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Two Novel Diastereoselective Three-Component Reactions of Alkenes or 3,4-Dihydro-(2*H*)-pyran with Urea/Thiourea–Aldehyde Mixtures: [4 + 2] Cycloaddition vs Biginelli-Type Reaction

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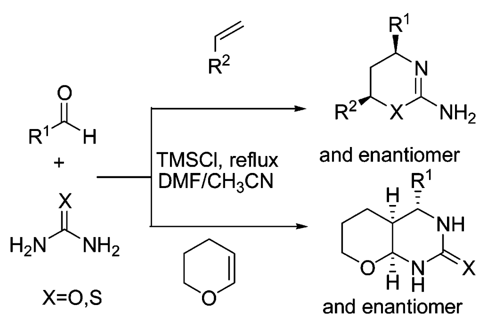
ABSTRACT



Two novel diastereoselective three-component reactions of alkenes or 3,4-dihydro-(2*H*)-pyran with urea/thiourea–aldehyde mixtures are described.

Numerous classical multicomponent reactions[1] (MCRs) employ the in situ condensation of aldehydes, amines, or amides to give reactive imine or enamine derivatives, which subsequently react with other different components in processes such as the Mannich reaction,[2] the Strecker reaction,[3] and the Biginelli reaction[4] to name but a few. It is also well-known that *N*-acylimines are valuable partners in cycloaddition reactions,[5] acting as dienophiles[6] or dienes[7] in [4 + 2] cycloadditions.

We recently disclosed a novel three-component, one-pot reaction[8] involving alkynes, urea or thiourea, and aldehydes.

It was found that the intermediary *N*-acyliminium ions undergo a hetero [4 + 2] cycloaddition with alkynes. In light of this, we considered that the analogous mechanism might be utilized for alkenes instead of alkynes (Scheme 1). Herein, we report two three-component reactions of alkenes or 3,4-dihydro-(2*H*)-pyran with urea/thiourea-aldehyde mixtures.

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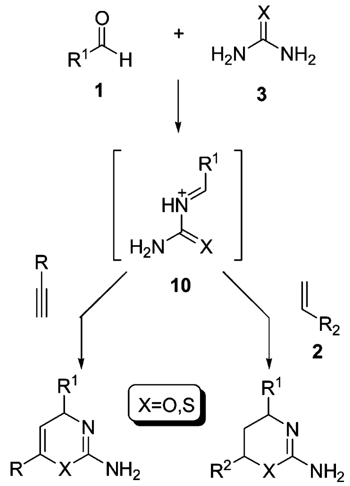
Scheme 1



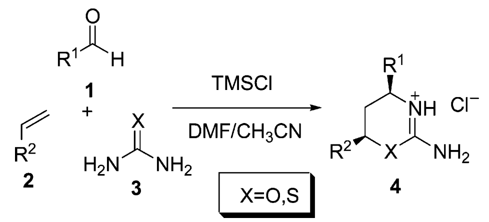
We initiated our studies by subjecting benzaldehyde (**1a**), styrene (**2a**), and thiourea to TMSCl in CH_3CN/DMF (2/1) at reflux temperature, which afforded 2-amino-4-phenyl-6-*p*-tolyl-5,6-dihydro-4*H*-1,3-thiazin-3-ium chloride **4a** in 91% yield (Table 1, entry 1). Only the *cis* diastereomer (with respect to R^1 and R^2) was observed as determined by NOE experiments and X-ray crystallography (Figure 1).

Because of its great facility and low cost, we proceeded to examine the scope of this transformation with various aromatic aldehydes, aromatic alkenes, and urea or thiourea (Table 1). All products were isolated as single *cis* diastereomers. The regioselectivity of the [4 + 2] cycloaddition of both the *N*-acyliminium ion and *N*-thioacyliminium processes with an alkene is well documented.[5,7] Encouraged by the results obtained from the reaction with alkenes, we turned our attention to 3,4-dihydro-(2*H*)-pyran **5**. To our surprise, 3,4-dihydro-(2*H*)-pyran **5** did not follow the same rules as alkenes. However, the reaction of **5** with urea and 4-methylbenzaldehyde proceeded smoothly to deliver 4-*p*-tolyl-hexahydro-1*H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-one **6a** in 86% yield (Table 2, entry 1). Although three chiral centers are created, only one diastereomer is formed in a highly selective way (Figure 2).[9]

To test this type of MCR, the scope of the reaction was investigated with various aromatic aldehydes and urea or thiourea under the same protocol. All reactions proceeded smoothly to provide corresponding hexahydro-4-phenyl-1*H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-ones or hexahydro-4-phenyl-1*H*-pyrano[2,3-*d*]pyrimidine-2(8a*H*)-thiones (Table 2).

Scheme 2 shows a possible mechanism for this Biginelli-type reaction, which is based on the mechanism suggested by Overman.[10] The formation of **6** is considered to be a stepwise cyclocondensation of 3,4-dihydro-(2*H*)-pyran **5** with the *N*-acyliminium ion intermediate **10** generated from an aldehyde and urea. The stepwise nature of this cyclocondensation contrasts with the first hetero Diels−Alder reaction of *N*-acyliminium ion intermediate **10**. As shown in Scheme

Table 1. Multicomponent Reaction of Aryl Alkenes, Urea or Thioureas, and Aryl Aldehydes for the Synthesis of **4a**−**n**[a,b]



entry	R^1	X	R^2	product	yield[c] (%)
1	C_6H_5	S	4-$CH_3C_6H_4$	**4a**	91
2	C_6H_5	S	C_6H_5	**4b**	79
3	4-$CH_3C_6H_4$	S	C_6H_5	**4c**	92
4	4-$CH_3OC_6H_4$	S	C_6H_5	**4d**	88
5	2-FC_6H_4	S	C_6H_5	**4e**	85
6	4-$CH_3C_6H_4$	O	C_6H_5	**4f**	78
7	4-$CH_3C_6H_4$	S	4-$CH_3C_6H_4$	**4g**	88
8	2-FC_6H_4	S	4-$CH_3C_6H_4$	**4h**	87

[a] While we tried as many reactions with urea as thiourea, only benzaldehyde proceeded smoothly with urea and styrene to give the corresponding product. More details about this kind of reactions may be described on the basis of further study. [b] Reaction conditions: **1** (5 mmol), **2** (5 mmol), and **3** (6 mmol), TMSCl (5 mmol), DMF/CH_3CN (1.5 mL/3 mL), reflux, 10 h. [c] Isolated yields.

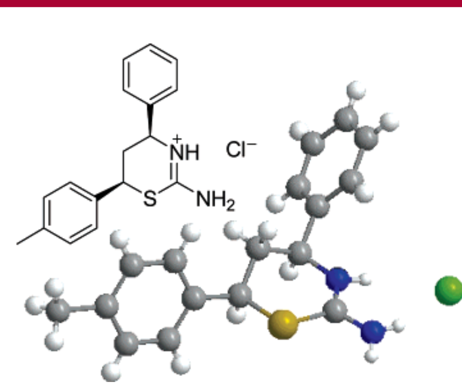


Figure 1. X-ray crystal structure of compound **4a**.

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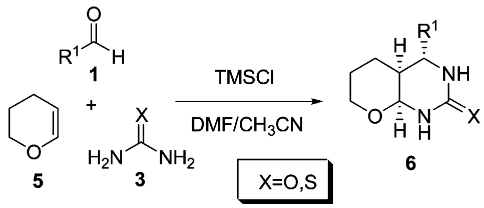
Table 2. Multicomponent Reaction of 3,4-Dihydro-(2*H*)-pyran, Urea or Thioureas, and Aryl Aldehydes for the Synthesis of **6a**−**n**[a]



entry	R^1	X	product	yield[b] (%)
1	4-$CH_3C_6H_4$	O	**6a**	86
2	C_6H_5	O	**6b**	89
3	4-$CH_3OC_6H_4$	O	**6c**	79
4	4-ClC_6H_4	O	**6d**	92
5	C_6H_5	S	**6e**	86
6	2-FC_6H_4	S	**6f**	89
7	4-$CH_3C_6H_4$	S	**6g**	83
8	4-$CH_3OC_6H_4$	S	**6h**	80
9	4-FC_6H_4	S	**6i**	84
10	2-$CH_3OC_6H_4$	S	**6j**	90
11	3-$NO_2C_6H_4$	S	**6k**	87

[a] Reaction conditions: **1** (5 mmol), **5** (5 mmol), and **3** (6 mmol), TMSCl (5 mmol), DMF/CH_3CN (1.5 mL/3 mL), reflux, 10 h. [b] Isolated yields.

2, initial addition of **5** to **10** in an *exo* fashion would lead to one limiting reactive conformer of the intermediate 2,3,4,5-tetrahydropyrylium **8**. On the other hand, *endo* addition of **5** to **10** would lead to reactive intermediate 2,3,4,5-tetrahydropyrylium conformer **9**. The severe steric interaction between the tetrahydropyrylium cycle and urea group disfavors the reaction via **9**, and the observed product **6** arises from the trapping of intermediate **8**.

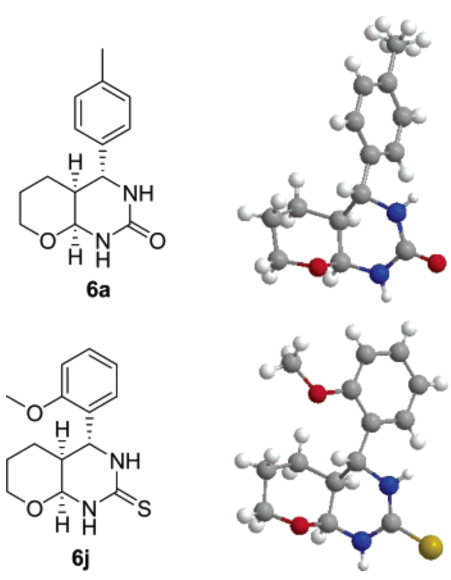
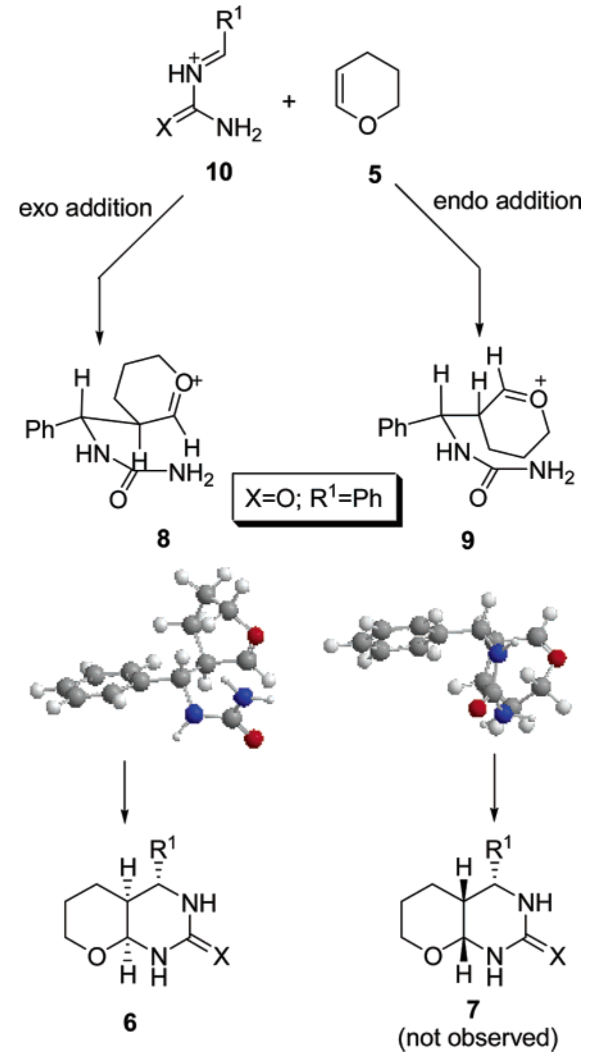


Figure 2. X-ray crystal structure of compounds **6a** and **6j**.

Scheme 2. Proposed Mechanism of the Cyclocondensation



In conclusion, we have developed two new multicomponent reactions; the first reaction constitutes a facile synthesis of 2-amino-5,6-dihydro-4*H*-1,3-thiazin-3-ium chloride salts[11] or 2-amino-5,6-dihydro-4*H*-1,3-oxazin-3-ium chloride salts,[12] while the second one is a simple three-component process leading to hexahydro-4-phenyl-1*H*-pyrano[2,3-*d*]pyrimidin-2(8a*H*)-ones or hexahydro-4-phenyl-1*H*-pyrano[2,3-*d*]pyrimidine-2(8a*H*)-thiones. Further determination of the scope and limitations of this process is still under investigation.

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Supporting Information Available: Experimental procedures and spectral data for all compounds and crystallographic information file (CIF) for **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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