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Synthesis of some novel N-arylhydrazone derivatives of N-phenyl anthranilic acid

Bharat Parashar[1]*, P. B. Punjabi[1], G. D. Gupta[2] and V. K. Sharma[1]

[1]Department of Chemistry, M. L. S. University, Udaipur, (Rajasthan), India.
[2]ASBASJSM college of Pharmacy, Ropar, Punjab, India.

**E-mail: bharat.research@gmail.com*

ABSTRACT: A series of N-Arylhydrazone derivatives of N-phenyl anthranilic acid were synthesized by starting with esterification of N-phenyl anthranilic acid followed by reaction with hydrazine hydrate to yield hydrazide derivative. The target compounds were synthesized by acid-catalyzed condensation of the hydrazide **2** with the corresponding aromatic ketone/aldehydes and their structures were confirmed by physico-chemical and spectral data like IR and NMR.
KEYWORDS: Hydrazones, hydrazide-hydrazones and N-phenyl anthranilic acid.

INTRODUCTION

Hydrazones possessing an azometine -NHN=CH- proton constitute an important class of compounds for new drug development. Therefore, many researchers have synthesized these compounds as target structures. These observations have been guiding for the development of new hydrazones that possess varied biological activities. Hydrazide-hydrazones compounds are not only intermediate but they are also very effective organic compounds in their own right. Hydrazones have been demonstrated to possess, among other, antimicrobial[1], antimycobacterial[2], antidepressant[3], anticonvulsant[4], analgesic-anti-inflammatory[5], antimalarial[6-7], leishmanicidal[8], anticancer[9], antiviral[10] and vasodilator activities[11]. So in the present communication, some novel N-arylhydrazone derivatives of N-phenyl anthranilic acid were synthesized.

EXPERIMENTAL

Melting points were determined by open capillary method and are uncorrected. The purity of the compounds was ascertained by percolated TLC using silica gel G. The spots were visualized by using iodine vapors. The IR spectra were recorded on Perkin- Elmer I.R. Spectrophotometer. The ^{1}HNMR spectra were obtained using a Brucker DRX300 MHz spectrophotometer.

Synthesis of methyl 2-(phenyl amino) benzoate(1):

N-phenyl anthranilic acid (3mmol) in acetone was refluxed with dimethyl sulphate (6mmole) and potassium carbonate (3mole) on a water bath for 2hrs. The reaction mixture was allowed to cool at room temperature and inorganic salt was filtered off. The filtrate was concentrated and poured into crushed ice. The precipitate was filtered and recrystallized with ethanol.

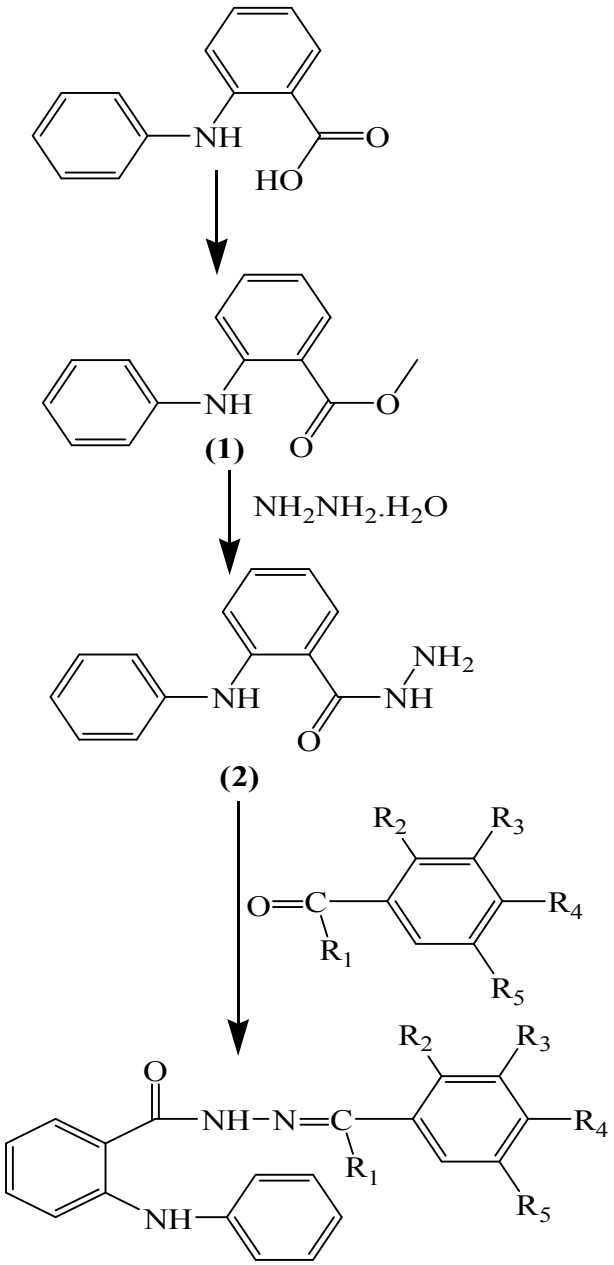
Synthesis of 2-(phenylamino)benzohydrazide(2):

A solution of **1** (3mmole) in ethanol and refluxed with 99% hydrazine hydrate (6mmole) for 4 hrs and poured into ice cold water. The precipitate was filtered and recrystallized with diethyl ether.

Synthesis of N-arylhydrazone derivatives of N-phenyl anthranilic acid (3a-3j):

A mixture of 1.9 mmol of hydrazide **2** and 1.9 mmol of the corresponding aldehyde/ ketone derivative in 20 ml of absolute ethanol was stirred at room temperature for 0.5 to 1h, in the presence of two drops of conc. hydrochloric acid as a catalyst. The end of the reaction was observed by TLC, and the hydrazones **3a-3j** were isolated by concentration of the reaction mixture under reduced pressure, followed by neutralization with a 10% aqueous solution of sodium bicarbonate. The resulting precipitate was filtered, washed with 10 ml water and crystallized from a suitable solvent.

SCHEME-1

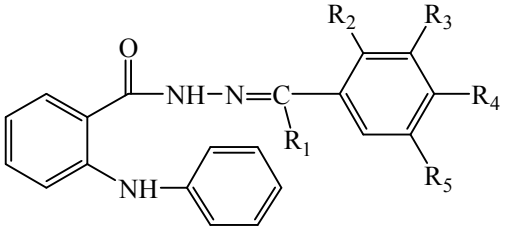


(3a-3j)

RESULTS AND DISCUSSION

The structures of the synthesized compounds were confirmed by thin layer chromatography (TLC), mp, I.R. and ^{1}H N.M.R. spectral analysis. The compounds (3a-3j) were obtained by the treatment of N-phenyl anthranilic acid with dimethyl sulphate in the presence of acetone and potassium carbonate yields methyl 2-(phenyl amino) benzoate (1). The compound 1, on further treatment with hydrazine hydrate in ethanol, affords 2-(phenylamino)benzohydrazide(2) and finally hydrazide reacted with different aromatic aldehyde/ketones in the presence of catalytic amount of conc. hydrochloric acid yields different N-arylhydrazone derivatives of N-phenyl anthranilic acid (Scheme 1). The yield was found to be in the range of 62-78%. The compound 3a was confirmed by IR spectral data showing characteristic bands at 3423 and 3325 cm^{-1} indicating the presence of two –NH groups and sharp band at 1515 cm^{-1} indicated the presence of C=N group. Compound 3e showed the presence of –OCH_3 group by indicating a sharp peak at 1193 cm^{-1}. The NMR proton singlet peak at δ 9.124-9.156 ppm and 8.009 ppm revealed the presence of both –NH groups.

Table 1: Physical constants of N-arylhydrazone derivatives of N-phenyl anthranilic acid



Compound	R_1	R_2	R_3	R_4	R_5	Mol. Formula	M. Wt.	R_f	M.P. (°C)	Yield (%)
3a	H	H	H	H	H	$C_{20}H_{17}N_3O$	315	0.62	180	73
3b	H	OH	H	H	H	$C_{20}H_{17}N_3O_2$	331	0.57	155	76
3c	H	H	H	OH	H	$C_{20}H_{17}N_3O_2$	331	0.52	216	68
3d	H	H	OMe	OH	H	$C_{21}H_{19}N_3O_3$	361	0.41	160	78
3e	H	Br	OH	OMe	H	$C_{21}H_{18}BrN_3O_3$	440	0.70	235	64
3f	H	H	OH	OMe	H	$C_{21}H_{19}N_3O_3$	361	0.68	206	72
3g	H	H	H	Cl	H	$C_{20}H_{16}ClN_3O$	349	0.44	180	66
3h	H	H	H	$N(Me)_2$	H	$C_{22}H_{22}N_4O$	358	0.54	242	62
3i	H	OH	$C(Me)_3$	H	$C(Me)_3$	$C_{28}H_{33}N_3O_2$	444	0.42	196	69
3j	Me	H	H	H	H	$C_{21}H_{19}N_3O$	329	0.56	187	73

TABLE 2: Spectral data of N-arylhydrazone derivatives of N-phenyl anthranilic acid

3a	IR (cm^{-1}): 1699 (C=O), 3423, 3325 (NH), 1515 (C=N), 2956 (Ar-CH) ^{1}HNMR (δ ppm) : 6.774-7.747 (m, 13 H, Ar), 9.114-9.32 (bs, 1H, NH), 8.147 (s, 1H, NH), 1.613 (s, 1H, CH)
3b	IR (cm^{-1}): 1691 (C=O), 3371, 3213 (NH), 1560 (C=N), 3548 (OH), 2929 (Ar-CH) ^{1}HNMR (δ ppm) : 6.71-7.62 (m, 13H, Ar), 9.325 (s,1H, NH), 8.41 (s,1H, NH),2.997 (s,1H, CH), 11.52-11.81 (s,1H, OH)
3c	IR (cm^{-1}): 1693 (C=O), 3315, 3267 (NH), 1552 (C=N), 3465 (OH), 2939 (Ar-CH) ^{1}HNMR (δ ppm) : 6.722-7.819 (m,13H, Ar), 8.236 (s,1H, NH), 9.299-9.523 (bs,1H, NH), 3.236 (s,1H, CH), 11.543 (s,1H,OH)
3d	IR (cm^{-1}): 1701 (C=O), 3301, 3195 (NH), 1546 (CH), 3469 (OH), 3031 (Ar-CH) ^{1}HNMR (δ ppm) : 6.784-7.525 (m, 13H, Ar), 8.331(s, 1H, NH), 8.031 (s, 1H, NH), 1.568 (s, 1H, CH), 9.101 (s, 1H, OH), 3.913-3.956 (s, 3H, CH_3)
3e	IR (cm^{-1}): 1693 (C=O), 3251, 3128 (NH), 1552 (C=N), 3556 (OH), 1193 (OCH_3), 3105 (Ar-CH) ^{1}HNMR (δ ppm) : 6.734- 7.865 (m,11H, Ar), 8.712 (s, 1H, NH), 9.124-9.394 (bs, 1H, NH), 2.479 (s, 1H, CH), 11.868 (s, 1H, OH), 3.22-3.879 (m, 3H, CH_3)
3f	IR (cm^{-1}): 1701 (C=O), 3369, 3249 (NH), 1519 (C=N), 3591 (OH), 1192 (OCH_3) ^{1}HNMR (δ ppm) : 6.967-7.003 (m, 12H, Ar), 9.259 (s, 1H, NH), 8.742(s, 1H, NH), 2.413 (s, 1H, CH), 11.311-11.504 (s, 1H, OH), 3.177-3.8 (s, 1H, CH_3)
3g	IR (cm^{-1}): 1679 (C=O), 3364 (NH), 1632 (C=N), 736 (C-Cl), 2923 (Ar-CH) ^{1}HNMR (δ ppm) : 6.77-7.783 (m, 13H, Ar), 9.306-9.308 (bs, 1H, NH), 8.116 (s, 1H, NH), 1.253 (s, 1H, CH)
3h	IR (cm^{-1}): 1699 (C=O), 3359, 3184 (NH), 1598 (C=N), 1363 ($N(CH_3)_2$), 3037 (Ar-CH) ^{1}HNMR (δ ppm) : 6.969-7.700 (m,13H, Ar), 9.124-9.156 (bs,1H, NH), 8.009 (s, 1H, NH), 3.025-3.079 (s, 1H, CH), 6.697- 6.797 (m, 6H, CH_3)
3i	IR (cm^{-1}): 1685 (C=O), 3157 (NH), 3396 (OH), 1630 (C=N), 2869 ($(CH_3)_3$), 2951 (Ar-CH) ^{1}HNMR (δ ppm) : 6.728-7.671 (m, 11H, Ar), 11.772-11.871 (bs, 1H, NH), 9.354 (s, 1H, NH), 1.369 (s, 1H, CH), 12.040 (s, 1H, OH), 3.133 (s, 9H, $CH_3)_3$, 1.247 (s, 9H, $(CH_3)_3$)
3j	IR (cm^{-1}): 1676 (C=O), 3366 (NH), 1633 (C=N), 2971 (Ar-CH), 2864 (CH_3) ^{1}HNMR (δ ppm) : 6.820-7.608 (m, 14H, Ar), 9.084-8.985 (bs,1H, NH), 7.838 (s, 1H, NH), 2.322 (s, 3H, CH_3)

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