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TRIPHOSGENE: A VERSATILE REAGENT FOR BISCHLER-NAPIERALSKI REACTION

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Abstracts - Triphosgene causes direct formation of quaternary benzo[*c*]phenanthridines such as anti-tumor active nitidine (**2a**) chloride by Bischler-Napieralski reaction of 2-phenyl-1-(*N*-methylformamido)naphthalenes under heating in acetonitrile.

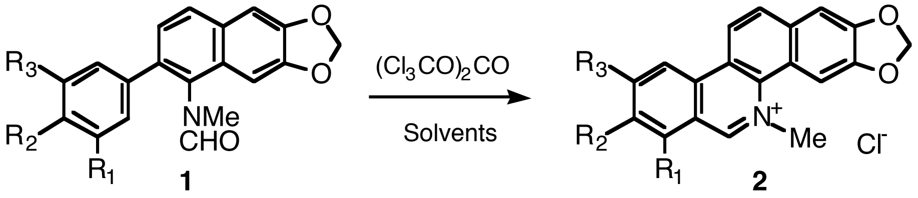
Bischler-Napieralski reaction (BNR)[1] is one of the most important method for construction of an isoquinoline skeleton. Phosphorus oxychloride ($POCl_3$) is widely used for the cyclization reagent. We[2] had reported that quaternary benzo[*c*]phenanthridines (**2**) could be directly prepared from 2-phenyl-1-(*N*-methylformamido)naphthalenes (**1**) by BNR with $POCl_3$ in acetonitrile (MeCN) in the studies on their structure-activity relationship for anti-tumor acitivity. A commercially available triphosgene [$(Cl_3CO)_2CO$], a crystalline stable solid, could be used as a toxic gaseous phosgene substitute and increasing reports, especially patents, have appeared on the use of it as a synthetic tool for a variety of purposes since reintroduction by Eckert *et al.*[3] In this note we describe the availability of triphosgene as a dehydrating reagent for isoquinoline construction by BNR of tertiary formamides.

Although it is known that secondary formamides (RNHCHO) convert into isonitriles (RNC) by dehydration reaction with triphosgene in the presence of a base,[3] *N*-substitution of them should result in no isonitrile formation. Thus, we examined the BNR of 2-phenyl-1-(*N*-methylformamido)naphthalenes (**1**) using triphosgene, expecting to lead to direct formation of quaternary benzo[*c*]phenanthridines (**Table 1**).

Treatment of a dimethoxy-substituted tertiary formamide (**1a**) in 1,1,2-trichloroethane with triphosgene in the presence of triethylamine under reflux afforded a desired nitidine chloride[2] (**2a**) in 83% isolated yield (Run 1). Triethylamine as a base was not intrinsically needed for the cyclization (Run 2) and the most effective cyclization was observed when the reaction was carried out under milder conditions (at 60 °C in MeCN for 0.5 h) than in boiling 1,1,2-trichloroethane for 24 h (Run 3). Application of this BNR with triphosgene under the conditions noted in run 3 to other substrates such as a trimethoxy-substituted (**1b**) and methylenedioxy-methylenedioxy-substituted tertiary formamides (**1c**) smoothly afforded the corresponding cyclized benzo[*c*]phenanthridine (**2b**)[2] (Run 4) and avicine (**2c**)[2] as chlorides (Run 5).

Thus, easily handling triphosgene was found to act as an alternative dehydrating reagent for construction of isoquinoline skeletons by BNR of tertiary formamides.

Table 1. BNR of 2-Phenyl-1-(*N*-methylformamido)naphthalenes (**1**) with Triphosgene



a: R_1=H, R_2=R_3=OMe
b: R_1=R_2=R_3=OMe
c: R_1=H, R_2+R_3=OCH_2O

Run	**1**	Solvents	Et_3N	Temp	Time (h)	**2** (%)
1	a	Cl_2CHCH_2Cl	+	reflux	24	83
2	a	Cl_2CHCH_2Cl	—	reflux	24	85
3	a	MeCN	—	60°C	0.5	91
4	b	MeCN	—	60°C	0.5	78
5	c	MeCN	—	60°C	0.5	80

A Typical Experiment

Nitidine (2a) Chloride: A solution of **1a** (0.102 g, 0.278 mmol) and triphosgene (0.179 g, 0.602 mmol) in MeCN (2.5 mL) was stirred at 60 °C (bath temperature) for 0.5 h. After addition of ice-water yellow precipitates were collected by filtration followed by recrystallization with EtOH-ether to directly give nitidine chloride (**2a**) (0.098 g, 91%), mp 285-292 °C (lit.,[2] mp 285-292 °C).

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