Synthetic Approaches Towards some New 1,2-Dihydro-2-(heterocyclyl)-3H-indazol-3-ones

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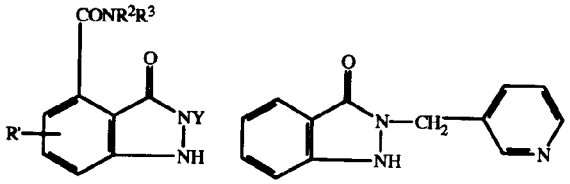
(Received 15th October, 1994, revised Ist July, 1995)

Summary: Two different synthetic approaches *viz.* reductive cyclization of N-heterocyclyl-2-nitrobenzanilides (**3**) and the base catalysed cyclization of 2-azido-N-heterocyclylbenzanilides (**7**) were adopted towards some new 2-heterocyclylindazol-3-ones (**4**). However, both methods proved to be less successful and based upon the results of these investigations, a safe strategy involving the heteroarylation at N-2 of the 1-carboethoxyindazolone giving (**8**) followed by deprotection at N-1 to furnish (**4**) was suggested for preparation of 2-heterocyclyindazolones.

Introduction

2-Substituted indazolones [1] are an important class of heterocycles which finds a number of useful application.

Colour couplers of indazolinone type had long been used to produce colour photographic images. Thus, 5-(steraroylamino)-3-indazolinone is major ingredient of an emulsion for positive motion picture films [2]. Indazolone derivatives were tested for antihyperlipodemic activity [3] in male mice. The N-2-butylindazolone was the most active compound. 4-carbamoylindazol-3-ones [4] (**1**). (R^1= H, alkyl, alkoxy halo, OH, CN, CF_3: R^2=H, alkyl: R^3=H, alkyl, alkenyl) are potent 5-lipoxygenase (5-LPO) inhibitors. Thus, 1,2-dihyro-2-methyl-4-(pentylcarbamoyl)-3H-indazol-3-one had ED_{50} of 30-100 mg/kg orally in rats for 5-LPO inhibition.



(1) (2)

1,2-Dihydroindazol-3-ones are potent 5-lipoxygenase inhibitors [5,6] with various degrees of selectivity. Structure activity relationship (SAR) studied indicated that while N-1, N-2 unsubstituted derivatives and N-1 substituted derivatives are orally inactive. N-2-alkyl derivatives are orally active and inhibit both 5-LPO and cyclogenase (CO). In contrast, N-2-benzyl derivatives are selective for 5-LPO but possess weak oral activity. Some of the 2-methylheterocyclyl derivatives were also studied. In particular the 1,2dihydro-2-(3-pyridylmethyl)-3H-indazol-3- one (**2**) was a highly selective, potent orally active inhibitor of 5-LPO and should be a useful agent for elucidating the *in vivo* roles of leukotrienes.

Thermal transfer sheets containing inks coloured with indazolonederivatives have been patented [7]. An ink containing 6-chloro-3-indazolinone gave images with good storage stability and good light resistance.

We have already reported [8] the convenient synthesis of 2-arylindazoloines by reductive cyclization of N-aryl-2-nitrobenzanilide using zinc and sodium hydroxide. The easy access to 2-arylindazolones by reductive cyclization prompted the attempts to synthesize the 2-heteroaryl indazolones by a similar possible cyclization of 2-nitro-N-heterocyclylanilides.

Reductive cyclization of N-heterocyclyl-2-nitrobenzanilides (A)

The attempts to extend the zinc-sodium hydroxide-methanol reductive cyclization procedure to the synthesis of 2-hetero-cyclyl-1,2-dihydro-3H-indazoline-3-ones (**4**) from the N-heterocyclyl-2-nitrobenzanilides (**3**) were carried out. Thus, anilides (**3,a-p**) were prepared by reaction of 2-nitrobenzoyl chloride with heterocyclyl amines in dry pyridine followed by recrystallization from

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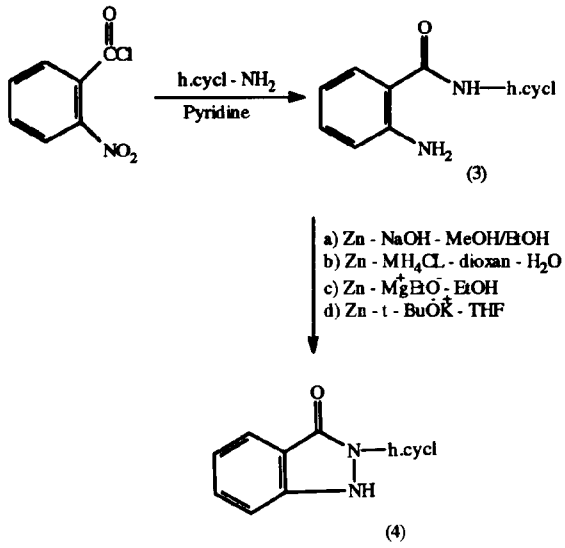
appropriate solvent, Table-1 gives the physical data for these compounds.



Scheme-1

2-Nitrobenzanilides are beautifully coloured, nicely crystalline compounds [9,10]. IR shows broad peak for -CONH at 3230-3330 cm^{-1} distinct and sharp peaks at 1602-1650 cm^{-1} and 1530-1535 cm^{-1} for CO and NO_2 stretching vibrations respectively. Whereas the 2-nitro-N-arylbenzanilides rearrange to 2-(2-hydroxyphenylazo)benzoic acids on exposure to light [11] these heterobenzanilides were quite stable towards light and had good thermal stability as indicated by their high melting points (Table-1).

Table-1: 2-Nitro-N-heterocyclylbenzanilides (3).

(3)	N-(heterocyclyl)	m.p.°	yield (%)	Recryst solvent(s)
a	2,5-thiazolyl	243-245	64.5	DMF-ethanol
b	1,3,4-thiadiazolyl	222-224	14.5	DMF
c	1,2,4-Triazolyl	136-139	54.0	DMF
d	2,3,4,5-tetrazolyl	276	58.5	H_2O
e	2-benzothiazolyl	206-208	53.5	ethanol
f	2-benzimidazolyl	184-189	62.5	ethanol
g	8-quinolinyl	195-196	80.5	ethyl acetate
h	2-pyridyl	135-137	57.6	DMF-H_2O
i	3-pyridyl	85-88	54.4	ethanol
k.	4-pyridyl	216-218	52.5	DMF-H_2O
l	methyl(3-pyridyl)	120-122	51.5	ethyl acetate
m	2,5-pyrimidyl	144-146	56.5	DMF-H_2O
n	2,6-pyrimidyl	173-175	64.5	DMF-H_2O
o	3,5-dimethyl-2,6-pyrimidyl	134-136	30.0	ethanol
p	cyclohexyl	145-146	56.5	ethanol

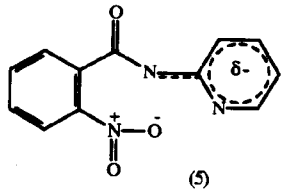
Following procedure for reductive cyclization of these heterocyclyl anilides were tried on different substrates with variable reflux time and other conditions. Unlike 2-nitro-N-arylbenzanilides which are quite soluble in ethanol. Most of the heterocyclyl-2-nitrobenzanilides are soluble only in DMF and not even in dioxan or glyme (Table-1) therefore, substrate insolubility was a major problem.

Chart-1 summarise the results of the different reagents and the reaction conditions employed.

Chart-1

Reagents used	Observations; comments
1. Zn-NaOH-MeOH/EtOH [8]	Only one or two anilides (3) could be cyclized to (4) while majority of them hydrolysed back to 2-nitro-benzoic acid and the amines.
2. Zn-NH_4Cl. dioxan-H_2O [12]	Reduction of -NO_2 to NHOH stage occurred successfully but further cyclodehydration to (4) could not be achieved.
3. Zn-MeOMg/EtOMg MeOH/EtOH	Employed as non-hydrolytic reductive cyclization conditions but resulted in unidentized products.
4. Zn-t-BuO -K'+-dry THF	Non-hydrolytic conditions but there was no evidence of reduction resulted in complicated products.

A probable reason for failure of heterobenzanilides to cyclize, might be the electron withdrawing nature of the ring nitrogens, resulting in the engagement of negative charge (produced by removal of proton by the base) as shown in intermediate (5) which is not longer available for attack to the electrophilic centre.



(5)

A good check to this hypthesis can be made by using the thiophen, furan or pyrrole type derivatives in which the heteroatoms are known to be electron donating; however, such amines are not readily available, the idea could not be tested.

It was therefore decided to test the Ardakani and Smalley method [12,13] involving base induced cyclization of o-azidobenzanilides.

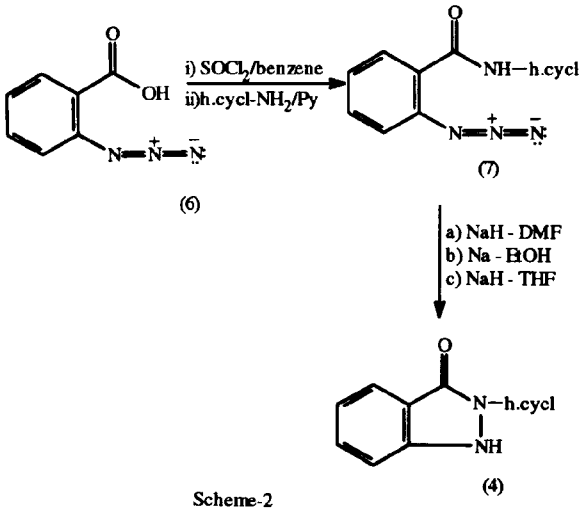
Cyclization of N-(o-azidobenzoyl)heteroaryl amines: (Route B)

This procedure starts with the synthesis of o-azidobenzoic acid from anthranilic acid. Thus, anthranilic acid (2-aminobenzoic acid) was converted into diazonium salt by reaction with sodium nitrite in dilute sulfuric acid at 0-5°C. The diazonium salt was then treated with sodium azide, thereby replacing the diazo-with the azido group to furnish the 2-azidobenzoic acid (**6**). The acid was converted to 2-azidobenzoyl chloride by reaction with thionyl chloride. Treatment of heterocyclyl amines with 2-azidobenzoyl chloride in dry pyridine afforded the 2-azidoheterocyclylbenzanilides (**7**). These are crystalline compound with sharp melting points (Table-2).

Table-2: 2-Azido-N-heterocyclylbenzanilides (7)

(7)	N-(heterocyclyl)	m.p. °C	yield (%)	Solvent
a	2-(1,3-thiazolyl)	154-155	55.5	ethanol
b	2-(1,3,4-thiadiazolyl)	160	59.1	ethanol
c	2-(1,3,4-triazolyl)	158-161	43.5	ethanol
d	5-(1,2,3,4-tetrazolyl)	a	–	–
e	2-(1,3-benzothiazolyl)	171-172	38.0	ethanol
f	2-(1,3-benzimidazolyl)	133-135	29.5	ethanol-water
g	1-(8-quinolinyl)	128	80.5	ethanol
h	2-pyridyl	62	74.0	ethyl acetate
i	3-pyridyl	90-92	72.5	ethanol
j	3-pyridylmethyl	140-142	51.5	ethyl acetate
k	2,5-pyrimidyl	b	–	–
l	2,6-pyrimidyl	118-119	34.0	ethyl acetate
m	3,5-dimethyl-2,6-pyrimidyl	141-142	21.9	ethanol
n	3,4-dimethylphenyl	198-200	30.0	ethanol
o	p-(N,N-diethyl-aminophenyl	62-64	52.0	ethanol

a-sticky product; b-very poor yield



Scheme-2

IR shows broad peak for -CONH at 3230-3330 cm^{-1}, a strong absorption at 2110-2120 cm^{-1} for azido group in addition to the carbonyl absorption at 1650 cm^{-1}.

The method was first established by cyclization of 2-azidobenzoyl-N-(3,5.-dimethylphenyl)-anilide to 2-(3',5'-dimethylphenyl)1,2-dihydro-indazolin-3-one in 30% yield giving a clean products.

The cyclization of 2-azidoheterocyclylanilides were carried out using sodium hydride in dry DMF. In cases where the cyclization did not seem to occur using NaH-DMF, the experiments were repeated using sodium hydride in dry tetrahedrofuran (THF), sodium in ethanol, and potassium hydroxide in ethanol (all at reflux temperature) as suggested by the Ardakani and Smalley [13].

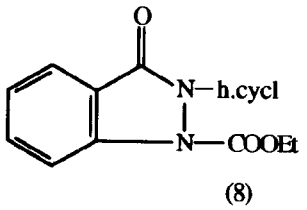
The results of these investigations, (summarized in Table-3) clearly suggest that both of the procedures viz. reductive cyclization of 2-nitrobenzanilides or base induced cyclization of 2-azidobenzanilides although valuable in the synthesis of 2-arylindazolones, did not prove to be good for synthesis of 2-heterocyclylindazolones.

Table-3: 1,2-Dihydro-2-(heterocyclyl)-3H-indazol-3-ones (4)*

(4)	2-(heterocyclic)	m.p.°	yield (%)	method
e	2-benzothiazolyl	246-248	78.0	B
h	2-pyridyl	200-201	94.5	B
i	3-pyridyl	90-92	72.5	B
j	methyl(3-pyridyl)	181-182	51.5	A
o	3,4-dimethylphenyl	198-200	30.0	A,B

*only the confirmed products mentioned.

It could be concluded that the best approach towards the synthesis of 2-heteroaryl derivatives should involve, first the protection of N-1 of unsubstituted 1,2-dihydro-3H-indozol-3-one by carboethoxylation followed by treatment with appropriate heterocyclyl halides to produce (**8**) and subsequent hydrolytic removal of carboethoxy



(8)

h.cycl = heterocyclyl

group to (4). By application of this procedure nitro- and cyano-substituted aryl derivatives could also be synthesized (difficult to obtain by other routes) which should prove useful to study the effects of these substituents on thermal rearrangements [14] of 2-substituted aryl indazolones.

Experimental

Melting points were determined using a MEL-TEMP MP-D apparatus and are uncorrected. The IR spectra were recorded on a Hitachi spectrophotometer Model-270 as KBr dises or as neat liquids.

(Reductive cyclization of 2-nitro-N-heterocyclyl-benzanilides)

Route A

N-heterocyclyl-2-nitrobenzanilides (3a,-p)

2-Nitrobenzoylchloride (5.56g.0.030 mol) was added drop wise to a cold solution of appropriate heteroarylamine (0.03mol) in dry pyridine (25 ml). The mixture was stirred for 20-25 minutes and then poured into cold water (200 ml) to precipitate the N-(2-nitrobenzoyl)heterocyclyl-amines (**3a-p**).

Melting points, percent yields, recrystallization solvent are given in Table-1.

General procedure for cyclization to 2-Arylindazolones

Solution of N-aryl-2-nitrobenzanilides (3a-l,0.2 ml) in methanol (55 ml) (or in ethanol) and sodium hydroxide (3.32g, 0.083 mol) in water (76 ml) were mixed with sitrring, treated with zinc powder (3.92 g, 0.06 mol) and heated under reflux with stirring, for 13-15 hours. The reaction mixtures were filtered while hot to remove the inorganic material, concentrated to half their volumes and diluted with water. Any unreacted starting materials were filtered off, and the filtrates cooled in ice. On acidification of the latter with 1M sulfuric acid, the products were directly precipitated or in some cases the acidified filtrates were extracted with ethylacetate, dried (Na_2SO_4) and solvent rotary evaporated to leave brownish solids which were precipitated with ethyl acetate-petroleum ether to afforded the indazolones.

2-Azidobenzoylchloride (6)

Thionyl chloride (25 ml, 0.34 mol) was added dropwise to a solution of 2-azidobenzoic acid (3) (40g, 0.245 mol) in dry benzene (250 ml). After reflux for one hour, the solvent and excess of thionyl chloride was rotary evaporated to afford 2-azidobenzoylchloride (**6**) (35.5g, 0.196 mol, 80%) which was stored in dark, cool place. IR (KBr): 2100.1770 cm-1.

Preparation of N-(2-azidobenzoyl)-heterocyclyl-amine (7)

2-Azidobenzoylchloride (**6**) (0.01 mol) was added dropwise to a cold solution of heterocyclyl amines (0.011 mol) in pyridine (25 ml). The mixture was stirred for 15 min., then poured into cold water (200 ml) to precipitate the N-(2-azidobenzoyl)heterocyclylamines (**7,a-o**). Recrystallized from aqueous ethanol (Table-2).

General procedure for cyclization to 2-heterocyclylindazolones

N-(2-azidobenzoyl)heterocyclylamine (**7**) (0.5 g) were heated with sodium hydride (0.6g) in dry N,N-dimethylformamide (15 ml) at 80°C for 3 h. Loss of nitrogen was observed and the reaction mixture diluted with water and the solid filtered off. Recrystallization with ethyl acetate-petroleum ether afforded 2-heterocyclylindazol-3-ones (**4**) (Table-3).

References

1. Baiocchi, G. Gorsi and G. Palazzo, *Synthesis*, 641 (1978).
2. J.J. Jacob, *U.S.* **2**, 673, 801 (1954).
3. S.D. Wyrick, P.J. Voorstad, G. Cocolas and I.R. Hall, *J. Med. Chem.*, **27**, 768 (1984).
4. S.J. Foster, P. Bruneau, H.R.E.Walker and R.M. McMillan, Br. *J. Pharmacol.*, **99**, 113 (1990).
5. P. Bruneau and R. Andre, *Eur. Pat. Appl.* EP **355**, 970 (Cl.CO7D231/56) (1990): *Chem. Abstr.*, **113**:78384z (1990).
6. R.M. McMillan and S.J. Foster, *Agents and Action*, **24**, 114 (1988).
7. J. Sugafuji, H. Saito, N. Nistani, *Jpn. Kokai Tokkyo Koho* JP 02 32, 894 [90, 32, 894] (1988).
8. C.W. Bird, C.J. Chng, N.H. Rama and Aamer

Saeed, *Synth. Commun.*, **21** (4), 545 (1991).
9. P. Grammaticakis, *Bull. Soc. Chim. Fr.*, 1956 (1960).
10. C.R. Clark, C.M. Lin and R.T. Sanson, *J.Med. Chem.*, **29**, 1534 (1986).
11. B.C. Gunn and M.F.G. Stevens, *J. Chem. Soc. Perkin Trans. 1*, 1682 (1973).
12. C.W. Bird and M. Latif, *Tetrahedron*, **36**, 529 (1980).
13. M.A. Ardakani and R.K. Smalley, *Tetrahedron Lett.*, 4765 (1979).
14. T. Kametani, K. Sota and M. Shio, *J. Heterocycl. Chem.*, **7**, 815 (1970); C.W. Bird, *Tetrahedron*, **21**, 2179 (1965).