A chemo- and regio-selective three-component dihydropyrimidinone synthesis†

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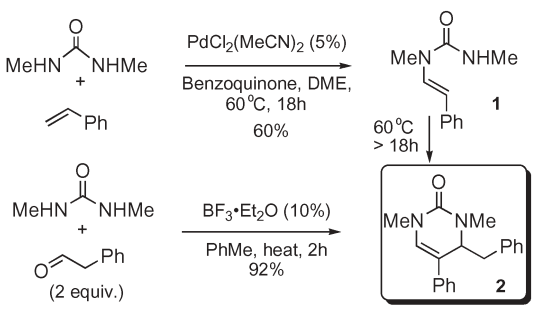
A selective three-component coupling, involving co-condensation of aldehyde pairs with substituted ureas under Lewis acid catalysis, provides rapid access to highly functionalised dihydropyrimidinones; sulfamides react analogously.

In 1933 Folkers and Johnson[1] reported that urea (H_2NCONH_2) reacts with phenylacetaldehyde in ethanol at reflux, catalysed by hydrochloric acid, to give 4-benzyl-5-phenyl-dihydropyrimidinone. In the context of modern efforts towards developing multi component reactions (MCRs) it is surprising that no further work appears to have been reported on the extension of this potentially useful reaction. During recent studies involving the development of Pd(II)-catalysed methods for diamination of alkenes,[2] we noted that *N,N′*-dimethyl urea (DMU) added to styrene to produce the enamide **1** (Scheme 1),[3] and, over longer periods of time, the dihydropyrimidinone **2** (16%, 72 h). It was subsequently found that simply heating two equivalents of phenylacetaldehyde with DMU in the presence of $BF_3{\cdot}Et_2O$ (10%) as a catalyst afforded **2** in 92% yield. Herein we report on the development of this reaction sequence to facilitate condensation of a range of *N*- and *N,N′*-substituted ureas with aldehydes. Intriguingly, the reaction proceeds with high chemo- and regio-selectivity when pairs of aldehydes are co-reacted, to generate the hetero-condensation products in good yield.

The reaction between two molecules of aldehyde and one of urea has similarities to the well-established three-component Biginelli reaction[4,5] (aldehyde, β-ketoester and urea/thiourea), where research is now focused on development of milder conditions and asymmetric modifications.[6] Recently Pan *et al.*[7] reported that bicyclic and spirocyclic fused pyrimidinones are generated *via* an efficient MCR between urea or thiourea with cyclic ketones and aromatic aldehydes. The reaction requires a full equivalent of TMSCl as promoter,[8] there being no reaction when a range of other Lewis acids systems, including $BF_3{\cdot}Et_2O$, were tested. In contrast, the reaction of DMU with phenylacetaldehyde proceeds efficiently with catalytic quantities of $BF_3{\cdot}Et_2O$ in toluene,[9] Scheme 1. We thus sought to examine the scope of the condensation with a range of aliphatic aldehydes and found that, in general, the homocoupling was complete within 2–5 h, Table 1. Generally, yields were slightly higher (~10%) when molecular sieves were employed, suggesting potential reversibility due to hydrolysis of intermediates, although once formed, the dihydropyrimidinone products were stable. Use of *N,N′*-dimethylsulfamide led to the corresponding cyclic sulfamide, entries 11–13.



Scheme 1 Discovery and optimization of a novel dihydropyrimidinone synthesis.

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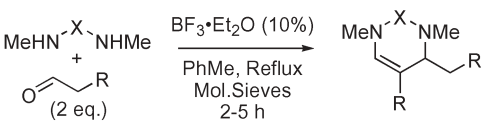
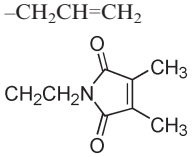
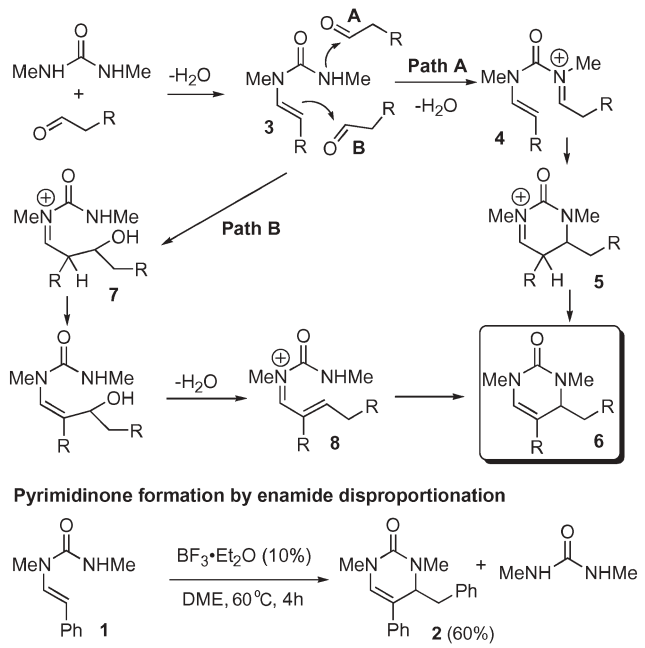
In the reaction of DMU with phenylacetaldehyde the formation of enamide **1** could clearly be seen by TLC, thus confirming **1** as an early intermediate in the overall sequence to the pyrimidinone **2**. Significantly, subjecting a pure sample of **1** (prepared from Pd(II) sequence) to the $BF_3{\cdot}Et_2O$ conditions results in the formation of **2** (60%) plus the formation of DMU. We suggest that the generation of the pyrimidinones proceeds by initial formation of the enamide **3** through an aldehyde/DMU condensation, Scheme 2. Enamide **3** can react further with another equivalent of aldehyde by two

Table 1 Homocoupling of aldehydes with DMU and sulfamides



Entry	X	R	Pyrimidinone yield (%)
1	CO	–Ph	92
2	CO	$-CH_2Ph$	86
3	CO	$-CH_3$	74[a]
4	CO	$-CH_2CH_3$	70
5	CO	$-CH_2CH_2CH_3$	87
6	CO	$-CH(CH_3)_2$	62
7	CO	$-CH_2(CH_2)_2CH_3$	88[a]
8	CO	$-CH_2(CH_2)_3CH_3$	86[a]
9	CO	$-CH_2CH{=}CH_2$	76[a]
10	CO		25
11	SO_2	–Ph	51
12	SO_2	$-CH_2Ph$	53
13	SO_2	$-CH_3$	52

[a] 3 eq. of aldehyde added to urea solution at reflux.



Pyrimidinone formation by enamide disproportionation

Scheme 2 Possible mechanisms for condensation.

pathways. Firstly, further reaction with the secondary nitrogen would lead to the iminium ion **4** (Path A). This could then undergo cyclisation to the iminium ion **5** followed by proton loss to the afford the product **6**. It is equally plausible that the reaction involves attack of the β-carbon in **3** on the aldehyde to generate the iminium ion **7** (Path B). This species can then undergo proton loss and dehydration to generate the α,β-unsaturated iminium ion **8**, which then undergoes cyclisation to **6**.

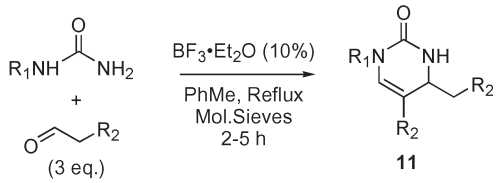
We then explored the possibility of developing this sequence into a 3-component *hetero*coupling by studying the reaction of DMU with phenylacetaldehyde and other aldehydes, Table 2. Simply heating equimolar mixtures of the two aldehydes generated the hetero **9** and homo-coupled pyrimidinone **10** in a ratio of 3.8 : 1 (Entry 1). This surprisingly selective result (4 possible products) indicates that phenylacetaldehyde reacts first because it results in a conjugated enamide. Use of two equivalents of phenylpropionaldehyde gave an improved ratio of 6.25 : 1 in an impressive 89% yield (Entry 2). Further equivalents of phenylpropionaldehyde

Table 2 Heterocoupling of aldehydes with DMU

Entry	R (eq.)	**9** : **10**	Yield (%)
1	$-CH_2Ph$ (1)	3.8 : 1	68
2	$-CH_2Ph$ (2)	6.25 : 1	89
3	$-CH_2Ph$ (3)	7.5 : 1[a]	77
4	$-CH_2CH_3$ (2)	4.3 : 1[b]	67
5	$-CH(CH_3)_2$ (2)	3 : 0[c]	45

[a] Homocoupling product of phenylpropionaldehyde observed as side product (23%); [b] Homocoupling product of propionaldehyde observed as side product (10%); [c] No **10** formed but 15% of other isomeric product of **9** observed.

Table 3 Selective homocoupling of aldehydes with mono-substituted ureas



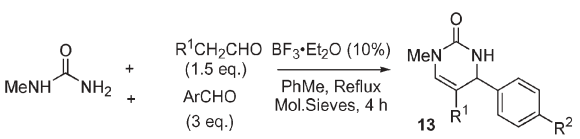
Entry	R_1	R_2	**11** Yield (%)
1	–Me	$-CH_2CH_2CH_3$	67
2	–Me	–Ph	59
3	–Ph	–Ph	56
4	–Ph	$-CH_2CH_2CH_3$	62

increased the **9** : **10** ratio slightly but at the expense of overall yield due to the competing formation (23%) of the phenylpropionaldehyde homocoupled product (Entry 3).

We then explored the reaction of monosubstituted ureas with aldehydes in a homocoupling sequence. Initially it was speculated that the most nucleophilic nitrogen would be likely to influence the enamide formation and thus control the ultimate regiochemistry of the overall coupling. In the four examples studied only one regioisomer of the pyrimidinone was observed which indicated that the substituted urea nitrogen is the most nucleophilic and forms the enamide, Table 3. For entries 3 and 4, however, we were surprised to observe that the product was formed from an enamide which itself was formed from apparent attack of the *N*-phenylurea on the aldehyde by the inherently much less nucleophilic aniline nitrogen. We suggest that this high degree of chemoselectivity can be attributed to attack by the unsubstituted nitrogen, which would lead to unproductive and reversible imine rather than enamide formation.[10]

Further elaboration of this principle with mono-substituted ureas allowed the realisation of a selective three component coupling with two different aldehydes to yield the single pyrimidinones **13** in reasonable yields (Table 4). Key to the success of this was the use of aryl aldehydes. According to the mechanisms outlined in Scheme 2, these cannot form an enamide and thus selectivity is assured in a heterocoupling sequence.

Table 4 Selective three-component coupling of mono-substituted ureas with aliphatic and aromatic aldehydes



Entry	R^1	R^2	**13** Yield (%)
1	$-CH_2CH_2CH_3$	–H	60
2	$-CH_2CH_2CH_3$	–Cl	59
3	$-CH_2CH_2CH_3$	–OMe	51
4	$-CH_2Ph$	–H	60

In summary, we have demonstrated that ureas and sulfamides undergo a useful three-component coupling sequence to provide pyrimidinones in moderate to high yields. The reaction has proved to be of broad scope, reproducible, operationally simple and allows the rapid assembly of dihydropyrimidinones containing

functionality suitable for further elaboration (*e.g.* **14** to **15**).[11] This methodology produces complimentary products to those obtained by the well known Biginelli reaction and as such should prove to be useful in the synthesis of potentially pharmacologically important molecules.

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Notes and references

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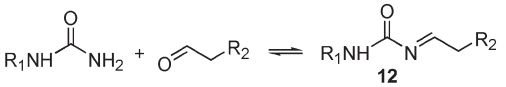
8 In addition to ketone–benzaldehyde coupling, these authors observed *homocoupling* of a few aliphatic aldehydes with urea to give pyrimidinones analogous to those reported in this study. Interestingly, under our conditions ($BF_3{\cdot}Et_2O$ catalysis) the only reactions observed between, for example, phenylacetaldehyde and acetone were those of homocoupling of the more reactive aldehyde with the DMU (60%).
9 Reactions with TsOH gave pyrimidinones but were very sluggish and did not proceed to completion. Reactions without any acid catalyst gave no product.
10 For example, initial condensation *via* the primary nitrogen would yield the imine **12** rather than the enamide. This imine would be unlikely to condense with another aldehyde and thus be succeptible to hydrolysis back to the urea and the aldehyde.



11 For example, rapid assembly of the 7,6-fused pyrimidinone **15** was achieved in two steps from DMU and 4-pentenal followed by RCM of the resulting pyrimidinone diene **14** with Grubbs I catalyst.