Study of *cis/trans* and *endo/exo* Diastereoselectivity in the [4+3]-Cycloaddition Reaction of 2-Functionalized Furans and Dimethyloxyallyl Cation: Preparation of Versatile Cycloheptane Synthons

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A study on the influence of steric and electronic effects of a function attached at C-2 of furans in the yield and diastereoselectivity of [4+3] cycloaddition reactions with oxyallyl cations is presented. In almost all studied furans a *cis* diastereospecificity and a high *endo* diastereoselectivity is observed. Increasing bulkyness of the function attached at C-2 of furans, increases the *endo* diastereoselectivity, but decreases yield. Increasing the electronic density of the furan system, by an electron donating group attached at C-2, increases yield and diastereoselectivity.

In relation with our interest in the preparation of polyfunctionalized cycloheptanes as synthetic precursors of biologically active natural products, in our research group we have carried out a systematic study of [4C(4π)+3C(2π)] cycloaddition reactions of C-2 functionalized furans as dienes with 1,3-dimethyl-oxyallyl cation as dienophile, (see Figure 1). Our primary interest in such study was to know the influence of the type of function attached at C-2 of furan in the yield and stereoselectivity of cycloaddition reactions.

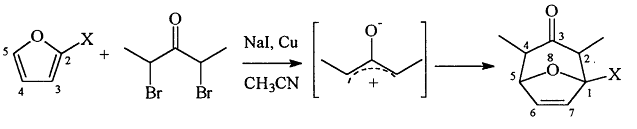

Figure 1. [4+3] Cycloaddition reaction.

We have not found in the literature any reference regarding a similar systematic study. Only, there are a few examples[1] where furans substituted at C-2 by aryl or alkyl groups are used as dienes in such reactions, but none with a function linked to C-2 through an heteroatom which is of our major interest here.

From C-2 functionalized furans it is possible to obtain bicyclic cycloadducts having on C-1 an organic function which facilitates openning of the oxygen bridge. This methodology has some advantages with respect to other synthetic approches because at least four different organic functions are introduced in the cycloadduct, since the beginning, maintaining at the same time the relative stereochemistry of substituents in the cycloheptane system. These features make the aforementioned cycloadducts very versatile and useful synthons, (see Figure 2).

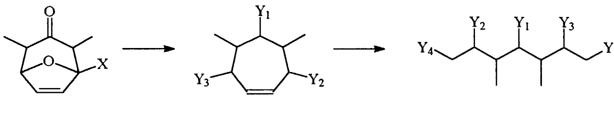

Figure 2. Syntethic applications of bicyclic cycloadducts.

In this work we have carried out [4+3] cycloaddition reactions of sixteen different 2-substituted furans, (see Table 1), we reacted the first four substrates, (entries 1 to 4), in order to evaluate mostly the steric effects on the yield and diastereoselectivity in the cycloaddition reaction. Substrates from entries 5 to 8 were considered to study steric and electronic effects. Entries from 9 to 16 were evaluated to observe the influence of the presence of an heteroatomic linkage, between the organic function and the C-2 atom of furan, in the outcome of cycloaddition reactions. In these experiments, 1,3-dimethyloxyallyl cation was used as dienophile. This cation is symmetric and it does not present regiochemistry problems, which considerably simplifies this study. It was generated *in situ* [1, 2, 3, 4] from 2,4-dibromo-3-pentanone by treatment with Cu / NaI in MeCN at 60 °C.

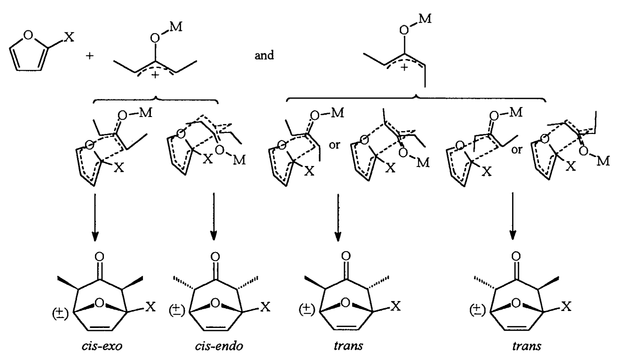

Figure 3. Possible diastereomeric cycloadducts.

From the evaluated furan substrates, four racemic diastereoisomeric cycloadducts are possible, depending on the relative position of substituents on C-1, C-2 and C-4 in the bicyclic system. As can be seen in Figure 3, considering a concerted mechanism for the cycloaddition reaction and depending on both the type of coupling, (extended or compact), and the configuration of oxyallyl cation, (*ZZ* or *ZE*), it is possible to obtain *endo/exo* and *cis/trans* cycloadducts respectively. In the present work we have studied both, reactivity of 2-functionalized furans evaluated by the parameters conversion and yield, and *cis-trans* as well as *endo-exo* diastereoselectivity in the cycloaddition reaction. These data have been obtained by ^{1}H-NMR and GC analysis and all experiments were carried out under the same standard conditions, [2a, 3, 14] in order to make results comparable. In

Table 1. Results of [4+3] cycloaddition reactions.

Furan Substrate			**Cycloaddition Results**			
Entry	**X**	**Preparation (Bibl.)**	**Yield (%)**[14]	**Conversion (%)**[14]	**Diastereo-selectivity**	
					cis:trans	endo:exo
1	H	6	63	100	100	80:20
2	Me	6	77	93	100	92:8
3	^{t}Bu	7	9	60	100	67:33
4	Ph	8	60	66	100	97:3
5	COOEt	6	27	97	100	97:3
6	COOCh	9	22	63	100	100
7	COH	6	25	10	68:14:14:5	
8	CH(OCH$_2$CH$_2$O)	10	54	100	100	60:40
9	OMe	6	84	96	100	67:33
10	OSiMe$_3$	6	86	100	100	95:5
11	OSiMe$_2$^{t}Bu	11	29	100	100	98:2
12	OCOPh	12	16	86	100	83:17
13	OCO^{t}Bu	13, 12	93	100	100	95:5
14	OCOOEt	12	100	37	100	100
15	OPO(NMe$_2$)$_2$	6	21	98	100	93:7
16	NO$_2$	6	13	82	100	96:4

Table 1, results from the evaluated 16 different furan models are shown. Furans were commercially available or synthesized according to the indicated bibliographic references.

From data quoted in Table 1 it is worth noting the *cis* diasterospecificity obtained in 15 of the 16 experiments carried out under our reaction conditions, the [4+3] cycloaddition, takes place *via* an oxyallyl cation having a "W" configuration.[1b, 2, 4a] This dienophile is trapped by the furan diene, through a concerted mechanism, affording exclusively the *cis* cycloadduct.

Even though it is not possible to observe neat steric and/or electronic effects, because both act simultaneously, (stereoelectronic effects[5]), we have selected appropriate furane substrates in order to rationalize how the type of substituents at C-2 of furans can affect conversion, yield and stereoselectivity. Peering at data from Table 1 allows to withdraw certain important conclusions: increasing size of substituent X increases *endo* diastereoselectivity. This phenomenon is induced by the steric repulsion between the bulky substituent and a methyl group of the oxyallyl cation. Compare, for example, entries 1,2,3, also 5,6 and 10,11 or 12,13. Also, it is possible to observe how rising bulkyness of the C-2 groups decreases conversion and/or yield, (see for example entries 2, 3,4 also 5,6 and 10,11). This is due to the lower accesibility of furan diene by the oxyallyl cation.

The presence of electron-withdrawing groups at C-2, (see entries 5-7 and 15,16), weakens substituted furans as dienes affording low to moderate yields of cycloadducts.

If alkyl groups, with slight electron-donating character, are anchored to position 2 of the furane ring, yields turn from moderate to good, (compare entries 1-4). Inserting groups with marked electron donating properties, (X=OR, OCOR, OSiRRR'), we obtain the best yields and conversions.

Finally, comparing entries 2 *versus* 9 and 5 *versus* 14, in which the only structural variation is the presence of an oxygen tether, we can appreciate a clear increase of yield in the reaction, by insertion of that oxygen atom. The origin of these results could be interpreted on the basis of the electron-donating nature of the sp^3 oxygen bearing two pairs of non-shared electrons, and in the fact that the bulky groups are farther apart in 10 and 14 than in 2 and 5 respectively.

In every cycloaddition experiment, the diastereoisomeric ratio was evaluated by GC and/or ^{1}H NMR. Cycloadducts were isolated from the reaction mixture and purified by column chromatography, and spectroscopically characterized. The stereochemical assignment of diastereoisomeric cycloadducts was carried out in an unequivocal way by a careful correlation of spectroscopic properties of the *cis* and *trans* as well as the *endo* and *exo* diastereoisomers, on the basis of 1D and 2D ^{1}H- and ^{13}C-NMR experiments: DEPT, COSY-45, COSY-90, DQF-COSY, HETCOR, HMBC, HMQC and PS-NOESY and ROESY.

In conclusion, we have submitted 16 different C-2 substituted furans to [4+3] cycloaddition reactions, obtaining a wide variety of C-1 functionalized 8-oxabyclo[3.2.1]-6-octen-3-one systems, with yields from moderate to good, *cis* diastereospecificity in almost all cases, and very high *endo* diastereoselectivity. All furans and cycloadducts were properly purified and physically and spectroscopically characterized.

At the moment we are applying these new properly fuctionalized bicyclic cycloadducts to the synthesis of bioactive natural products. Results from this work will be published at due curse.

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