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Efficient Synthetic Route to Access Linear and Angular Dibenzonaphthyridines

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Abstract—An efficient procedure has been proposed for the synthesis of linear and angular phenyl-substituted dibenzonaphthyridines from anilinoquinolines and benzoic acid in up to 85% yield using Eaton's reagent (a solution of phosphorous pentoxide in methanesulfonic acid) as condensing agent instead of polyphosphoric acid which previously afforded less than 50% yield of the same compounds. Apart from benzoic acid, ethyl benzoate and benzoyl chloride can be used in the synthesis of dibenzonaphthyridines according to the proposed procedure, but the yields are lower.

Keywords: Eaton's reagent, anilinoquinolines, dibenzonaphthyridines.

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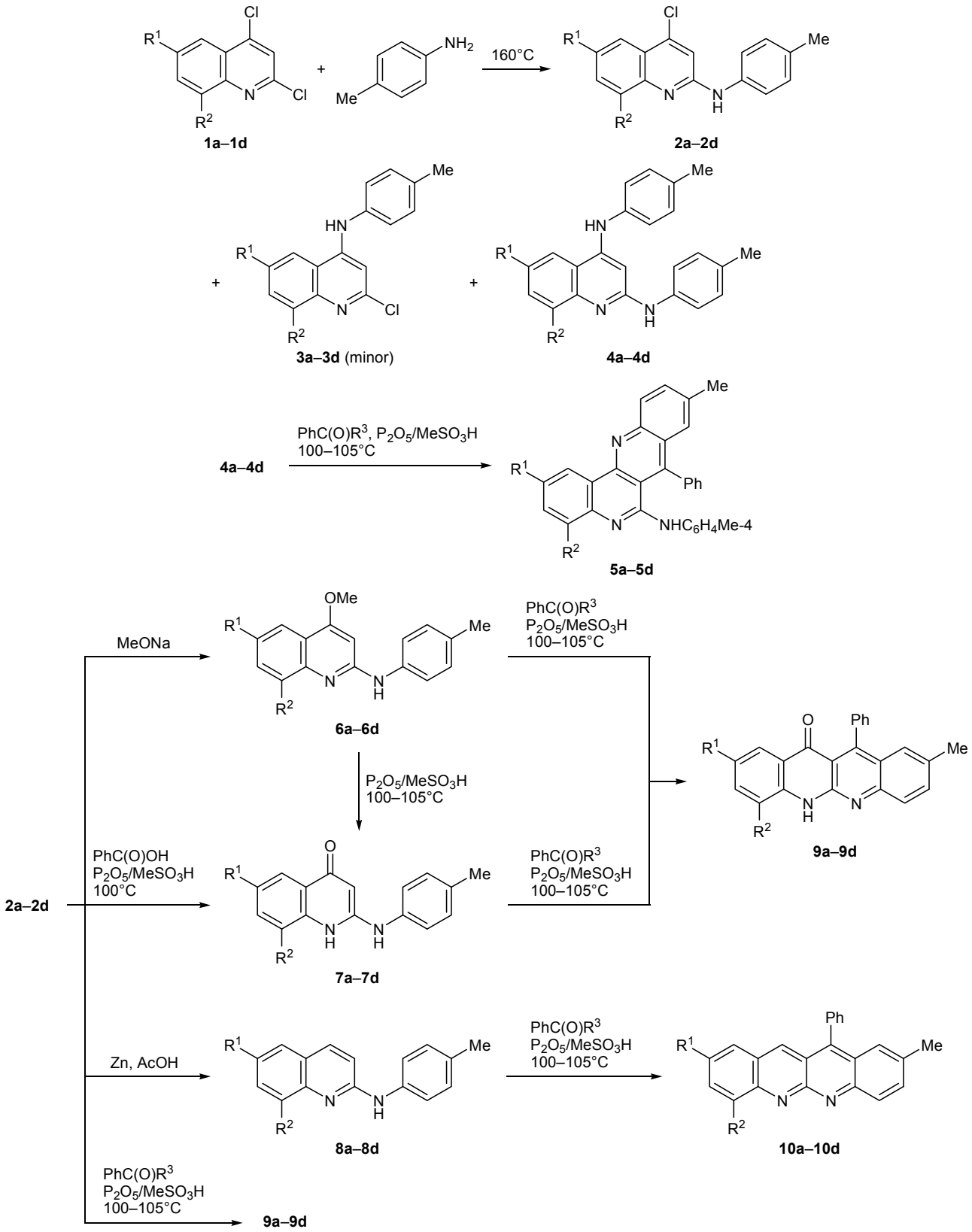
After the discovery of cinchona alkaloids, quinoline core is widely used as parent structure to synthesize compounds of medicinal importance, especially those possessing antimalarial [1] as well as other kinds of biological activities [2–4]. Quinoline derivatives have recently been examined for their function in the inhibition of tyrosine kinases, proteasome, and topoisomerase, tubulin polymerization, and DNA repair [5]. Quinoline nucleus is present in many natural alkaloids exhibiting antitumor activity, e.g., camptothecin [6, 7]. Some synthetic anilinoquinoline derivatives proved themselves as antimalarials [8] and were used as precursors to synthesize heterocycles like indoloquinolines [9] and dibenzonaphthyridines [10].

In recent years, the chemistry of naphthyridines and their functional derivatives has attracted interest from synthetic organic chemists owing to the broad spectrum of their biological activities such as anti-arrhythmic [11], analgesic [12], anti-HIV [13, 14] and anticancer [15]. In addition, they act as selective 3-phosphoinositide-dependent kinase-1 inhibitors [16]. There are many reports on the synthesis of functionalized naphthyridines [17, 19], linear dibenzonaphthyridines [20, 21] and angular dibenzonaphthyridines [22, 24]. However, there are only a few methods to construct dibenzonaphthyridines through anilinoquinolines as intermediate products [10, 25]. One of these methods is based on the reaction of anilinoquinolines with benzoic acid in the presence of polyphosphoric acid (PPA) as catalyst, which is known as Bernthsen reaction. In our previous report [26], Bernthsen reaction conditions were employed to synthesize linear and angular dibenzonaphthyridines starting from chloroquinolines through intermediate anilinoquinolines. Interestingly, the yields of dibenzonaphthyridines depended on the substituent in the anilinoquinoline and reaction temperature. However, the yields did not exceed 50%. In this connection, the present work was aimed at improving the yield of final dibenzonaphthyridines by changing the reaction condition. We made an attempt to utilize Eaton's reagent (a mixture of phosphorus pentoxide and methanesulfonic acid at a ratio of 1:10) as an alternative to PPA (mixture of phosphorous pentoxide and orthophosphoric acid) in the synthesis of linear and angular dibenzonaphthyridines. Eaton's reagent is a commercially available and inexpensive material proposed in 1973, and it has been found to be a good alternative to PPA [27]. The advantages of Eaton's reagent over PPA are its lower viscosity which makes it easier to handle, easy separation procedure during work up, and high yields of the products [28].

Scheme 1.



1–**10**, R^1 = Me, R^2 = H (**a**), R^1 = H, R^2 = Me (**b**), R^1 = Cl, R^2 = H (**c**), R^1 = R^2 = H (**d**); R^3 = OH, OEt, Cl.

Scheme 1 represents the synthesis of linear and angular dibenzonaphthyridines utilizing Eaton's reagent. The solvent-free reaction of 2,4-dichloroquinolines **1a**–**1d** with *p*-toluidine at 160°C gave a mixture of anilinoquinolines **2**, **3**, and **4** in which compound **3** was the minor product. The reaction of bis-anilinoquinolines **4** with benzoic acid in the presence of polyphosphoric acid (3 g of P_2O_5 in 1.5 mL of H_3PO_4) at 50 to 55°C afforded more stable angular dibenzonaphthyridine isomers **5a**–**5d** in 35–40%. The same reaction in the presence of Eaton's reagent (1 g of P_2O_5 in 5 mL of $MeSO_3H$) gave the same products in up to 80–85% yield at lower reaction temperatures (25–30°C). Similarly, compounds **2**, **6**, and **7** were converted to **9**, and **8** to **10**, using Eaton's reagent. In all cases, the yields increased significantly with simultaneous reduction of the reaction temperature. The maximum temperature in the synthesis of dibenzonaphthyridines was 100°C. Table 1 compares the yields and reaction temperatures in the synthesis of dibenzonaphthyridines using PPA and Eaton's reagent.

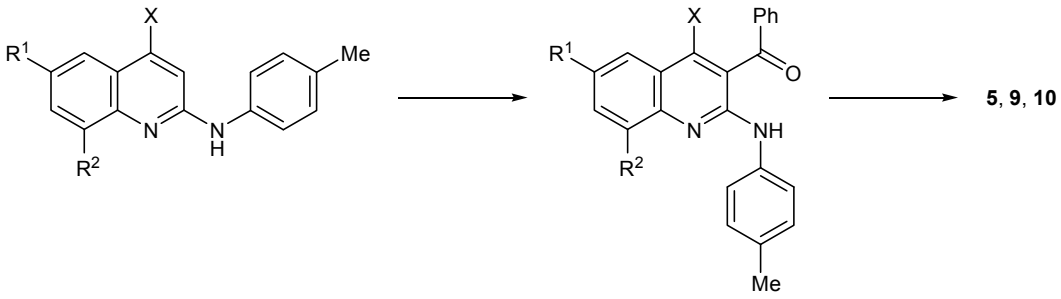
We also tried to use ethyl benzoate and benzoyl chloride instead of benzoic acid. However, the yields were lower than in the reactions with benzoic acid. A plausible reaction mechanism (Scheme 2) involves initial benzoylation at the 3-position of the quinoline moiety and subsequent cyclization through the *ortho* position of the *p*-tolylamino group on C^4 to produce angular dibenzonaphthyridines or on C^2 to afford linear dibenzonaphthyridines. Comparison of the yields given in Table 1 shows that benzoic acid is a more efficient reagent than benzoyl chloride and that the latter is more efficient than ethyl benzoate.

In conclusion, an efficient synthetic route has been proposed to obtain linear and angular dibenzonaphthyridines from anilinoquinolines and benzoic acid in

Table 1. Synthesis of angular and linear dibenzonaphthyridines **5a**–**5d**, **9a**–**9d**, and **10a**–**10d** from anilinoquinolines **2**, **4**, and **6**–**8** in the presence of polyphosphoric acid (PPA) and Eaton's reagent

Initial compound no.	Product no.	PPA (R^3 = OH)		Eaton's reagent			
		temperature, °C	yield, %	temperature, °C	yield, %		
					R^3 = OH	R^3 = OEt	R^3 = Cl
4a	**5a**	50–55	38	25–30	80	40	45
4b	**5b**	50–55	40	25–30	85	42	48
4c	**5c**	50–55	35	25–30	82	42	50
4d	**5d**	50–55	35	25–30	84	38	48
6a	**9a**	140–145	20	100–105	68	28	32
6b	**9b**	140–145	22	100–105	72	26	30
6c	**9c**	140–145	19	100–105	70	30	32
6d	**9d**	140–145	23	100–105	70	30	32
7a	**9a**	90–95	49	40–45	82	38	42
7b	**9b**	90–95	51	40–45	82	40	45
7c	**9c**	90–95	50	40–45	84	42	44
7d	**9d**	90–95	52	40–45	85	44	42
2a	**9a**	230–235	10	100–105	35	18	20
2b	**9b**	230–235	10	100–105	35	15	18
2c	**9c**	230–235	12	100–105	30	15	22
2d	**9d**	230–235	10	100–105	32	16	20
8a	**10a**	190–195	10	100–105	40	15	20
8b	**10b**	190–195	12	100–105	45	15	22
8c	**10c**	190–195	10	100–105	42	18	25
8d	**10d**	190–195	12	100–105	45	15	22

Scheme 2.



up to 85% yield using Eaton's reagent. The proposed procedure is superior to that utilizing polyphosphoric acid as condensing agent where the yields are lower than 50%. In addition, benzoic acid has been found to be a more efficient reagent than benzoyl chloride and ethyl benzoate in the conversion of anilinoquinolines to dibenzonaphthyridines.

EXPERIMENTAL

General procedure for the synthesis of dibenzonaphthyridines using Eaton's reagent. A mixture of 1 g of phosphorous pentoxide and 5 mL of methanesulfonic acid was stirred for 15 min at room temperature. The corresponding anilinoquinoline (1.00 mmol) and benzoic acid (or ethyl benzoate or benzoyl chloride, 1.00 mmol) were added to the resulting solution, and the mixture was heated to a temperature indicated in Table 1. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured onto crushed ice. Due to low viscosity of Eaton's reagent, the workup procedure was much easier than with the use of highly viscous polyphosphoric acid. The products were isolated by filtration and were identified by TLC and NMR data. The yields are given in Table 1.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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