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A Convenient Synthesis of 4-Chloro- and 4-Bromocinnolines from o-Aminophenylacetylenes

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A CONVENIENT SYNTHESIS OF 4-CHLORO- AND 4-BROMOCINNOLINES FROM *o*-AMINOPHENYLACETYLENES

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Abstract

4-Chlorocinnolines and 4-bromocinnolines have been obtained in fair to good yields by diazotation of *o*-aminophenylacetylenes with sodium nitrite and concentrated hydrochloric acid or hydrobromic acid at temperatures between 25 and 30°C.

As a part of our studies on intramolecular cyclization with acetylenic derivatives we investigated the cycloaddition of the diazo group to vicinal acetylenic functions in aromatic and heteroaromatic compounds. This type of cyclization named after its discoverer von Richter¹ is used to synthesize 4-hydroxycinnolines from 2-alkynylanilines and involves treatment of the latter compounds with sodium nitrite and hydrochloric acid. It is assumed²⁻³ that a diazonium intermediate is attacked by water resulting in the hydroxycinnolines⁴⁻⁶. The conventional conditions for preparing these compounds involve heating at ~90°C after performing the diazotation reaction.

We could isolate 4-chloro- and 4-bromocinnolines in fair to good yields, respectively, when after the diazotation procedure the reaction mixtures were kept at 25 to 30°C instead of being heated at 90°C. If after this treatment the temperature was increased to 90°C, hydrocinnolines were formed.



It is generally assumed that in the Richter reactions the primary diazonium intermediate undergoes attack of water affording hydroxycinnolines. Our investigations suggest that at least a considerable part of the latter compounds are formed via the corresponding halogen derivatives. Our procedure constitutes an efficient and direct preparative method for chloro- and bromocinnolines; the chloro derivatives have been obtained also from the corresponding hydroxy compound by treatment with phophorus oxychloride and phosphorus pentachloride³, but yields were low.

Procédure

To 40 ml of a 36 % aqueous solution of hydrochloric acid or 47 % aqueous solution of hydrobromic acid was added with cooling below 0°C 0.585 g (0.005 mol) of *o*-ethynylaniline. Subsequently 16 ml of a 15 % (by weight) aqueous solution of sodium nitrite was added dropwise over 10 min with stirring while keeping the temperature of the reaction mixture at -15°C, then the mixture was stirred at 28°C (internal temperature) during the time indicated in the table. The solution was neutralized with a concentrated aqueous solution of sodium hydrogen carbonate, after which three extractions with diethyl ether were performed. After concentration of the dried (MgSO₄) extracts under reduced pressure the residue was chromatographed through an Al₂O₃ (neutral) column, using a mixture of chloroform and diethyl ether as eluent. After evaporation of the table.

The o-aminophenylacetylenes were synthesized in high yields from o-iodoanilines and the corresponding acetylene⁷.

R	X	Time (min) at 28°C	Yield (%)	m.p (°C) Crystall. solvent	Remarks
Ph	Cl	15	41	118-119	a
				hexane-C ₆ H ₆ (3 : 1)	
–Ph	Br	15	86	150-151	
-CH ₂ OPh	Cl	20	46	112-113	
				C ₆ H ₆	
- <i>n</i> -C ₆ H ₁₃	Cl	10	39	71-72	
				hexane	
-C ₆ H ₄ - <i>p</i> -CH ₃	Cl	10	44	145-145.5	
				hexane- $C_6H_6(4:1)$	
-C ₆ H ₄ - <i>p</i> -CH ₃	Br	25	90	125-125.5	
				hexane- $C_6H_6(3:1)$	
-C ₆ H ₂ -2,4,5-(CH ₃) ₃	Cl	10	49	111-112	
				hexane- $C_6H_6(2:1)$	
-C ₆ H ₂ -2,4,5-(CH ₃) ₃	Br	15	85	151-152	b
				hexane- $C_6H_6(1:1)$	
$-C_6H_4-p-NO_2$	Cl	15	11	178-179	b
				hexane- $C_6H_6(1:1)$	
$-C_6H_4-p-NO_2$	Br	90	56	164-165	
				hexane- $C_6H_6(1:1)$	
$-C_6H_4-p$ -Br	Cl	10	37	151-152	
				hexane- $C_6H_6(1:1)$	
C(CH ₃) ₂ OH	Cl	30	18	90-91	b
				hexane- $C_6H_6(1:1)$	
C ₆ H ₄ <i>p</i> -OCH ₃	Br	15	93	118-119	
				hexane- $C_6H_6(1:1)$	
-C ₆ H ₄ <i>o</i> -NO ₂	Br	45	61	184-185	
				C ₆ H ₆	

Table

All products give satisfactory micro analytical results.

a. Lit.³ gives m.p. 119-120°C

b. Decreased yield because of smooth hydrolysis to form hydroxycinnolines.

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