HETEROCYCLIZATION WITH IMINIUM SALTS AND N-YLIDES

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Abstract

Novel 2,3a,6a-triazaphenalene and 1-thia-2a,5a-diaza-acenaphthene ring systems were synthesized and their ring transformation reactions affording polycycles with bridgehead nitrogen atom were investigated. 1,3-Dipolar cycloaddition of isoquinoline N-ylides with azomethines and olefines were studied and the regio- and stereoselectivity of the reaction were proved by structure elucidation and quantum chemical calculations.

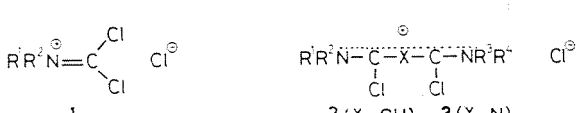
Introduction

During the past one and a half decade we have been interested in the synthesis of nitrogen bridgehead policycles of expected human therapeutic effect. This aim was achieved by elaborating versatile heterocyclyzation methods using reactive polar intermediates like iminium salts and N-ylids as well.

Results and Discussion

Synthesis of condensed polycycles with iminium synthons

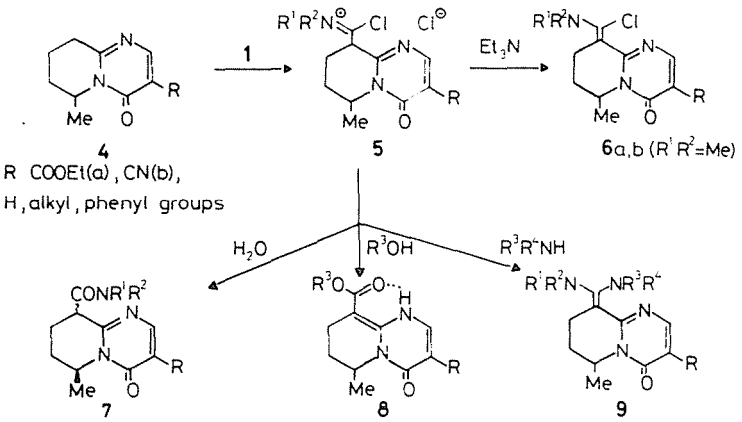
Earlier we reported on the advantageous applications of phosgen-iminium chlorides (*1*) and 1,3-trimethynecyanines (*2*, *3*) generated from *1* in the preparation of 1,3-benzoxazines, quinolines, quinazolines, pyrido[1,2-a]-pyrimidines and pyrido[1,2-a]triazines, respectively [1,2,3]. These reagents (Fig. 1) belonging to the family of iminium synthons are known to possess extreme electrophilicity and so they can readily react with O,S,N- and C-nucleophiles at mild conditions.



1 2 (X : CH), 3 (X = N)

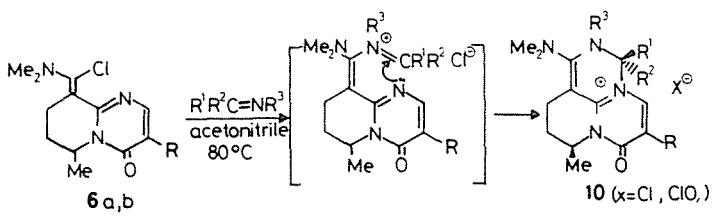
Fig. 1

For pharmacological considerations tetrahydro-pyrido[1,2-a]pyrimidin-4-ones (*4*) were chosen to be chemically developed by bringing about amide chloride moiety with *1*, which is capable of cyclizations and other transformations (Scheme 1) [4]. Compound *4a* is the intermediate of Probon—an analgesic pharmaceutical—developed by Mészáros in Chinoin [7]. The pseudo-acid character of CH_2-9 group in compounds *4* toward different electrophiles have been already reported [5, 6].



Scheme 1

Tautomerism and cis/trans isomerism of compounds *7*, *8* and *9* were investigeted by ^1H, ^{13}C and ^{15}N NMR spectroscopy [8, 9]. Antiasthmatic activity of derivatives of type *7* was observed [10]. Compound *6* of α-chloroenamine structure was found to undergo stepwise cycloaddition with azomethines affording the novel 2,3a-diaza-6a-azoniaphenalenium quaternary salts (Scheme 2) [11].

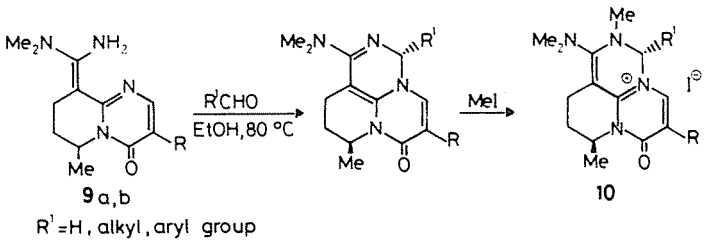


Scheme 2

We developed several other methods starting from *5*, *7* and *9* for synthesizing the neutral tricycle (2,3a,6a-triazaphenalene) [8, 12].

The structure proving approach of *10* was achieved by condensing *9* (R^3,R^4 = H) with aldehydes followed by quaternisation (Scheme 3) [8].

The quaternary tricycle (*10*) is extremely sensitive toward nucleophiles. The reaction taking place at C-4 atom is accompanied by N3a-C4 bond fission



Scheme 3

and subsequent recyclization with C5-R group (R = COOEt, CN) affording mesomer betaines of different kinds. The site of the nucleophilic attack was supported by the nucleophil molecular potential map of *10* [13] and unambiguously proved by chemical, NMR spectroscopic and X-ray crystallographic evidences [13, 14] (Fig. 2).

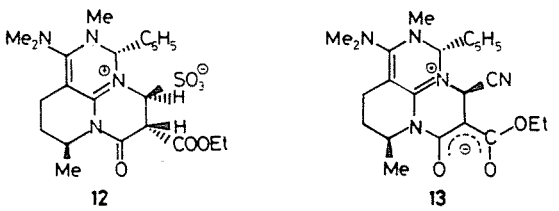


Fig. 2

The structures of the ring transformation products obtained with OH^- (*14a*), hydrazine (*15*) and various C-nucleophiles e.g. malonester (*16*), cyanoacetates (*17*), malononitrile (*18*) were determined by ^1H, ^{13}C NMR spectroscopy and X-ray crystallography, respectively [14, 15] (Fig. 3).

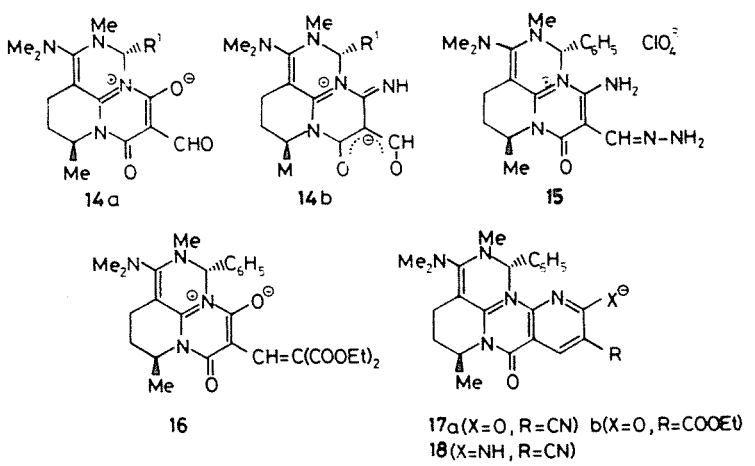
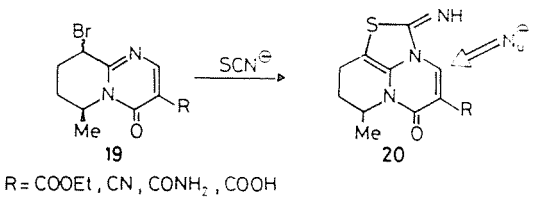


Fig. 3

Similar degenerate ring transformation was observed with 1-thia-2a,5a-diazaacenaphthene (*20*) which is also a new policycle prepared from *19* with thiocyanates (*16*) (Scheme 4).

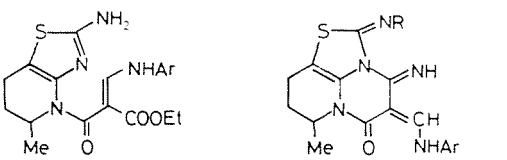


19 20

R = COOEt, CN, $CONH_2$, COOH

Scheme 4

Compound *20* can readily be attacked by even aromatic amines at the same carbon atom as shown previously furnishing ring cleaved (*21*) and recyclized (*22*) products, respectively [17] (Fig. 4).



21 21a(R=H), b(R=aryl group)

Fig. 4

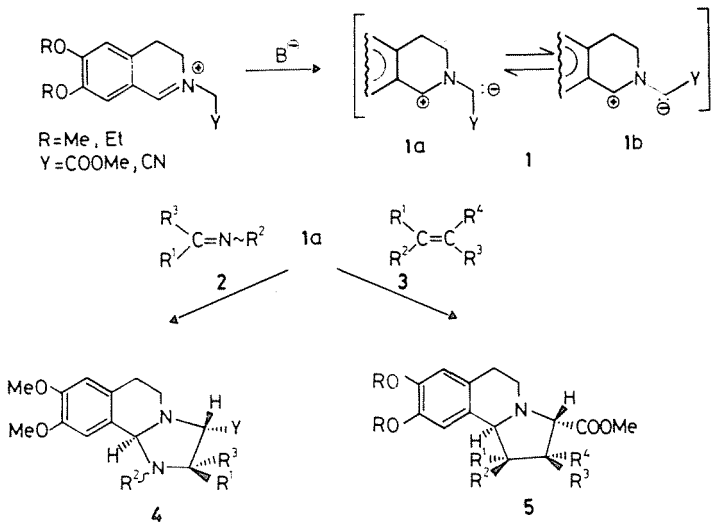
Reactions shown for 2,3a,6a-triazaphenalenes and 1-thia-2a,5a-diaza-acenaphthenes as well require extreme mild conditions (room temp., short time) providing novel and easy accessibility of bridgehead nitrogen polycycles of more elaborated structure.

1,3-Dipolar Cycloadditions of 3,4-Dihydro-6,7-dialkoxyisoquinoline Ylides

We have investigated the cycloaadition reactions of azomethines and olefins with ylide *1* generated from the appropriate isoquinolinium salts (Scheme 5).

The results of the preparative experiments and the structure elucidation, as well, clearly showed that the reactions took place regiospecifically and indicated also that the cycloadducts formed could only be derived from the cisoid form (*1a*) of the ylide. These statements were supported by the results of FMO and PMO calculations using CNDO/2 and CNDO/S methods [18].

Though the cycloadditions proved to be regiospecific, a variety of reactions with different diastereoselectivities could be observed. The dia-

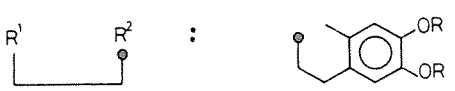


Scheme 5

stereoselectivities of the reactions are dependent on the structures of dipolarophiles (*2*, *3*) and can be interpreted by comparing the influences of both the steric (⌧) and electronic (↶) interactions occurring in the transition states (Fig. 5).

It can be deduced from the results of the additions of azomethines that steric interactions act as main governing factors influencing the diastereoselectivities of the reactions. The results of formation of adducts *4* are summarized in Table 1 [18, 19, 20].

Azomethines (*2*) used as dipolarophiles were either of cyclic type (*a* – *e*) or of E-geometry (*f* – *h*).



In the cases of the cycloadditions of olefines secondary orbital-interactions were found to predominate the stereochemistry. When reacting *1* with olefines (Ar—CH=CH—Z) of E type the cycloaddition results in the formation of only one product. In these cases the orientation *i* is highly preferable because of the energetically favourable electronic effects irrespective to the steric hindrances (Ar = C, Z = A). Changing the aromatic substituent (C) to an ester group (dimethylfumarate) the orientations become energetically comparable thus two products will form again. However, in the reaction of dimethyl maleate (A = B = COOMe) orientation *i* is both sterically and electronically favourable.

The results are summarized in Table 2 [18, 21].

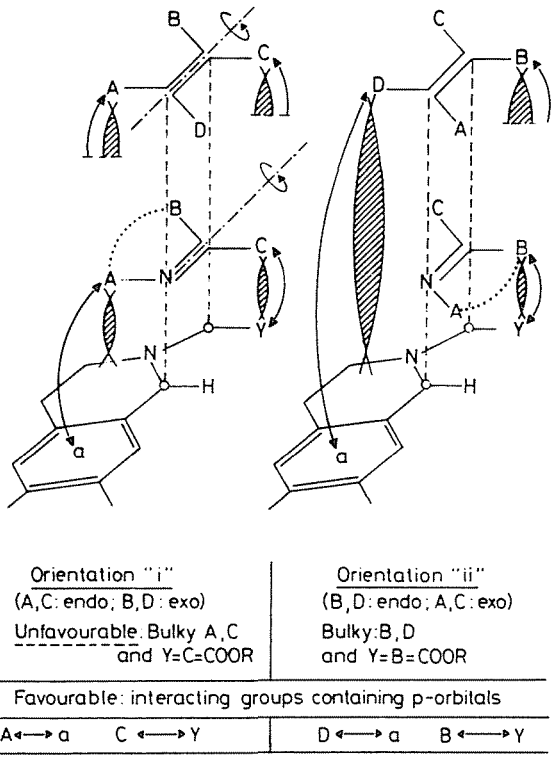


Fig. 5

Table 1

4	R^1	R^2	R^3	Y	%	Orientation
a	⌊——⌋		H	CN	28	i
b	H	⌊——⌋		CN	72	ii
c	⌊——⌋		H	COOEt	100	i
d	—CH_2—		Ph	COOEt	60	i
e	Ph	—CH_2—		COOEt	40	ii
f	C_6H_4—NO_2(p)	Ph	H	COOMe	65	ii
g	H	Ph	C_6H_4—NO_2(p)	COOMe	35	i
h	Ph	Me	H	COOMe	100	ii

Table 2

5	R^1	R^2	R^3	R^4	5	Orientation
a	H	NO_2	H	Ph	Et	
b	H	CN	H	Ph	Et	
c	H	COMe	H	$C_6H_4OMe(p)$	Et	i
d	CO_2Et	CO_2Et	H	Ph	Me	
e	H	CO_2Me	CO_2Me	H	Me	
f	H	CO_2Me	H	CO_2Me	Me	i 80%
g	CO_2Me	H	CO_2Me	H	Me	ii 20%

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References

1. Antus-Ercsényi, Á., Bitter, I.: Acta Chim. Hung., *99*, 29 (1979)
2. Bitter, I., Szőcs, L., Tőke, L.: Acta Chim. Hung., *107*, 55 (1981)
3. Bitter, I., Szőcs, L., Tőke, L.: Acta Chim. Hung., *107*, 171 (1981)
4. Hermecz, I., Bitter, I., Horváth, Á., Tóth, G., Mészáros, Z.: Tetrahedron Lett., 2557 (1979)
5. Bitter, I., Hermecz, I., Tóth, G., Dvortsák, P., Bende, Z., Mészáros, Z.: Tetrahedron Lett., 5039 (1979)
6. Hermecz, I., Breining, T., Mészáros, Z., Tóth, G., Bitter, I.: Heterocycles, *14*, 1953 (1980)
7. Mészáros, Z., Knoll, J., Szentmiklósi, P., Dávid, Á., Horváth, G., Hermecz, I.: Arzneim.-Forsch., *22*, 815 (1972)
8. Tóth, G., de la Cruz, C., Bitter, I., Hermecz, I., Pete, B., Mészáros, Z.: Org. Magn. Res., *20*, 229 (1982)
9. Bitter, I., Pete, B., Tóth, G., Hermecz, I., Mészáros, Z.: Heterocycles, *23*, 1093 (1985)
10. Hermecz, I., Breining, T., Vasvári-Debreczy, L., Mészáros, Z., Bitter, I., de Vos, C., Rodriguez, L.: J. Med. Chem., *26*, 1494 (1983)
11. Bitter, I., Pete, B., Hermecz, I., Tóth, G., Simon, K., Mészáros, Z.: Tetrahedron Lett., 2891 (1982)
12. Bitter, I., Pete, B., Tóth, G., Hermecz, I., Mészáros, Z.: Heterocycles, *23*, 1167 (1985)
13. Bitter, I., Pete, B., Hermecz, I., Simon, K., Tóth, G., Náray-Szabó, G., Mészáros, Z.: Heterocycles, *20*, 1891 (1983)
14. Bitter, I., Pete, B., Hermecz, I., Simon, K., Tóth, G., Mészáros, Z.: Heterocycles, *20*, 579 (1983)
15. Bitter, I., Pete, B., Tóth, G., Hermecz, I., Mészáros, Z.: Heterocycles, *23*, 2549 (1986)
16. Bitter, I., Tóth, G., Pete, B., Almásy, A., Hermecz, I., Mészáros, Z.: Heterocycles, *23*, 2289 (1985)

17. BITTER, I., TÓTH, G., PETE, B., HERMECZ, I., MÉSZÁROS, Z.: Heterocycles, *24*, 69 (1986)
18. BENDE, Z., TŐKE, L., WEBER, L., TÓTH, G., JANKE, F. and CSONKA, G.: Tetrahedron, *40*, 369 (1984)
19. BENDE, Z., SIMON, K., TÓTH, G., TŐKE, L. and WEBER, L.: Liebigs Ann. Chem. 924 (1982)
20. BENDE, Z., BITTER, I., TŐKE, L., WEBER, L., TÓTH, G. and JANKE, F.: Liebigs Ann. Chem. 2146 (1982)
21. TÓTH, G., JANKE, F., BENDE, Z., WEBER, L. and SIMON, K.: J. Chem. Soc. P I. 1961 (1983)

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