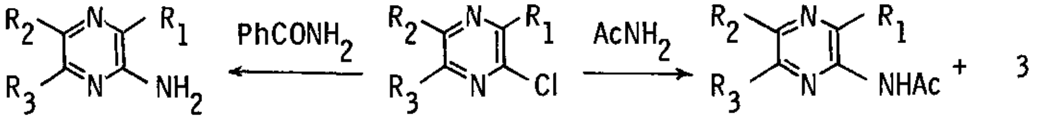
HETEROCYCLES, Vol 14, No 3, 1980

A SIMPLE METHOD FOR THE PREPARATION OF SOME AMINO N-HETEROAROMATICS

Tokuhiro Watanabe, Etsuko Kikuchi, Wataru Tamura, Yasuo Akita,
Mayumi Tsutsui, and Akihiro Ohta
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji,
Tokyo 192-03, Japan

Abstract —— The heating of some halogenated pyrazines, pyridines, and quinolines with benzamide in the presence of potassium carbonate gave the corresponding amino derivatives. The similar reaction using acetamide afforded acetamido derivatives, together with amines in some cases.

The replacement of halogen groups using amino derivatives is often used for the introduction of amino groups into N-heteroaromatics. In our previous work,[1] N-methylformamide and N,N-dimethylformamide were also proved to be excellent reagents for the synthesis of methylamino and dimethylamino heteroaromatics, respectively. This paper reports a method for the preparation of amino N-heteroaromatics by heating of halogenated heteroaromatics with acetamide or benzamide in the presence of potassium carbonate.



3 1 2

a: $R_1 = R_3 = Et$, $R_2 = H$
b: $R_1 = R_3 =$ iso-Pr, $R_2 = H$
c: $R_1 = R_3 =$ iso-Bu, $R_2 = H$
d: $R_2 = R_3 = Ph$, $R_1 = H$
e: $R_1 = R_3 = Ph$, $R_2 = H$
f: $R_1 = R_2 = Ph$, $R_3 = H$

Scheme 1

The general procedure is as follows: (1) A mixture of halogenated amine (5 mmol), benzamide (10 mmol), and potassium carbonate (5 mmol) was heated at 180-230° for 1 hr. During the heating, refluxing of benzonitrile and water was recognized. When cooled, the reaction mixture was subjected to column chromatography on silica gel (Wakogel C-200, 50 g) and eluted with hexane, methylene chloride, and a mixture of methylene chloride-ethyl acetate, successively. The product was purified by recrystallization or distillation. (2) A mixture of the starting halogenated amine (5 mmol), potassium carbonate (25 mmol), and acetamide (25 g) was refluxed for 14 hr. The reaction mixture was then poured into water (150 ml), and extracted with methylene chloride. The product was purified by column chromatography on silica gel (Wakogel C-200, 25 g).

Table 1. Reaction of Halogenated Pyrazines, Pyridines, and Quinolines

	With acetamide			With benzamide	
Starting material	Yield of amides b) (%)	mp (°C)	Yield of amines b) (%)	Yield of amines b) (%)	mp or bp/Torr (°C)
1a [2]	54	103-103.5	12	80	152/12 [7] 154.5-155 c)
1b [2]	48	82-83		36	280-281 182-183 c)
1c [2]	75	102-103		70	140-141
1d [2]	84	219-220		63	226-227 [8]
1e [2]	33	198-199	37	97	187-188 [7]
1f [2]	48	190-192	35	84	137-138
2-Br-pyridine a)	1	69-71 [4]	23	10	123-128/40 [9]
2-Cl-quinoline a)	68	129-130 [5]		54	129-130 [5]
4-Cl-quinoline [3]	17	179-180 [6]		26	152-153 [6]

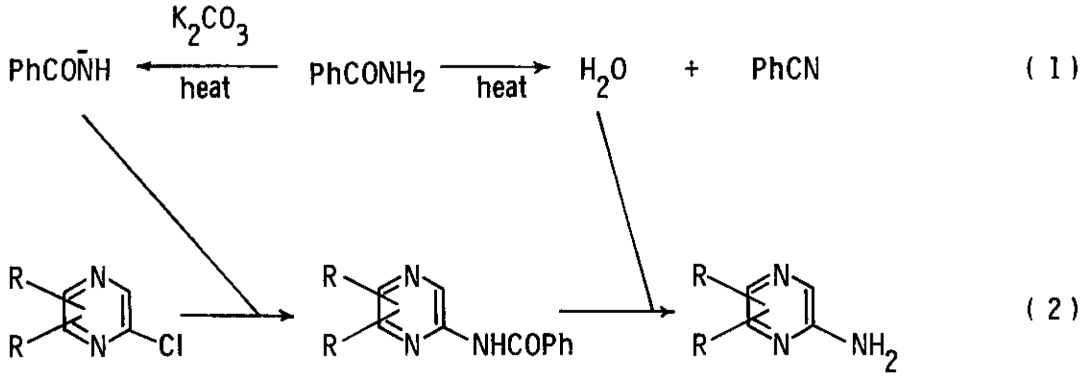
a) Commercially obtained.

b) Yield of purified products is given.

c) Mp of the picrate.

This method was applied for the preparation of some amino-pyrazines, -pyridines, and -quinolines, and its results are shown in Table 1. This result indicates that the reaction using benzamide is especially suited for the preparation of amino N-heteroaromatics, except when the starting materials used have a low boiling point or are unstable on heating.

As shown in this Table, acetamide gave mainly acetamido derivatives, moreover, together with amino compounds in some cases, while only the amino compounds were obtained by the reaction with benzamide. This amination may start with the formation of an acylamido anion.[10] In the case of the reaction with benzamide, generation of benzonitrile and benzoic acid was confirmed, which may be formed at the high temperature according to equations, (1) and (2).



Scheme 2

Although 3-bromopyridine and 3-bromoquinoline were submitted to this procedure, starting materials were recovered. Application of this reaction to other heteroaromatics is in progress and will be described later.

REFERENCES

1. T. Watanabe, Y. Tanaka, K. Sekiya, and A. Ohta, Synthesis, 1979, in press.
2. A. Ohta, N, Takahashi, T. Ohwada, M. Matsunaga, and Y. Akita, Chem. Pharm. Bull. (Tokyo), 26, 1322 (1978).
3. M. Hamana, Yakugaku Zasshi, **71**, 263 (1951).
4. Yu. N. Sheinker, Doklady Akad. Nauk S.S.S.R., **113**, 1080 (1957) [Chem. Abstr., **51**, 14718h (1957)].
5. E. Ochiai, K. Kokeguchi, M. Shimizu, and H. Nishizawa, Yakugaku Zasshi, **63**, 258 (1943).
6. R. Royer, J. Chem. Soc., 1803 (1949).
7. G. T. Newbold, F. S. Spring, and W. Sweeny, J. Chem. Soc., 1855 (1948).
8. A. Hirschberg and P. E. Spoerri, J. Org. Chem., **26**, 1907 (1961).
9. C. R. Hauser and M. J. Weiss, J. Org. Chem., **14**, 310 (1949).
10. J. Zabicky, ''The Chemistry of Amides'', John Wiley & Sons, New York, p. 187 (1970).

Received, 20th December, 1979