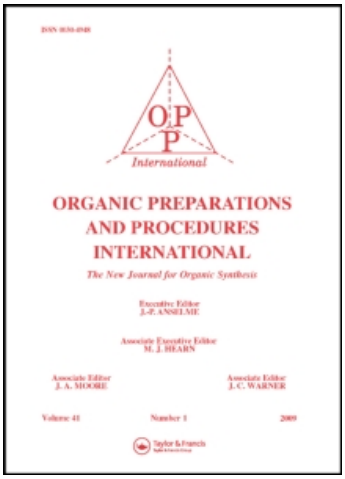


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A CONVENIENT METHOD FOR SYNTHESIS OF 4 (3H)-QUINAZOLINONES

Takuzo Hisano[a]; Kiyokatsu Shoji[a]; Masataka Ichikawa[a]
[a] Faculty of Pharmaceutical Sciences, Kumamoto University, Kumamoto, JAPAN

To cite this Article Hisano, Takuzo , Shoji, Kiyokatsu and Ichikawa, Masataka(1975) 'A CONVENIENT METHOD FOR SYNTHESIS OF 4 (3H)-QUINAZOLINONES', Organic Preparations and Procedures International, 7: 6, 271 — 275
To link to this Article: DOI: 10.1080/00304947509355161
URL: http://dx.doi.org/10.1080/00304947509355161

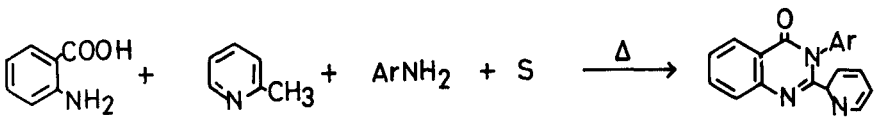
ORGANIC PREPARATIONS AND PROCEDURES INT. 7(6), 271-275 (1975)

A CONVENIENT METHOD FOR SYNTHESIS OF 4(3H)-QUINAZOLINONES

Takuzo Hisano*, Kiyokatsu Shoji and Masataka Ichikawa

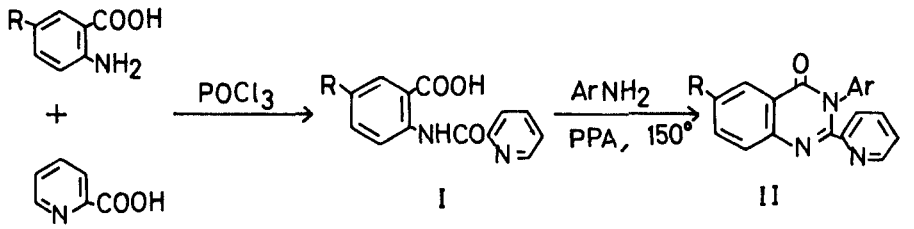
Faculty of Pharmaceutical Sciences, Kumamoto University
5-1 Oe-honmachi, Kumamoto 862, JAPAN

Efforts to prepare a series of 2-pyridyl-3-phenyl-4(3H)-quinazolinone by reactions between anthranilic acid, picolines, and anilines in the presence of sulfur[1] have enjoyed only limited success. For example, dechlorination occurred during the cyclization of chloroanilines in this reaction and gave preferentially dechlorinated quinazolinones. The ease of dechlorination varies with the position of chlorine atom in the aniline and decreases in order of ortho, meta and para.[2]



A similar attempt for obtaining nitroquinazolinones by use of nitroanthranilic acids has also failed completely. Other attempts to obtain the quinazolinones by condensations of 2-picolinoylaminobenzoic acids (I) with anilines in the presence of phosphorus trichloride have proved unsatisfactory when applied to 3-ortho-substituted phenyl derivatives of the quinazolinones. We have found, however, that the latter compounds are obtained smoothly and in yields three times

greater than those obtained by the previous methods and by the condensation of 2-picolinoylaminobenzoic acids (I) with anilines in the presence of polyphosphoric acid (PPA).

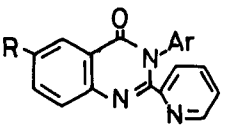


The 2-(2-pyridyl)-3-substituted-phenyl-4(3H)-quinazolinones (II) prepared by this method are recorded. The structural assignments of the quinazolinones are based on satisfactory elemental analyses and IR spectra [1670-1690 cm^{-1}(C=O)] as already described.[3]

EXPERIMENTAL

2-Picolinoylaminobenzoic Acid (I).- To a mixture of 13.7 g. (0.1 mole) of anthranilic acid and 13.5 g. (0.11 mole) of 2-picolinic acid in 25 ml. of toluene, 15 ml. (0.16 mole) of $POCl_3$ was added dropwise at room temperature with stirring and the mixture was then heated in an oil bath under reflux for 30 min. After cooling in an ice bath, a crystalline mass was collected by suction and dissolved in 10% aq. Na_2CO_3 soln. The alkaline solution was neutralized with 10% HCl and the resulting crystals were collected by suction, washed with H_2O, dried and recrystallized from H_2O-MeOH, giving 2-picolinoylaminobenzoic acid as colorless prisms, mp. 176-177°, in 76% yield.

Table I



Compound	R	Ar	MP(lit.) (°C)	Yields(%) Sulfur	PCl_3	PPA
IIa	H	o-ClPh	170	-	-	60.1
IIb	H	m-ClPh	155(155)[2]	7.5[2]	-	54.3
IIc	H	p-ClPh	195(195)[2]	10.8[2]	-	34.1
IId	H	o-NO_2Ph	150-151	-	14.1	48.6
IIe	H	m-NO_2Ph	188-189	-	84.5	36.6
IIf	H	p-NO_2Ph	194-195	-	11.6	29.6
IIg	NO_2	o-NO_2Ph	202-203	-	8.2	30.0
IIh	NO_2	m-NO_2Ph	284-285	-	66.7	-
IIi	NO_2	p-NO_2Ph	250-251	-	54.4	-

Compd.	Appearance ():recryst. solvent	Formula	Analysis(%) Calcd. (Found) C	H	N
IIa	colorless needles (ether-pet ether)	$C_{19}H_{12}O_3N_3Cl$	68.37 (68.20)	3.62 (3.43)	12.59 (12.63)
IId	yellow needles (pet ether)	$C_{19}H_{12}O_3N_4$	66.38 (66.62)	3.49 (3.34)	16.28 (16.13)
IIe	pale yellow needles (EtOH)		(66.72)	(3.62)	(16.27)
IIf	pale yellow plates (EtOH)		(66.07)	(3.77)	(16.10)
IIg	pale yellow needles (EtOH)	$C_{19}H_{11}O_5N_5$	58.61 (58.40)	2.82 (2.87)	17.99 (17.72)
IIh	pale yellow needles (EtOH)		(58.59)	(2.86)	(17.73)
IIi	pale yellow needles (EtOH)		(58.67)	(2.78)	(17.63)

Anal. Calcd. for $C_{13}H_{10}O_3N_2$: C, 64.46; H, 4.13; N, 11.57. Found: C, 64.49; H, 4.17; N, 11.30.

5-Nitro-2-picolinoylaminobenzoic acid was prepared from 5-nitroanthranilic acid and 2-picolinic acid in the same manner as above, and recrystallized from MeOH; the product was obtained as light yellow needles, mp. 265-266°, in 41% yield.

Anal. Calcd. for $C_{13}H_9O_5N_3$: C, 54.35; H, 3.13; N, 14.63. Found: C, 54.13; H, 3.14; N, 14.51.

2-(2-Pyridyl)-3-nitrophenyl-4(3H)-quinazolinones (II). General Procedure.- To a solution of 0.033 mole of 2-picolinoylaminobenzoic acid and 0.036 mole of a nitroaniline dissolved in 30 ml. of dry xylene, 0.020 mole of PCl_3 was added dropwise at 0-5°. The mixture was stirred for 1 hr. at room temperature and then refluxed at 150° for 20 hr. After the reaction was completed, the solvent was evaporated in vacuo and the residue dissolved in a small portion of $CHCl_3$ and chromatographed over 70 g. of Al_2O_3 (300 mesh), chloroform being used eluent. From the first eluted fraction, a crude crystalline mass was obtained and purified by recrystallization.

2-(2-Pyridyl)-3-nitroaryl-6-nitro-4(3H)-quinazolinones were prepared from 5-nitro-2-picolinoylaminobenzoic acid and nitroanilines in the same manner as above.

2-(2-Pyridyl)-3-aryl-4(3H)-quinazolinones (PPA Method).- To a mixture of 0.033 mole of 2-picolinoylaminobenzoic acid or its 5-nitro derivative and 0.036 mole of an aniline, 7 g. of PPA was added and the mixture then heated at 150° for 16 hr. The reaction mixture upon treatment with an ice water afforded a

solid which was dissolved in a small portion of $CHCl_3$ and chromatographed as described above, giving the products listed in Table I.

ACKNOWLEDGEMENT.- The authors wish to thank the members of the Analytical Department of this Faculty for the microanalyses and the spectral measurements. We are also grateful to Mr. M. Nakatomi, President of Hisamitsu Pharmaceutical Co. Inc., for the supply of several chemicals.

REFERENCES

* To whom inquires should be directed.

1.- T. Hisano, T. Nishi and M. Ichikawa, Yakugaku Zasshi, 92, 582(1972).

2.- T. Hisano and Y. Yabuta, Chem. Pharm. Bull.(Tokyo), 22, 316(1974).

3.- T. Hisano, M. Ichikawa, A. Nkagawa and M. Tsuji, Chem. Pharm. Bull.(Tokyo), 23, 1910(1975).

(Received September 30, 1975; in revised form November 20, 1975)