13 \times \text{CH}_2$) 1.69 (quint, J = 6.6, 2H, CH_2 -2'), 3.86 (t, J = 6.6, 2H, CH_2 -1'), 7.34 (d, J = 9.1, 1H, H-7). 8.21 (dd, J = 9 and 2.1, 1H, H-6), 8.46 (d, J = 2.1, 1H, H-4). ^{13}C Nmr (75 MHz, DMSO- d_6): δ = 13.86 (C-16'), 22.04 (C-15'), 25.86 (C-2'), 27.72, 28.38, 28.64, 28.78, 28.85, 28.93 and 28.97 (C-3' to C-14'), 43.31 (C-1'), 111.85 (C-7), 114.18 (C-3a), 120.46 (C-4), 125.39 (C-6), 139.95 (C-5), 145.50 (C-7a), 158.18 (C-3). *Anal.* Calcd for $\text{C}_{22}\text{H}_{37}\text{N}_3\text{O}_3$; C 67.49, H 9.52, N 10.73. Found; C 67.40, H 9.59, N 10.85.

2-Nitro-6,11-dihydro-13H-indazolo[1,2-b]phthalazin-13-one (9). A mixture of **2** (179 mg, 1 mmol), α,α' -dibromo-*o*-xylene (264 mg, 1 mmol) and DMF (2 ml) was stirred and heated at 150 °C for 5 h. Then a mixture of conc. hydrochloric acid/water (1:1, v/v, 10 ml) was added and refluxed for one h. The resulting solid was collected by filtration. Recrystallization from acetone yielded 270 mg (95%) of **9**, mp: 212 - 214 °C. ^1H Nmr (300 MHz): δ = 4.85 (s, 2H, CH_2 -6), 5.11 (s, 2H, CH_2 -11), 7.28 - 7.43 (m, 5H, H-4 and H-7 to H-10), 8.48 (dd, J = 9 and 2.3, 1H, H-3), 8.84 (d, J = 2.3, 1H, H-1). ^{13}C Nmr (75 MHz): δ = 43.85 (C-11), 50.48 (C-6), 111.36 (C-4), 118.77 (C-13a), 121.43 (C-1), 126.54, 126.96, 127.35, 127.76, 127.94, 128.28 and 128.31 (C-3, C-6a, C-7 to C-10, and C-10a), 143.25 (C-2), 150.69 (C-4a), 161.13 (C-13). *Anal.* Calcd for $\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_3$; C 64.05, H 3.94, N 14.94. Found; C 64.01, H 3.77, N 14.92.

ACKNOWLEDGMENTS

Financial support by the Spanish DGICYT (PB94-0742) is gratefully acknowledged.

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Received, 13th September, 1996