# A NOVEL SYNTHESIS OF QUINAZOLINES AND 1,4-BENZODIAZEPINES

Jan Bergman, Anna Brynolf, and Björn Elman

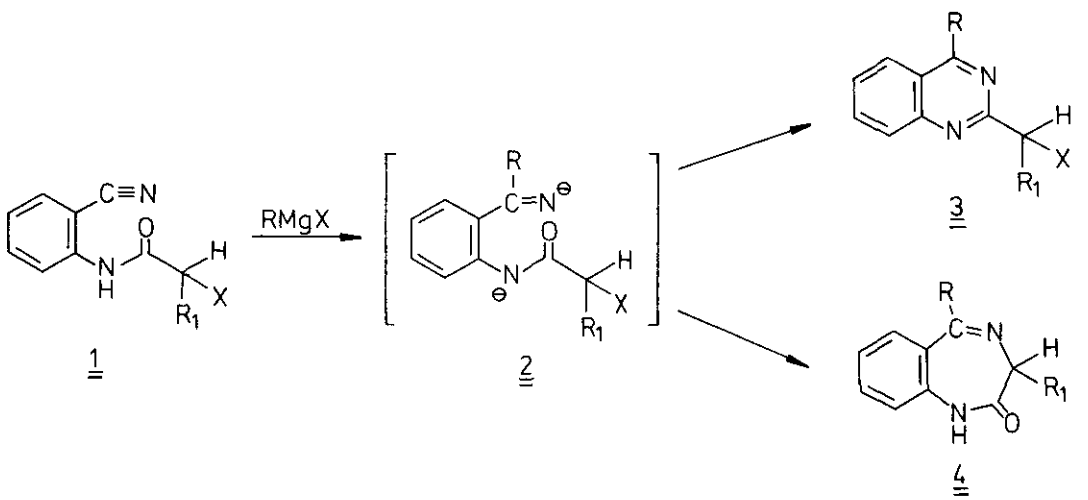
Department of Organic Chemistry, Royal Institute of Technology,

S-100 44 Stockholm, Sweden

Abstract - The synthesis of 1,4-benzodiazepines and quinazolines from o-aminobenzonitriles is reported. For the formation of the 1,4-benzodiazepines a mechanism involving an intermediate aziridinone is proposed.

o-Aminobenzonitrile (anthranilonitrile) is nowadays readily available by reaction of o-nitrotoluene with ammonia in the vapour phase[1] or by ammoxidation[2] of o-toluidine and related processes.[3] Hence this interesting bifunctional compound has gained importance as a starting material in organic synthesis. In this paper we would like to report new approaches to quinazolines and 1,4-benzodiazepines based on N-acylated o-aminobenzonitriles.

The starting-point of this work was a speculation that compounds of the general structure 1, might upon treatment with RMgX or RLi, in spite of the presence of acidic hydrogen atoms, give rise to 1,4-benzodiazepin-2-ones (4) or/and quinazolines[4] (3) via the common intermediate[5] (2). (Scheme 1)

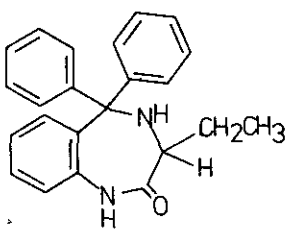



Scheme 1

It was also expected that the nature of the substituents (R, $R_1$ and X), where R and $R_1$ is hydrogen, alkyl or aryl and X is Cl or Br, should have a strong influence on the product pattern and that even other ring-systems, such as quinolines[6] might be formed.

The first experiment, interaction of 1 ($R_1$=H,X=Cl) with $C_6H_5MgBr$ in ether, gave 3 (R=$C_6H_5$, $R_1$=H, X=Cl) in a reasonable yield. The structure of 3 was proven by a conventional synthesis via *o-aminobenzophenone*. These results triggered the synthetic study summarized in note 8 using simple N-acylated anthranilonitriles as starting material. The procedure was found to constitute a fast and convenient route to quinazolines. Introduction of a second R-substituent (to yield e.g. 3,4-dihydroquinazolines[9] was never a disturbing side-reaction, not even when the amount of e.g. $C_6H_5Li$ was deliberately increased in the reaction with N-benzoylanthranilonitrile.

Attention was then turned to the reaction of $C_6H_5MgBr$ with derivatives of 1, where X=Br and $R_1$ = lower alkyl, because with a better leaving group we anticipated better chances to get 1,4-benzodiazepines. For instance in the case of $R_1$=$C_2H_5$ two compounds with spectral properties[10] in harmony with 1,4-benzodiazepines were obtained. Compound A had the composition $C_{17}H_{16}N_2O$ and compound B the composition $C_{23}H_{22}N_2O$, obviously by the result of the introduction of a second $C_6H_5$-group.[11] However the spectral (IR, PMR) properties of compound A were in disagreement with those of the known[12] compound (4 (R=$C_6H_5$, $R_1$=$C_2H_5$). The properties of B, at first tentatively assigned structure 5, required further studies and the structure was finally identified as the rearranged 1,4-benzodiazepin-3-one 6 by an X-ray investigation.[13] The structure of compound A was subsequently determined to 7.

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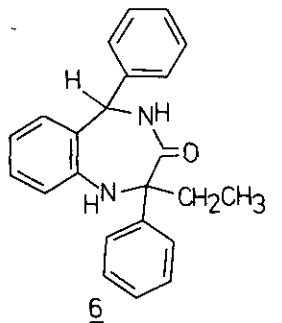


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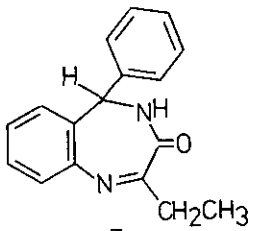


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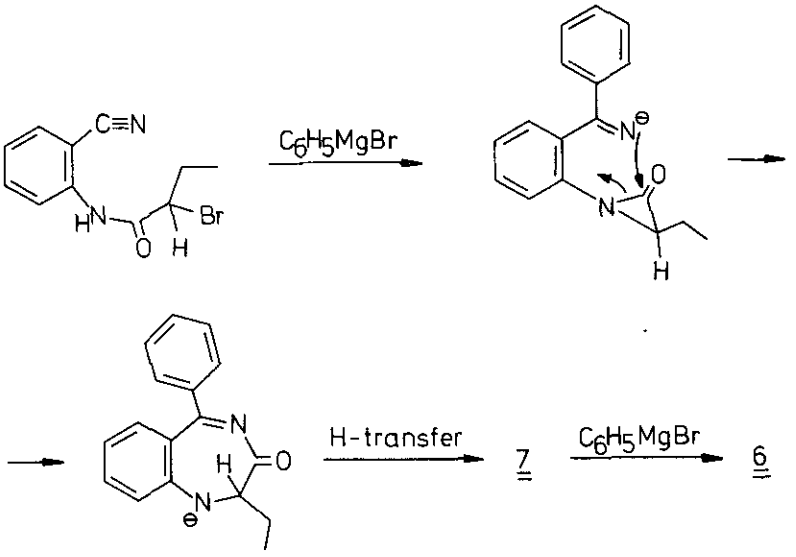
These results[14] can be rationalized in terms of formation of an aziridinone[15,16] (α-lactam) as the crucial intermediate, which subsequently is attacked intramolecularly by the imine anion as outlined in Scheme 2. A related rearrangement during the conversion (induced by $NH_3$) of 2-(N-β-bromoalkyl)-aminobenzophenones into 1,4-benzodiazepines has earlier been reported by[17] Kuftinec et al.




Scheme 2

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2. Yu. N. Litvishkov, M.R. Efendiev, R.G. Rizev, and F.M. Agaev, Azerb. Khim. Zhur., 52 (1980).

3. U.S. Pat. 4.137.254 (to Texaco).

4a. For a related cyclization involving the reaction of amines with o-acylaminobenzonitriles, see ref. 4b.

4b. K.E. Nielsen and E.B. Pedersen, Chem. Scripta, 18, 242 (1981).

5a. It is well-known[5b] that addition of RMgX to anthranilonitrile followed by hydrolysis will give reasonable yields of the corresponding ketone ($RCO\text{-}C_6H_4\text{-}o\text{-}NH_2$).

5b. R. Sikkar and P. Martinson, Acta Chem. Scand. B, 34, 551 (1980) and refs therein.

6a. 2-(2-Bromoacetamido)-3-cyano-4,5-dimethylacetophenone could be cyclized[6b] to 8-acetyl-4-amino-3-bromo-5,6-dimethyl-1H-quinolin-2-one even under weakly basic conditions.

6b. A.A. Fatmi, Diss. Univ. of Georgia (1981).

7a. The known[7b] compound 6-chloro-2-chloromethyl-4-phenylquinazoline was also similarly prepared.

7b. M. Oklobdzija, M. Japelj, and T. Fajdiga, J. Het. Chem., 9, 161 (1972).

8. Quinazolines prepared: 2-$CH_3$-4-$C_6H_5$, 58%, mp 48 °C; 2-$C_6H_5$-4-$C_6H_5$, 82%, mp 122 °C; 2-$CH_3$-4-(p-$C_6H_4$), 53%, mp 93 °C, 2-$CH_3$-4-$C_6H_5$-6-Cl 65%, mp 106 °C.

9. J.G. Smith and J.M. Sheepy, J. Het. Chem., 12, 231 (1975).

10. T.A. Scahill, Diss. Univ. of Kentucky (1981).

11a. Addition of RMgX to imines is a well-known reaction.[11b] See also ref. 18.

11b. R.E. Dessy and R.M. Salinger, J. Am. Chem. Soc., 83, 3530 (1961) and refs therein.

12. A.V. Bogatskii, S.A. Andronati, V.P. Gultyai, Yu. I. Vikhlyaev, A.F. Galatin, Z.I. Zhilina and T.A. Klygul, Zhur. Obshch. Khim., 41, 1358 (1971).

13. K.W. Törnroos, B. Karlsson, J. Bergman, and A. Brynolf, to be published.

14a. Reactions of $C_5H_5MgBr$ with 1 ($R_1$=$CH_3$) gave similar results, whereas 1 ($R_1$=aryl) gave the originally anticipated 1,4-benzodiazepin-2-ones. Thus α-chloro-α-phenyl-2-cyano-4-chloro-acetanilide gave the known[14b] compound 7-chloro-3,5-diphenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one.[14c]

14b. S.C. Bell, T.S. Sulkowski, C. Gochman, S.J. Childress, J. Org. Chem., 27, 562 (1962).

14c. We thank Dr. G. Field, Nutley, New Jersey for the kind submission of a sample.

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