Synthesis of Heterocycles via Nitrilium Salts; XV[1]. 2-Aminoquinazolines

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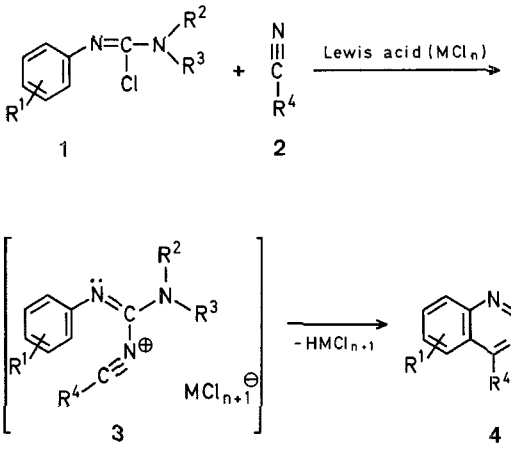
The reactivity of nitrilium salts toward high electron density centers situated in a suitable position in a molecule, has been previously utilized by our group for the preparation of several types of heterocyclic systems[1,2]. In the present communication we describe another interesting application of this heterocyclization principle which permited the development of a new and easy method of synthesis of 2-aminoquinazoline derivatives (**4**), that can be considered as an extension of the Meerwein's quinazoline synthesis[3]. The method involves the interaction of chloroformamidines (**1**), cyano compounds (**2**) and a Lewis acid (MCl_n) to give an intermediate non-isolated nitrilium salt (**3**) which, under the conditions employed, undergoes spontaneous cyclization.

The starting chloroformamidines (**1**) were prepared by the reaction of *N,N,N'*-substituted ureas or thioureas with triphenylphosphine and carbon tetrachloride[4] or from carbonimidoyl dichlorides and the corresponding secondary amines[5].



1 2 3 4

Synthesis of 2-Aminoquinazolines (4); General Procedure:
To a stirred mixture of the chloroformamidine **1** (0.05 mol), the cyano compound **2** (0.05 mol), and 1,2-dichlorobenzene (20 ml), tin(IV) chloride (0.05 mol) is added. The reaction mixture is heated for 1–2 h at 120–130°. In the preparation of compounds **4a–i** and **4w–z** a dark solution results which after cooling is poured into 20% aqueous sodium hydroxide (200 ml) and extracted several times with ether. The combined extracts are washed with water and treated with an excess of 20% hydrochloric acid. The cooled acidic solution is made basic with 20% aqueous sodium hydroxide and extracted again with ether. The combined extracts are dried with sodium sulfate and the solvent is removed in vacuo. In the case of compounds **4j–v** solid crystalline salts are formed which are filtered, washed with ether, and worked up as above. The residual 2-aminoquinazolines are purified by crystallization, vacuum distillation, or column chromatography. Yields and m.p.'s are listed in the Table.

Table. Preparation of 4-Aminoquinazolines (**4a–z**)

Product	R^1	R^2	R^3	R^4	Yield [%]	m.p.	Recrystallization solvent	Molecular formula[a]
4a	H	CH_3	C_6H_5	C_6H_5	70	90–92°	ethanol	$C_{21}H_{17}N_3$ (311.2)
4b	H	CH_3	C_6H_5	*p*-Cl—C_6H_4	85	109–111°	ethanol	$C_{21}H_{16}ClN_3$ (345.6)
4c	H	CH_3	*p*-Cl—C_6H_4	C_6H_5	70	132–134°	ethanol	$C_{21}H_{16}ClN_3$ (345.6)
4d	H	CH_3	*p*-Cl—C_6H_4	*p*-Cl—C_6H_4	65	114–115°	ethanol	$C_{21}H_{15}Cl_2N_3$ (380.1)
4e	H	CH_3	*p*-Cl—C_6H_4	S—C_2H_5	70	73–75°	ethanol	$C_{17}H_{16}ClN_3S$ (329.6)
4f	H	C_6H_5	C_6H_5	S—C_2H_5	85	106–107°	ethanol	$C_{22}H_{19}N_3S$ (357.2)
4g	H	C_6H_5	C_6H_5	C_6H_5	85	161–163°	ethanol	$C_{26}H_{19}N_3$ (373.2)
4h	H	C_6H_5	C_6H_5	CH_3	68	116–117°	ethanol	$C_{21}H_{17}N_3$ (311.2)
4i	H	C_6H_5	C_6H_5	$CH_2COOC_2H_5$	40	148–150°	ethyl acetate/petroleum ether	$C_{24}H_{21}N_3O_2$ (383.2)
4j	H	—$(CH_2)_2$—O—$(CH_2)_2$—		C_6H_5	75	112°	ethanol	$C_{18}H_{17}N_3O$ (291.1)
4k	H	—$(CH_2)_2$—O—$(CH_2)_2$—		*p*-Cl—C_6H_4	72	148°	ethanol	$C_{18}H_{16}ClN_3O$ (325.6)
4l	H	—$(CH_2)_2$—O—$(CH_2)_2$—		*m*-Cl—C_6H_4	78	126°	ethanol	$C_{18}H_{16}ClN_3O$ (325.6)
4m	H	—$(CH_2)_2$—O—$(CH_2)_2$—		*o*-Cl—C_6H_4	62	—[b]	—	$C_{18}H_{16}ClN_3O$ (325.6)
4n	H	—$(CH_2)_2$—O—$(CH_2)_2$—		CH_3	32	—[c]	—	$C_{13}H_{15}N_3O$ (229.1)
4o	H	—$(CH_2)_2$—O—$(CH_2)_2$—		*n*-C_3H_7	51	56°	ethanol	$C_{15}H_{19}N_3O$ (257.1)
4p	H	—$(CH_2)_2$—O—$(CH_2)_2$—		S—C_2H_5	50	86°	ethanol	$C_{14}H_{17}N_3OS$ (275.1)
4q	H	—$(CH_2)_5$—		C_6H_5	73	104°	ethanol	$C_{19}H_{19}N_3$ (289.1)

Table (continued)

Product	R^1	R^2	R^3	R^4	Yield [%]	m.p.	Recrystallization solvent	Molecular formula[a]
4r	H		$-(CH_2)_5-$	*p*-Cl—C_6H_4	62	98°	ethanol	$C_{19}H_{18}ClN_3$ (323.6)
4s	H		$-(CH_2)_5-$	S—C_2H_5	48	68°	ethanol	$C_{15}H_{19}N_3S$ (273.1)
4t	H	$-(CH_2)_2-N(CH_3)-(CH_2)_2-$		C_6H_5	52	97–98°	petroleum ether	$C_{19}H_{20}N_4$ (304.1)
4u	H	$-(CH_2)_2-N(CH_3)-(CH_2)_2-$		*p*-Cl—C_6H_4	40	121–122°	ethanol	$C_{19}H_{19}ClN_4$ (338.6)
4v	H	$-(CH_2)_2-N(CH_3)-(CH_2)_2-$		S—C_2H_5	39	73–74°	petroleum ether	$C_{15}H_{20}N_4S$ (288.1)
4w	6-Cl	CH_3	C_6H_5	CH_3	70	150–151°	ethyl acetate	$C_{16}H_{14}ClN_3$ (283.6)
4x	7-Cl	CH_3	C_6H_5	CH_3	60	b.p. 170–174°/ 0.05 torr[d]	—	$C_{16}H_{14}ClN_3$ (283.6)
4y	7-Cl	CH_3	C_6H_5	C_6H_5	65	100–102°	ethanol	$C_{21}H_{16}ClN_3$ (345.6)
4z	6,7-di-Cl	CH_3	*p*-Cl—C_6H_4	C_6H_5	72	131–132°	ethanol	$C_{21}H_{14}Cl_3N_3$ (414.5)

[a] Satisfactory microanalyses (C ±0.30%, H ±0.25%, N ±0.30%) and spectral data (I.R., ^{1}H-N.M.R.) were obtained for all products.

[b] Isolated by column chromatography (ethyl acetate/cyclohexane 1:2); $n_D^{18} = 1.6450$; m.p. of picrate: 252° (DMF/water).

[c] Isolated by column chromatography (ethyl acetate/cyclohexane 1:2); $n_D^{19} = 1.6205$; m.p. of picrate: 206° (acetonitrile).

[d] m.p. of picrate: 214–215° (acetonitrile).

Received: January 31, 1977

[1] Preceeding paper: XIV. C. Avellana, V. Gómez Parra, R. Madroñero, *Synthesis* **1976**, 252.

[2] F. Johnson, R. Madroñero, *Heterocyclic Synthesis Involving Nitrilium Salts and Nitriles under Acidic Conditions*, in *Advances in Heterocyclic Chemistry*, Vol. 6, A. R. Katritzky, A. J. Boulton, Eds., Academic Press, N. Y. 1966, p. 95.

[3] H. Meerwein, P. Laasch, R. Mersch, J. Nentwig. *Chem. Ber.* **89**, 224 (1956).

[4] R. Appel, K. Warning, K. D. Ziehn, *Chem. Ber.* **107**, 698 (1974).

[5] W. Ried, W. Merkel, *Chem. Ber.* **105**, 1532 (1972).