Letter

Efficient Synthesis of Mutagenic Imidazo[4,5-*f*]-quinoxalin-2-amines via Readily Accessible 2,1,3-Benzoselenadiazoles

Spiros Grivas

Department of Chemistry and Molecular Biology, Swedish University of Agricultural Sciences, P.O. Box 7015, S-750 07 Uppsala, Sweden

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Mutagenic di- and trimethyl-3*H*-imidazo[4,5-*f*]-quinoxalin-2-amines (e.g., MeIQx and 7,8-DiMeIQx; *6* in Fig. 1) along with other mutagenic and/or carcinogenic heterocyclic amines have been isolated in small amounts from broiled fish and meat, pyrolysates of amino acids and proteins, and from model reaction mixtures consisting of creatinine, hexoses and amino acids.[1–4] Some of these food mutagens are continuously desired in substantial quantities for toxicological studies and animal bioassay in various laboratories. To date, MeIQx and the related 3*H*-imidazo[4,5-*f*]quinolin-2-amines (IQ and MeIQ; *3* in Fig. 1) have been shown to develop carcinomas in rodents.[5,7] Consequently, much attention is currently paid to these compounds as a possible cause of human cancers.[7] The amount of MeIQx detected by LCEC (liquid chromatography with electrochemical detection)[8] in one gram of food grade beef extract was 3.1 ng; no IQ could be detected. One gram of bacteriological grade beef extract was found to contain 41.6 ng of IQ and 58.7 ng of MeIQx.[9]

The modification of existing synthetic methods and the introduction of new more convenient ones to produce these potent mutagens is a continuous challenge. The direct replacement of the chlorine atom of *2* by a methylamino group[10] is an obvious improvement of older methods to obtain IQ and MeIQ (*3*).[11–13] The latter methods involved *N*-methylation in the last step of the synthetic sequence, which produced other methylated products in addition to the desired one. This was regrettable, especially when the ^{14}C- or ^{13}C-labelled analogues of *3* were required.

When the synthesis of MeIQx (*6a*) was attempted, 7-chloro-2-methylquinoxaline (*4*) was therefore considered as starting material.[14] This would then be nitrated and subsequently treated with methylamine, reduced, and cyclized with cyanogen bromide by analogy with the route *1*→*2*→*3*. However, in contrast to the chloroquinolines (*1*) which could be easily nitrated to yield *2*,[10] the nitration of chloroquinoxalines (*4*) and their fluoro analogues was unsuccessful.[14,14a] Hence, 7-fluoro-2-methylquinoxaline was treated with methylamine under drastic conditions (steel autoclave, 16 h 170–180 °C) resulting in the 6-methylaminoquinoxaline which could then be nitrated to produce *5a*. The latter nitration is rather touchy and produces a considerable amount of tarry products. Moreover, nitration of the methylamino group and oxidation of the pyrazine methyl group has been observed.[14a] Again, *5a*[14] and *5b*[15] can be reduced and subsequently cyclized with cyanogen bromide to give MeIQx and 7,8-DiMeIQx.

In search of alternative routes to improve the synthesis of *5*, and consequently of MeIQx and 7,8-DiMeIQx, 5-chloro-4-nitro-2,1,3-benzoselenadiazole (*8*)[16] was investigated as possible starting material. Compound *8* was readily obtained

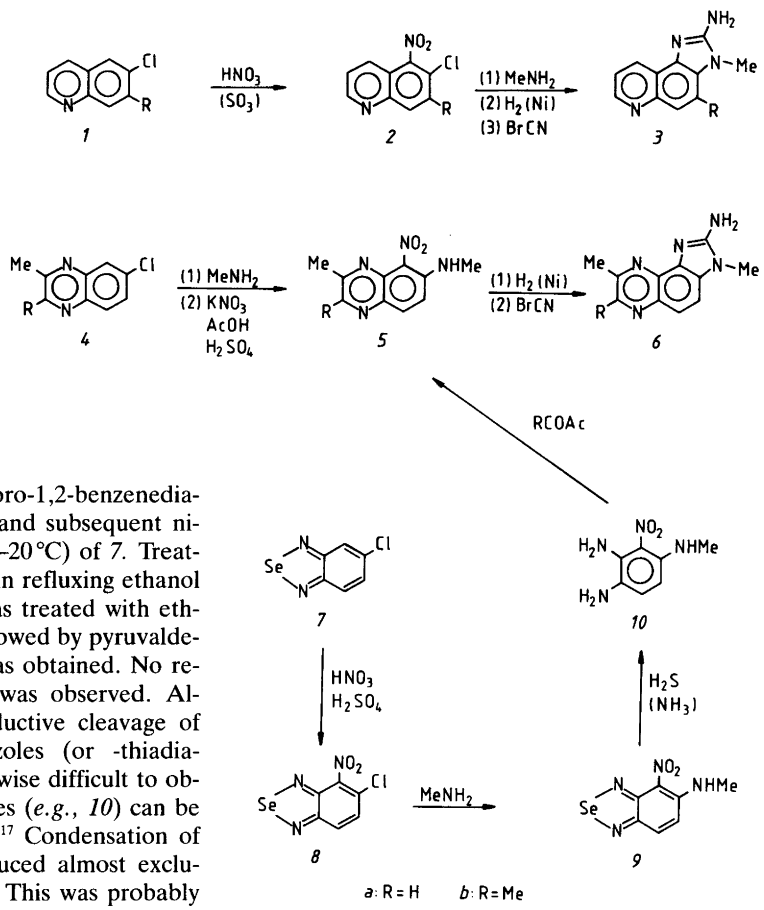

Fig. 1. Some of the IQ-type food mutagens *3a:* IQ, *3b:* MeIQ, *6a:* MeIQx and *6b:* 7,8-DiMeIQx, which may have a genotoxic potential for humans.[27-29]

in high yield by treating 4-chloro-1,2-benzenediamine with selenium dioxide and subsequent nitration (H_2SO_4/HNO_3, 1 h, 0–20 °C) of *7*. Treatment of *8* with methylamine in refluxing ethanol (1 h) afforded *9*. When *9* was treated with ethanolic ammonium sulfide followed by pyruvaldehyde or diacetyl, *5a* or *5b* was obtained. No reduction of the nitro group was observed. Alternatively, the selective reductive cleavage of nitro-2,1,3-benzoselenenadiazoles (or -thiadiazoles and -furoxans) to otherwise difficult to obtain nitro-1,2-benzenediamines (*e.g., 10*) can be achieved by hydroiodic acid.[17] Condensation of *10* with pyruvaldehyde produced almost exclusively the desired isomer *5a*. This was probably because the reaction preferentially occurred through the most reactive groups, i.e., the amino group which is not conjugated with the nitro group, and the aldehyde group.[18] In contrast, the condensation of 4-fluoro (or chloro)-1,2-benzenediamine with pyruvaldehyde yielded 20-25 % of the undesired 6-halo-2-methylquinoxaline.[14] The isomeric quinoxaline derivatives could be isolated only after treatment with methylamine and subsequent nitration (*cf. 4→5*). The yield of *5* from the commercially available 4-chloro-1,2-benzenediamine via *7*[19] was 45–48 %, while that via *4* was 21–23 %.

N,3-di- and *N*,2,3-trimethyl-5-nitro-6-quinoxalinamine (*5a* and *5b*, respectively) were identical to those synthesized by other methods.[14,15] The same strategy has been successfully applied to the synthesis of the MeIQx homologues 4,8- and 5,8-DiMeIQx. Experimental details will soon be published.[20,21]

Summarizing, the presently reported methodology does not require a steel autoclave, which is often a restriction when syntheses on larger scales are performed. In general, all the synthetic operations and work-up procedures to produce the title compounds via the selenium heterocycles are easy to perform and require less skill and labour compared to those previously reported.[14,15] Furthermore, the yield is doubled.

By searching the literature of the last 20 years, it becomes evident that the use of the easy to prepare 2,1,3-benzoselenadiazole derivatives which give a simple route to less accessible quinoxalines, has not been appreciated. Besides, the reductive cleavage of 2,1,3-benzoselenadiazoles and their subsequent condensation with α-dicarbonyls, their reaction with appropriate dien-

ophiles in a Diels-Alder fashion constitute an alternative route to obtain quinoxalines. Synthons for poor dienophiles (e.g., acetylene and its monosubstituted derivatives) have now been developed and can be used under ordinary laboratory conditions.[22-25] Recently, the synthesis of a quinoxaline suspected as an antiallergic agent was achieved via the condensation of 2,1,3-benzoselenadiazole with dimethyl acetylenedicarboxylate.[26]

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References

1. Grivas, S., Nyhammar, T., Olsson, K. and Jägerstad, M. *Mutat. Res. 151* (1985) 177.
2. Taylor, R., Fultz, E. and Knize, M. *J. Environ. Sci. Health 20* (1985) 135.
3. Miller, A. J. *Food Technol. 39* (1985) 75.
4. Sugimura, T. *Mutat. Res. 150* (1985) 33.
5. Ishikawa, F., Takaku, F., Nagao, M., Ochiai, M., Hayashi, K., Takayama, S. and Sugimura, S. *Jpn. J. Cancer Res. (Gann) 76* (1985) 425.
6. Ohgaki, H., Hasegawa, H., Kato, T., Suenaga, M., Ubukata, M., Sato, S., Takayama, S. and Sugimura, T. *Proc. Jpn. Acad. B61* (1985) 137.
7. Sugimura, T. In: Yamagata, T., Hirayama, T. and Hisamichi, S., Eds. *Recent advances in cancer control.* Excerpta Medica, Amsterdam, Oxford, Princeton 1983, pp. 63–72.
8. Grivas, S., and Nyhammar, T. *Mutat. Res. 142* (1985) 5.
9. Takahashi, M., Wakabayashi, K., Nagao, M., Yamamoto, M., Masui, T., Goto, T., Kinae, N., Tomita, I. and Sugimura, T. *Carcinogenesis 6* (1985) 1195.
10. Adolfsson, L. and Olsson, K. *Acta Chem. Scand. B37* (1983) 157.
11. Kasai, H., Nishimura, S., Wakabayashi, K., Nagao, M. and Sugimura, T. *Proc. Jpn. Acad. B56* (1980) *382.*
12. Kasai, H., Yamaizumi, Z., Wakabayashi, K., Nagao, M., Sugimura, T., Yokoyama, S., Miyazawa, T. and Nishimura, S. *Chem. Lett.* (1980) 1391.
13. Lee, C.-S., Hashimoto, Y., Shudo, K. and Okamoto, T. *Chem. Pharm. Bull. 30* (1982) 1857.
14. Grivas, S. and Olsson, K. *Acta Chem. Scand. B39* (1985) 31; (a) Grivas, S. *ibid.*, 213.
15. Olsson, K. and Grivas, S. *Acta Chem. Scand. B 40. In press.*
16. Bird, C., Cheesman, G. and Sarsfield, A. *J. Chem. Soc.* (1963) 4767.
17. Elvidge, J., Newbold, G., Percival, A. and Senciall, I. *J. Chem. Soc.* (1965) 5119.
18. Klicnar, J. and Kosek, F. *Coll. Czech. Chem. Commun. 30* (1965) 3102.
19. Efros, L. and Todres-Selektor, Z. *J. Gen. Chem. USSR 27* (1957) 1064.
20. Olsson, K. and Grivas, S. *Chem. Scripta, To be published.*
21. Nyhammar, T. and Grivas, S. *Acta Chem. Scand. B 40. In press.*
22. De Lucchi, O. and Modena, G. *Tetrahedron 40* (1984) 2585.
23. Hermeling, D. and Schäfer, H. *Angew. Chem. Int. Ed. Engl. 23* (1984) 233.
24. De Lucchi, O., Lucchini, V., Pasquato, L. and Modena, G. *J. Org. chem. 49* (1984) 596.
25. Carr, R., Williams, R. and Paquette, L. *J. Org. Chem. 48* (1983) 4976.
26. Liu, K.-C. and Shih, B.-J. *J. Taiwan Pharm. Assoc. 35* (1983) 171.
27. Dolara, P., Salvadori, M., Santoni, G. and Caderni, G. *Mutat. Res. 144* (1985) 57.
28. Tanaka, T., Barnes, W., Williams, G. and Weisburger, J. *Jpn. J. Cancer Res. (Gann) 76* (1985) 570.
29. Clayson, D. B. *Mutat. Res. 154* (1985) 205.

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