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Synthesis and reactivity of (1*S*)-*N*-(1-phenylethyl)maleimide towards nucleophiles: an application to preparation of chiral pyrroloisothiochroman and pyrrolobenzo[*d*]thiepine based on π-cationic cyclization

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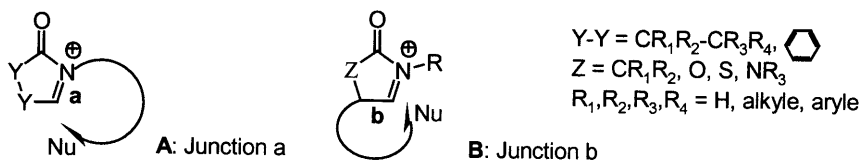
Abstract—Chiral pyrroloisothiochroman and pyrrolo[*d*]thiepine were obtained efficiently in four steps from *N*-alkylated maleimides via, successively, sulfurization, regioselective reduction followed by π-cationic cyclization of the *N*-acyliminium ion intermediates. These latter, in addition, led to conjugate enamides as a consequence of the dehydration reaction. © 2001 Elsevier Science Ltd. All rights reserved.

The α-amidoalkylation cyclization involving *N*-acyliminium ions is now widely regarded as a powerful methodology for carbon–carbon bond forming in organic synthesis.[1] During these processes the *N*-acyliminium ion species, which are generated in situ in acidic conditions most widely from stable α-hydroxylactams, α-alkoxylactams, carbamates and isomünchnone cycloadducts, are, in turn, capable of the capture of a weak tethered carbon nucleophile producing azapolycyclic systems, including a large variety of alkaloid products.[1,2]

As shown in Scheme 1, the cyclized products resulting in formation of a junction **a** as in form **A** are well documented.[1–3] In contrast, heterocycles obtained by formation of junction **b** (form **B**) are little explored and only a few reports concerning these species appear in the literature.[4a–d,5,6]

Because we are interested in developing *N*-acyliminium ion chemistry toward the formation–cleavage of the thioether linkage in *N*,*S*-fused polyheterocyclic systems[2c–e,7] and in the continuation of our program toward studies of *N*-arylthio(or aryloxo)alkylimides functionalities (Model I) in acidic medium, we investigated the cyclization process in succinimide series (form **B**) bearing an aryl(or aralkyl)thio R-S- group at C_3 position as an *N*-acyliminium ion precursor (Model II).

So, our strategy focused at the outset on construction of **N–C–C–S–R** functionality (Model II) by sulfurization of succinimide derivative at C_3, followed by trans-



Scheme 1.

Keywords: *N*-acyliminium ion; π-cationic cyclization; aza-compounds; isothiochroman; benzo[*d*]thiepine.

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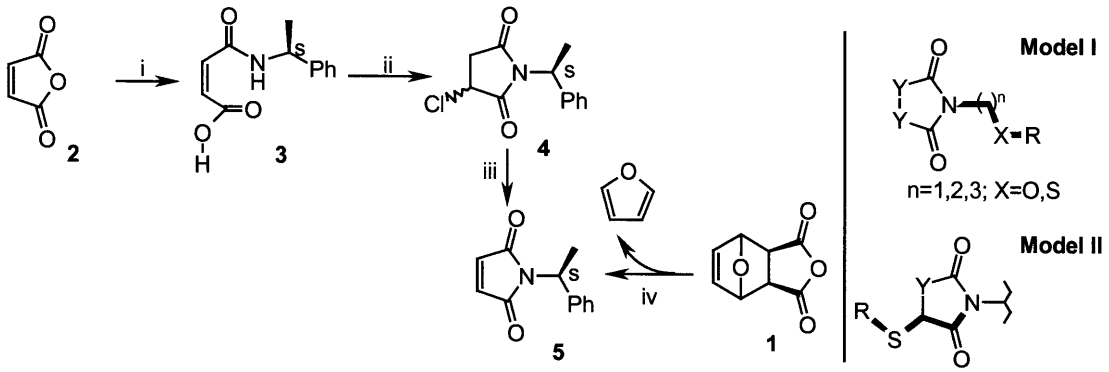
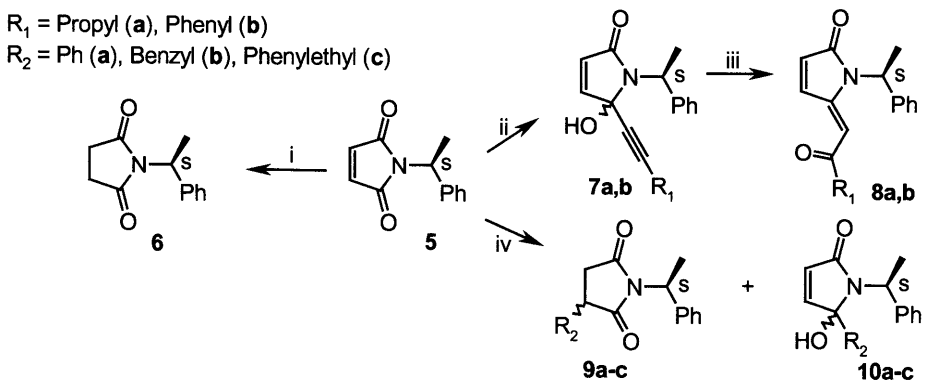
formation of its carbonyl group into hydroxy function as a key intermediate. In all cases, (1*S*)-*N*-(1-phenylethyl)maleimide **5** was used as a starting material. Construction of the latter was started with commercially available *exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride **1** by a newly tandem amine–anhydride cyclodehydration/retro-Diels–Alder reaction with release of furan in a 'one-pot' procedure (i.e. xylene, reflux, 12 h, 88%).[8,9a] This precursor was also obtained in another three-step sequence from maleic anhydride **2** with an overall yield of 73%[9b] (Scheme 2).

As depicted in Scheme 3, the substrate **5** was subjected to reduction, thionation and carbophilic addition in order to study the influence of steric and electronic effects in both reduction–addition and cyclization steps. Actually, reduction reaction of enone **5** was carried out with $NaBH_4$ in dry methanol at 0–5°C (monitored by tlc) and afforded only (*S*)-succinimide derivative **6** (98%),[10] which corresponds to a product of double bond C=C reduction. On the other hand, the enone–amide **5** was reacted with pentynyl(or phenylethynyl)lithium[11] in dry ether yielding the ω-carbinol lactam **7a** (65%) or **7b** (70%), which showed a 58/42 or 55/45 mixture of diastereoisomers inseparable by column chromatography. At this stage, it is worth mentioning that comparable diastereoselectivity was observed during the organolithium addition onto the carbonyl group of phthalimide bearing a chiral auxiliary.[11] The chemoselectivity of this organolithium addition reaction, as a 1,2-addition, was also confirmed by the formation of enamidone **8a** (84%) or **8b** (78%) as a single diastereoisomer from ω-alkynyl-ω-carbinol lactam **7a** or **7b** by a Meyer–Schuster rearrangement (i.e. PTSA, EtOH, reflux, 2 h).[12]

Under carbophilic addition conditions as pointed out in Table 1, with Grignard reagent as nucleophile, the Michael acceptor **5** led after hydrolysis to the 1,4- and/or 1,2-addition product(s) **9** and/or **10** in good yield(s). To avoid the formation of enamide, as a consequence of a dehydration reaction in the cases of substrates **9** and **10b**,**c** under an acidic influence,[13] a neutral hydrolysis under moderate temperature was necessary. Interestingly, the results given above show that the reactions proceeded with high to excellent yields and that the regiochemistry depended upon the nature (basicity) of the R_2 group in the Grignard reagent. In fact, exclusive 1,2- and 1,4-addition was obtained with phenylmagnesium bromide and phenylethylmagnesium bromide to give **10a** (79%) and **9c** (69%), respectively, whereas benzylmagnesium bromide gave in quantitative yield a separable mixture (silica gel, CH_2Cl_2) of the regioisomers **9b** and **10b** in 78:22 ratio.



Scheme 2. Reagents: (i) 1 equiv. of (*S*)-MeCH(CH_2)Ph, CH_2Cl_2, 0°C then 16 h at rt; (ii) 1 equiv. of $(COCl)_2$, 1 drop of DMF, 8 h at rt; (iii) 1 equiv. of NEt_3, CH_2Cl_2, 1 h at rt; (iv) 1 equiv. of (*S*)-MeCH(NH_2)Ph, xylene, 12 h at reflux.

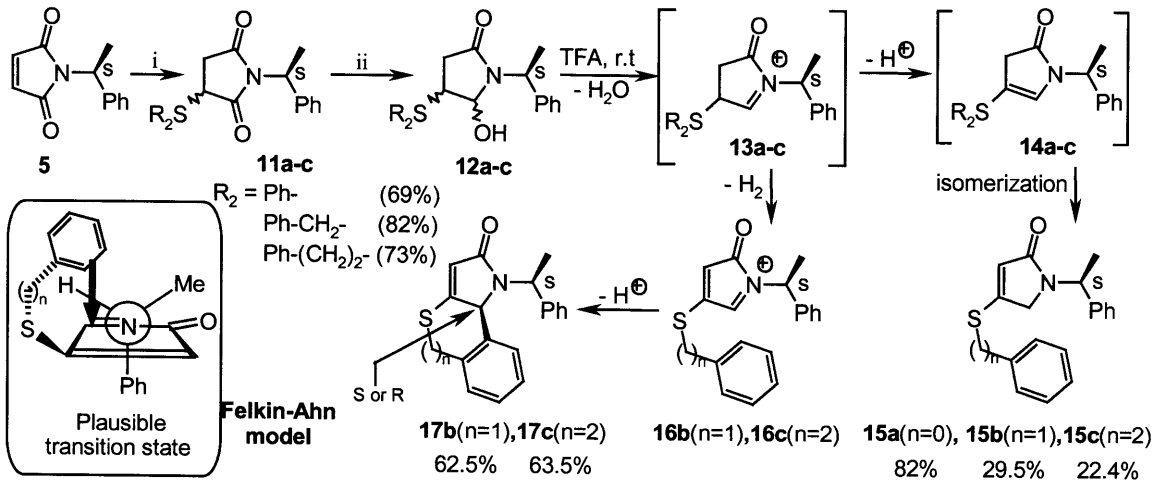


Scheme 3. Reagents: (i) 6 equiv. of $NaBH_4$, methanol, 0–5°C, 30 min; (ii) R_1-CC-Li, Et_2O, 0–25°C, 3 h; (iii) PTSA, ethanol, reflux, 2 h; (iv) R_2-MgX, see Table 1 for reaction conditions.

Table 1. Grignard reagent addition onto Michael acceptor enone **5**; derivatives **9** and **10** produced via Scheme 3

Products	R_2-MgX	Hydrolysis conditions[a]	Ratio of products **9**/**10**[b]	Diastereoisomeric ratio of products **9**/**10**[d]	Yield %
a	R_2=Ph; 1.2 equiv.	2 M NH_4Cl, 0–10°C	0/100	–; 86/14	79
b	R_2=$PhCH_2$; 3.5 equiv.	H_2O, 10–20°C	78/22[c]	56/44; 55/45	>99
c	R_2=$Ph(CH_2)_2$; 4.0 equiv.	H_2O, 10–20°C	100/0	57/43; –	69

[a] Reaction conditions: (1) R_2-MgX, CH_2Cl_2/ether (3/2), 1 h at 0°C then 3 h at rt. (2) Hydrolysis conditions.
[b] The ratios of the different diastereoisomers of products **9** and **10** has been determined, but their configurations could not be assigned with certainty.
[c] Regioisomer products **9**,**10b** were separated by chromatography on silica gel column using CH_2Cl_2 as eluent.
[d] The ratios of regio- and stereoisomer compounds were determined by ^1H NMR analysis.



Scheme 4. Reagents: (i) 1–1.2 equiv. of MeONa, 1–1.2 equiv. of R_2SH, C_6H_6, 40–60°C, 12 h; (ii) $NaBH_4$, MeOH, 0–5°C, 30 min.

Since it was possible that imides **11a**–**c** could provide to cyclic lactams **17** via π-aromatic cyclization, we explored the elaboration of different aromatic models, substituted by phenyl, benzyl and phenylethyl groups on the sulfur atom at C_3 position of succinimide ring to establish the generality and versatility of the synthetic approach depicted in Scheme 4.

Imides **11a**–**c** were readily obtained by a modified thionation procedure from enone–amide **5** (Scheme 4).[13] Regioselective reduction of chiral imides **11a**–**c** with $NaBH_4$ in MeOH at 0–5°C afforded α-hydroxylactams **12a**–**c** as diastereoisomeric mixtures in 69, 82 and 73% yields, respectively. These α-hydroxylactams were used in the next step without further purification.

The α-hydroxylactam **12a** was subjected to neat TFA at rt, and led to a stable conjugated pyrrolidinone **15a** (82%). This latter was a consequence of a deprotonation of *N*-acyliminium ion **13a** followed by isomerization of unstable enamide **14a**. Under these conditions, α-hydroxylactams **12b**,**c** furnished a separable mixture of **17b** (68%), **15b** (32%) in a 92% yield and **17c** (74%), **15c** (26%) in a 86% yield, respectively. Pyrrolidinones **15b**,**c** were formed in similar process advanced for **12a**, while **17b**,**c** required a π-aromatic intermolecular α-amidoalkylation cyclization of *N*-acyliminium ion intermediates **16b**,**c** obtained from *N*-acyliminium ions **13b**,**c** by spontaneous loss of an dihydrogen molecule (Scheme 4).[14,15] These observations were in contrast to these reported earlier for similar structures not bearing chiral auxiliaries.[4b–d,6]

The stereoselectivity observed during the π-cyclization of α-hydroxylactams in acidic medium seems to proceed probably through Felkin–Ahn like transition state (Scheme 4), which involves the approach of a nucleophile from the upper side to produce the adducts **17b** an **17c** as a single diastereoisomer.[11]

In summary, we have shown that the **N**–**C**–**C**–**S**–**R** functionality in pyrrolidine ring as an *N*-acyliminium ion precursor, produces efficiently new benzo[*c*]thiopyran **17b** and benzo[*d*]thiepine **17c** cycles fused to pyrrole ring via a tandem dehydrogenation/intramolecular arylation. However, in an interrupted π-cationic cyclization, the iminium salt intermediate **13** undergoes a deprotonation leading to the expected disubstituted pyrrolidinone **15b**,**c**.

Acknowledgements

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