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Modified multicomponent Biginelli–Atwal reaction towards a straightforward construction of 5,6-dihydropyrimidin-4-ones†

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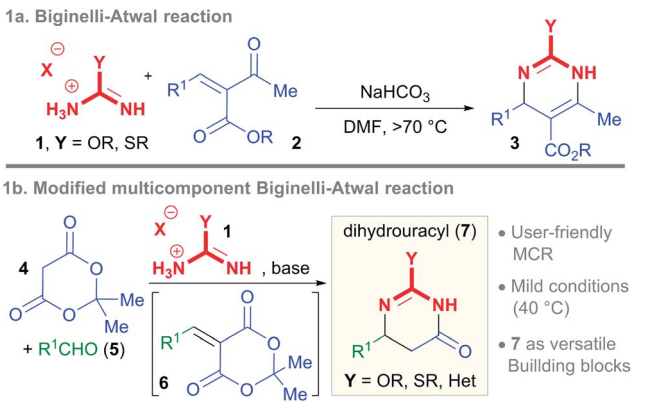
A straightforward access to 5,6-dihydropyrimidin-4-ones as racemic mixtures or enantiopure diastereoisomers was achieved thanks to a multicomponent Knoevenagel-aza-Michael-Cyclocondensation reaction involving Meldrum's acid and isourea derivatives. This constitutes not only a novel MCR of the original Biginelli–Atwal condensation but allows the construction of dihydrouracyl derivatives known as biorelevant diazole architectures.

Introduction

A great deal of methodological investigations have been driven by the elaboration of 3,4-dihydropyrimidines, a significant core structure of medicinal ingredients. In that context, the Biginelli condensation, a robust multicomponent reaction (MCR), stands out.[1] Involving a mixture of aldehyde, urea and acetoacetic ester derivative, this sequence, mostly promoted by acid additives, led to various substituted 3,4-dihydropyrimidines. In 1987, Atwal and colleagues proposed a complementary approach upon orthogonal basic conditions, allowed by the use of isourea ammonium salts derivatives **1** and enones **2**, pre-synthesized Michael-acceptors (Scheme 1a).[2] This alternative strategy not only extended the scope of the original Biginelli condensation – *i.e.*, larger tolerance of both aliphatic and more hindered aldehydes – but allowed the synthesis of new bioactive 1,4-dihydropyrimidines architectures **3** such as antihypertensive agents.[3] Unfortunately, despite Kappe's contribution in solid phase synthesis,[4] the MCR of Biginelli–Atwal's condensation is still challenging.[1a–e] We reasoned that a modified but multicomponent Biginelli–Atwal reaction could be feasible by starting from Meldrum's acid **4** in the presence of aldehydes **5** as precursors of reactive alkylidene derivatives **6** upon basic conditions,[5] ready to be engaged along a domino Knoevenagel-aza-Michael-Cyclocondensation (KaMC) reaction (Scheme 1b).[6] This approach would not only extend the scope of Meldrum's acid **4** connected to MCR[6,7] but also open a straightforward access to 5,6-dihydropyrimidin-4-ones **7**. Derivatives **7**, or dihydrouracyl derived thereof, are indeed representative backbones or precursors of naturally occurring and bioactive compounds,[8] β-amino acids and nucleobases.[9]

A literature survey pointed out that interesting multicomponent, likely KaMC reactions, between Meldrum's acid **4** and aldehydes were reported with urea component in refluxing AcOH,[10] heterocycles-embedded guanidine motif,[11] and guanidines itself,[12] although significant heating conditions are usually required and limit the scope of these approaches.[7] In one case,[12b] Balalaie performed a MCR with guanidinium carbonate in refluxing EtOH with aromatic aldehydes. Very recently, an encouraging perspective towards diversification was achieved using the benzamidine nucleophile allowing the use of a larger array of aldehydes such as some aliphatic ones in the presence of Et_3N in refluxing EtOH.[13]

We are pleased to report hereby on an innovative modified multicomponent Biginelli–Atwal reaction between Meldrum's acid **4**, isourea derivatives **1** and various type of aldehydes **5** upon smooth basic conditions (<40 °C). This eventually opens a straightforward access to 5,6-dihydropyrimidin-4-ones **7** both in



Scheme 1 Modified multicomponent Biginelli–Atwal reaction.

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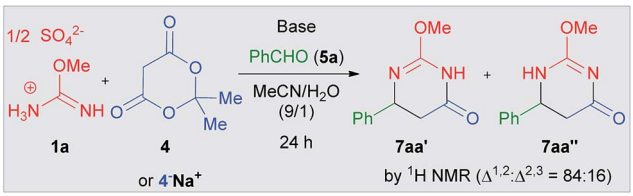
a racemic and unprecedented diastereoselective fashion toward enantiopure compounds.

Results and discussion

Towards a proof of principle, we carried out the MCR by mixing the commercially available ammonium salt of *O*-methylisourea **1a**, benzaldehyde **5a** and a stoichiometric amount of cesium carbonate in MeCN/H_2O mixture at 40 °C (Table 1). The desired dihydropyrimidin-4-ones **7aa** product was obtained with 59% of NMR yield (entry 1). The product **7aa** was observable as a mixture of tautomers **7aa′** ($\Delta^{1,2}$) and **7aa″** ($\Delta^{2,3}$) by ^{1}H NMR in $CDCl_3$ (**7aa′**/**7aa″** = 86/14). On the other hand, the domino sequence did not proceed without any mineral base to liberate the isourea free-base (entry 2). It was found that the reaction could be carried out by means of various bases with a potassium cation (entries 3) along with their sodium homologues (entries 4–6); the best result was obtained with sodium carbonate at 40 °C furnishing product **7aa** with 87% yield (entry 6). However, a sluggish reaction took place at 20 °C (entry 7). A solvent screening revealed this MCR could be carried out in EtOH or MeCN/H_2O solvents preferentially,[14] otherwise precipitation events were observed and led to erratic outcomes. Interestingly, the MCR sequence was also feasible with a stoichiometric amount of pre-formed Meldrum's acid enolate **4**$^-$**Na**$^+$ as a sodium salt without extra mineral base to provide uneventfully the dihydropyrimidinone **7aa** with 75% NMR yield in nearly neutral conditions (entry 8).

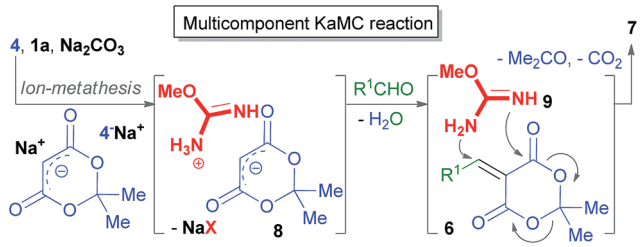
Accordingly, as far as the mechanism is concerned, we anticipate that a facile deprotonation of Meldrum's acid **4** (pK_a = 4.93 in water *versus* pK_a = 9 for the *O*-methylisourea ammonium salt **1a**)[6] would furnish the corresponding Meldrum's acid enolate **4**$^-$**Na**$^+$ allowing an ion-metathesis process giving rise to

Table 1 Proof of principle[a]



Entry	Base (1.1 equiv.)	Temp.	Yield[b] (%)
1	Cs_2CO_3	40 °C	59
2	—	40 °C	2
3	K_2CO_3	40 °C	79
4	NaOH	40 °C	79
5	$NaHCO_3$	40 °C	83
6	Na_2CO_3	40 °C	87
7	Na_2CO_3	20 °C	7
8	**4**$^-$**Na**$^+$[c]	40 °C	75

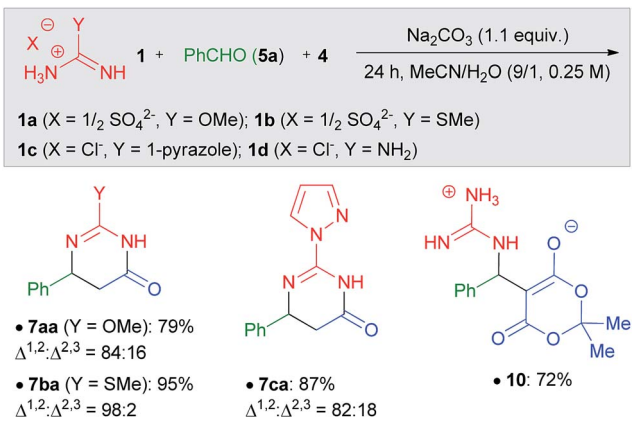
[a] Reaction performed at 0.1 M on 0.10 mmol scale with 1 equiv. of each components and 1.1 equiv. of base in MeCN/H_2O (9/1). [b] NMR yield determined by an internal standard. [c] Reaction performed with pre-synthesized sodium salt of **4** (**4**$^-$**Na**$^+$, 1 equiv.) without extra base.



Scheme 2 Mechanistic proposal.

the formation of ammonium salt **8** (Scheme 2). Then, the species **8** undergoes a Knoevenagel condensation to give very reactive Meldrum acid alkylidene **6**,[5,6] subsequently engaged into the domino aza-Michael-cyclocondensation reaction with the liberated isourea **9** en route to the elaboration of diazole **7aa** through a multicomponent KaMC reaction. Importantly, the synthesis of dihydropyrimidin-4-one **7aa** was also achieved in 70% yield by mixing pre-formed benzylidene Meldrum's acid **6a** (R^1 = Ph) and *O*-methylisourea isourea **9** as free-base, showing this multicomponent reaction likely takes place through an aza-Michael key step (*versus* a Mannich type process). As a practical issue, it is more convenient to use isoureas **1** as ammonium salts (usually the commercially and/or available form) rather than the hydroscopic free base counterpart **9**. First of all, this strategy minimizes the use of strong bases or high temperatures in order to liberate isourea **9**. Next, the rather facile addition reaction of isourea **9** in soft conditions (40 °C) is a welcomed issue of this KaMC sequence with respect to literature guanidine-based procedures generally requiring higher temperature to occur (*vide infra*).[7]

We were pleased to observe that these reaction conditions are not only compatible with ammonium salts of *O*-methylisourea **1a** (79% isolated yield), but also with thioisourea **1b** and pyrazole carboxamidine **1c** furnishing the corresponding diazoles **7aa–7ca** with isolated yields ranging from 79% to 95% after column chromatography (Scheme 3).[14] This last example constitutes a novel extension of the Overman approach of the Biginelli–Atwal reaction making use of carboxamidine



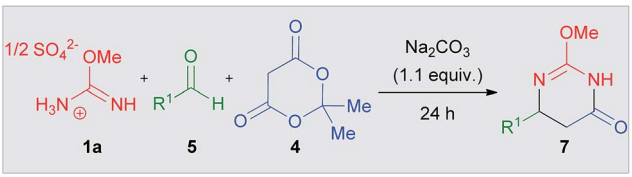
Scheme 3 Scope and limitation of isourea type nucleophiles.

derivatives **1c**.[15] Interestingly, the guanidinium salt **1d** led to an interrupted MCR affording the zwitterionic aza-Michael adduct **10**. Obviously, the subsequent proton transfer event is inhibited due to the high basicity of the guanidine part *versus* the 1,3-dioxanone moiety. Therefore, the lower pK_a of the isourea nucleophiles **1a–c** is key for the success of our multicomponent KaMC reaction in soft conditions.

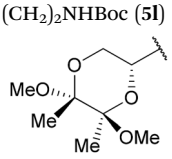
The scope of this multicomponent KaMC reaction with regard to various aldehydes **5** was investigated with *O*-methyl-isourea derivative **1a** (Table 2). Aromatic and heteroaromatic aldehydes (entries 1–4) were successfully transformed into the corresponding dihydropyrimidinones **7ab–7ae** with isolated yields ranging from 34% to 85%. Worthy of note, the 3-carboxyladehyde indole **5g** gave the diazole **7ag** in 62% isolated yield as soon as an *N*-Boc protected derivative was used (entry 5 *versus* 6). This outcome highlights electronic requirements of transient alkylidene Meldrum's acid **6** from which the ones displaying a push–pull effect tend to be reluctant to react. Importantly, this MCR sequence turned out to be compatible with a variety of aliphatic aldehydes either linear (**5h**,**5i**, 75–81%, entries 7 and 8), α-branched (**5j**,**5k**, 88–90%, entries 9 and 10) or possessing acidic-sensitive NHBoc functional group (**5l**) albeit with a slight decreased in yield in the last case (45%, entry 11). Moreover, a diastereoselective reaction was also demonstrated starting from readily available protected chiral glyceraldehyde **5m** developed by Ley's group to provide dihydropyrimidinone **7am** with >95 : 5 *dr* and 51% yield after column chromatography (minor isomer hardly seen on ^{1}H NMR).[16,17] In this case, the best result was obtained starting from Meldrum's acid enolate **4**$^-$**Na**$^+$, otherwise a more complex crude mixture was obtained. Although not identified after column, we cannot fully rule out the presence of the other diastereoisomers on the crude reaction mixture due to the presence of side products and tautomers. In the literature, the scope of multicomponent KaMC reactions with Meldrum's acid **4** mainly focused on aromatic aldehydes with very few successful examples involving aliphatic aldehydes; none of them displayed acid sensitive functional groups.[12a,12c,10,13] Pleasingly, this modified Biginelli–Atwal reaction shows an expended scope with regard to aldehyde component thanks to the smooth conditions developed.

Next, we were curious to see whether this MCR in soft conditions would tolerate a diastereoselective sequence, involving chiral isourea derivatives **11**,**12**, towards the formation of non-racemic products **13**. Furthermore, this would give a unique opportunity of exploring extra-molecular space (Table 3). Accordingly, we intended to capitalize on the readily availability of **12** (one-step from (*R*)-2-phenylglycinol) which was developed as useful chiral auxiliary by Dechoux and colleagues.[18,19] Following our optimized conditions (entry 1), using an equivalent of Na_2CO_3 and benzaldehyde **5a**, the MCR proceeded smoothly but furnished a 1 : 1 mixture of regioisomers **13a** and **14a** *versus* **15a** and **16a** from which the known *anti*-dihydropyrimidin-4-one **13a** was the major diastereomer.[18] We were delighted to see that base-free conditions, making use of enolate **4**$^-$**Na**$^+$ and ammonium salt **11**, not only favored regioisomers **13a** and **14a** (**13a**,**14a**/**15a**,**16a** = 66/34) but

Table 2 Scope and limitation with various aldehydes[a]

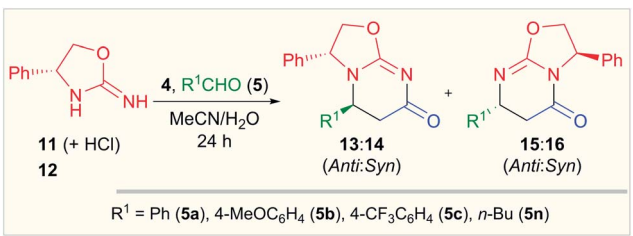


1a 5 4 7

Entry	Base (1.1 equiv.)	Yield[b] (%)
1	4-MeOC$_6$H$_4$ (**5b**)	74 (**7ab**)
2	4-CF$_3$C$_6$H$_4$ (**5c**)	79 (**7ac**)
3	2-BrC$_6$H$_4$ (**5d**)	85 (**7ad**)
4	3-pyridine (**5e**)	34 (**7ae**)
5	3-*N*-MeIndole (**5f**)	0 (**7af**)
6	3-*N*-BocIndole (**5g**)	62 (**7ag**)
7	(CH$_2$)$_2$Ph (**5h**)	81 (**7ah**)
8	i-Bu (**5i**)	75 (**7ai**)
9	i-Pr (**5j**)	90 (**7aj**)
10	Cy (**5k**)	88 (**7ak**)
11	(CH$_2$)$_2$NHBoc (**5l**)	45 (**7al**)
12	 (**5m**)	51 (**7am**)[c]

[a] Reaction conditions: Meldrum's acid **4** (0.50 mmol) in MeCN/H$_2$O (9/1) at 0.25 M at 40 °C for 24 hours with aldehyde **5** (1 equiv.) and isourea salt **1a** (1 equiv.). [b] Isolated yield after column chromatography of **7** observable by ^{1}H NMR as a mixture of $\Delta^{1,2}$: $\Delta^{2,3}$ tautomers (72 : 28 to 98 : 2). [c] Reaction performed with Meldrum's acid sodium salt of **4**$^-$**Na**$^+$ (1 equiv.) without extra base giving **7al** with >95 : 5 *dr* after column.

Table 3 Diastereoselective approach[a]



11 (+ HCl) **12**

13:**14** (*Anti*:*Syn*)

15:**16** (*Anti*:*Syn*)

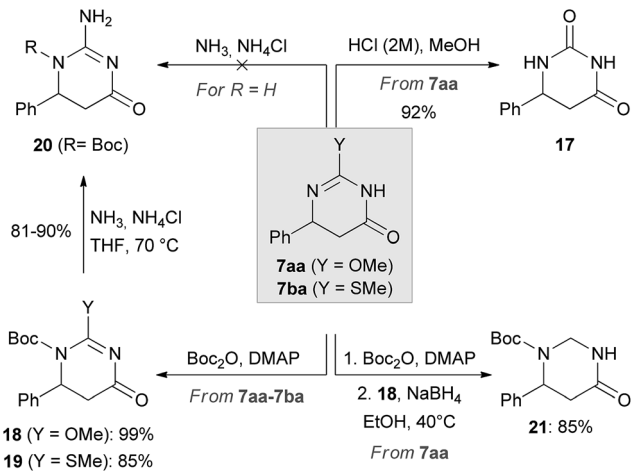
R^1 = Ph (**5a**), 4-MeOC$_6$H$_4$ (**5b**), 4-CF$_3$C$_6$H$_4$ (**5c**), *n*-Bu (**5n**)

Entry	Isourea	Conditions	Product (**13**/**14**/**15**/**16**)[b]	Yield[c] (%)
1	**11**	Na_2CO_3, 40 °C	45/5/43/7	—
2	**11**	**4**$^-$**Na**$^+$, [d]40 °C	61/5/29/5	—
3	**12**	40 °C	64/6/25/5	55% (**13a**)
4	**12**	40 °C	61/7/26/6	52% (**13b**)
5	**12**	40 °C	62/8/22/8	46% (**13c**)
6	**12**	40 °C	69/5/17/9	53% (**13n**)

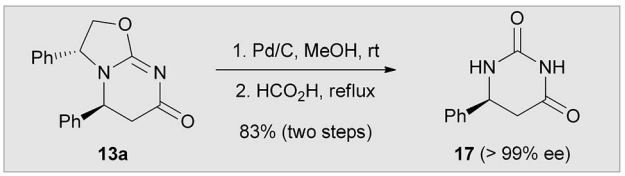
[a] Optimized reaction conditions: Meldrum's acid **4** (0.50 mmol) in MeCN/H$_2$O (9/1) at 0.25 M at 40 °C for 24 hours with aldehydes **5** (1.0 equiv.) and chiral isourea **12** (1.0 equiv.). [b] Ratio determined by NMR on the crude product. [c] Isolated yield of pure **13** after silica gel column chromatography. [d] Sodium salt **4**$^-$**Na**$^+$ of Meldrum's acid (1 equiv.) was used without extra-base.

revealed a good diastereoisomeric ratio of 92 : 8 (**13a : 14a**, entry 2).[20] Eventually, to prevent the detrimental effect of an external base, the multicomponent KaMC reaction was effected by chiral isourea **12** and native Meldrum's acid **4** to give similar outcomes (entry 3). Importantly, product **13a** was easily isolated by column chromatography with 55% yield as a sole diastereoisomer (entry 3). These reaction conditions were competent to synthesize the corresponding *anti*-diastereopure 5,6-dihydropyrimidin-4-ones **13b–13n** flanked by electron-rich and electron-poor aromatic rings (**13b,13c**) or an aliphatic chain (**13n**) pendants with isolated yields ranging from 46% to 53% with similar stereoselectivities as testify on the crude reaction mixture (entries 4–6). Although the regioselectivity issue of this sequence would deserve to be improved, this unprecedented diastereoselective modified Biginelli–Atwal MCR allows a straightforward access to enantioisomerically pure diazoles **13** in a one-step operation.

In order to highlight the usefulness of this synthetic sequence, we turned our attention to chemoselective transformations of these readily available heterocyclic platforms **7** (Scheme 4). In parallel to known α-alkylation and reduction reactions of the ketone moiety,[19,20] the methoxy-precursor **7aa** was easily hydrolyzed in high 92% yield into the dihydrouracyl **17**, following an improved literature procedure.[9a] Complete regioselective N^1-Boc-introduction (*vide infra*) was successfully performed to furnish products **18,19** in 85% to 99% yields respectively. This shows a similar behavior with Atwal's 1,4-dihydropyrimidine architectures allowing a chemoselective substitution towards specific structure modulation.[21] Although precursors **7aa**, **7ba** and **7ca** were reluctant to aminolysis condensation, the Boc-derivatives **18,19** were smoothly transformed into the corresponding guanidine-heterocycle **20** in more than 81% yield.[15] Interestingly, a smooth reduction of *N*-Boc dihydropyrimidin-4-ones **18** was achieved with $NaBH_4$ to furnish the corresponding tetrahydropyrimidinone **21** in 85% yield.[22] The position of the Boc-group was proven by ^{1}H NMR on this compound **21**, thanks to COSY experiment showing an exclusive cross-peak between NHCO and AB-system (NCH_2N).[14]



Scheme 4 Chemical transformations in action.



Scheme 5 Towards an enantiopure dihydrouracyl.

Eventually, in order to exploit the full potential of the diastereoselective MCR strategy (Scheme 5), the possibility to cleave the chiral auxiliary of **13a** was demonstrated to provide a readily access to enantiopure dihydrouracyl **17**.[18,23]

Conclusions

In summary, we have developed a straightforward access to 5,6-dihydropyrimidin-4(3*H*)ones **7** through an original multicomponent KaMC reaction involving Meldrum's acid **4**, various aldehydes **5** and isourea derivatives **1** upon smooth basic-conditions. The possibility to perform a diastereoselective approach from readily available enantiopure Dechoux's chiral isourea **12** was demonstrated. Eventually, chemoselective transformations were achieved onto this useful heterocyclic platforms en route to the construction of bio-pertinent architectures.

Acknowledgements

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