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Cyclic ketones and substituted α-keto acids as alternative substrates for novel Biginelli-like scaffold syntheses

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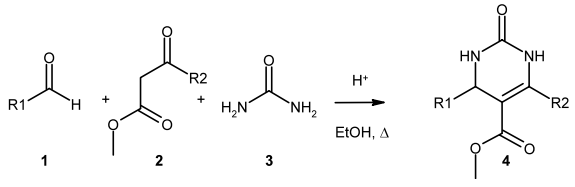
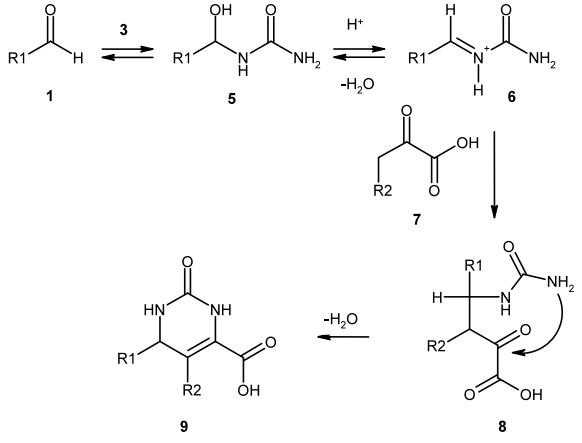
Abstract—The reactions of benzocyclic ketones and α-ketoacids as carbonyl components in the Biginelli reaction were investigated. These unusual Biginelli substrates furnished novel drug-like dihydropyrimidinone scaffolds suitable for further elaboration.

The use of multicomponent reactions (MCRs) to generate interesting and novel, drug-like scaffolds is replete in the recent chemical literature.[1] The production of dihydropyrimidinones via the well established Biginelli reaction certainly ranks as one of the most recognized and often used MCR's for the generation of novel pyrimidine scaffolds.[2] For example, dihydropyrimidinone C-5 amides were recently prepared and assayed as potent and selective α1A receptor antagonists for the treatment of benign prostatic hyperplasia.[2d] Prototypically, the reaction combines aldehydes (**1**) and β-ketoesters (**2**) with urea (**3**) to produce dihydropyrimidinones (**4**) having an ester moiety in the 5-position of the heterocycle (Scheme 1). The reaction, in its simplest form, is catalyzed by mineral acid, but many synthetic method modifications have been reported including a variety of Lewis and protic acids.[3] In addition, the Biginelli reaction has been performed successfully by microwave-assisted energy transfer.[4]

Our interest in the preparation of novel scaffolds for targeted library syntheses lead us to attempt the extension of this versatile reaction to other carbonyls or carbonyl equivalents. The use of α-ketoacids other than oxalacetic acid as the carbonyl component of the reaction gave us the opportunity to prepare dihydropyrimidinones having R2 and the acid group switched in the pyrimidinone (Scheme 2). Oxalacetic acid is already known to give decarboxylated dihydropyrimidinones in the Biginelli reaction.[5b] The use of substituted α-ketoacids is a more general reaction leading to scaffolds that are amenable to further elaboration. The reaction was generally run under a well-established protocol wherein we used a 1:1.5:1.5 ratio of ketoacid, aldehyde and urea, respectively. The acid catalyst was present as



Scheme 1. The prototypical Biginelli reaction.



Scheme 2. The α-ketoacid alternative reaction.

Keywords: Biginelli; α-keto acid; dihydropyrimidinone; pyrrolidinium tosylate.

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Table 1. α-Ketoacids to dihydropyrimidinecarboxylic acids[a], **9**

Entry	R_1	R_2	Yield (%)[b]	Acid cat.
1	*i*-Bu	Ph	22 (64)	HCl (BF_3·OEt_2, CuCl)[c]
2	Ph	Me	28 (50)	HCl (MsOH)
3	Ph	Ph	75	HCl
4	Tol	Ph	61	HCl
5	4-MeOPh	Ph	74	HCl
6	4-ClPh	Ph	56	HCl
7 (see Ref. 10)	4-NO_2Ph	Ph	63	MsOH
8	Ph	4-NO_2Ph	100	MsOH
9 (see Ref. 11)	Ph	4-HOPh	23 (85)	MsOH (pyrrolidine·TsOH)
10	4-ClPh	3-Indolyl	61	Pyrrolidine·TsOH

[a] *i*-Bu = isobutyl. Ph = phenyl. Me = methyl. Tol = tolyl. 4-MeOPh = 4-methoxyphenyl. 4-ClPh = 4-chlorophenyl. 4-NO_2Ph = 4-nitrophenyl. 4-HOPh = 4-hydroxyphenyl. MsOH = methanesulfonic acid. TsOH = toluene sulfonic acid.

[b] Yields are isolated yields. All reactions were carried out in ethanol under reflux for 24 h unless otherwise noted. All compounds were characterized by high field ^{1}H NMR (400 MHz), ^{13}C NMR, IR and mass spectroscopy.

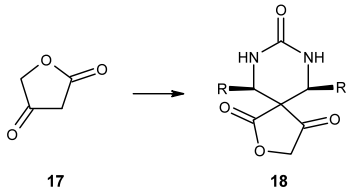
[c] See Ref. 6 for description of catalyst.

0.12 molar equivalents in the case of HCl and methanesulfonic acid or 0.2 molar equivalents in the case of pyrrolidinium tosylate. Assuming the accepted mechanism of the Biginelli reaction applies in the case of the α-ketoacids as presented here, then one can envision the initial formation of an *N*-acyliminium ion intermediate in the presence of acid followed by the nucleophilic addition of the enolate of the ketoacid.[5] The results of our initial set of scaffold syntheses covering a range of aldehyde and α-keto acid combinations are presented in Table 1. The reaction is catalyzed by acid, presumably by enhanced elimination of water from **5** to give the iminium ion in **6**, but also by enhanced enolization of **7**.

Accordingly, we sought out a milder acid catalyst to minimize side reactions and improve the modest yields found with HCl. Methanesulfonic and toluenesulfonic acids work well,[7] but in side-by-side comparisons, pyrrolidinium tosylate was found to give superior yields.

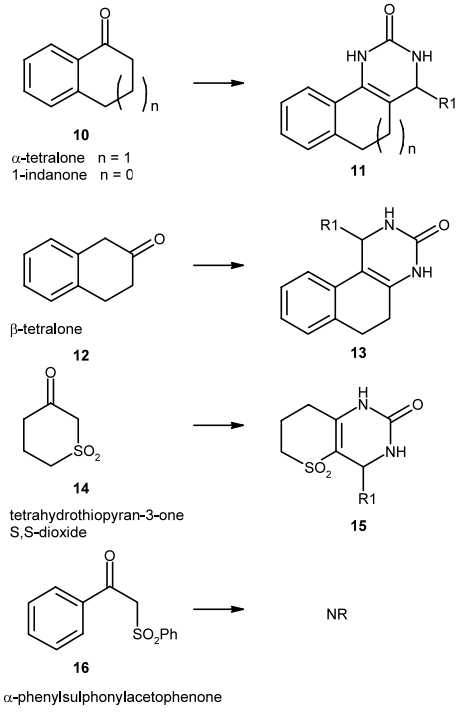
In an extension of the program to discover versatile routes to novel Biginelli scaffolds, it was also discovered that cyclic ketones with sufficiently acidic methylene groups provide a useful adjunct carbonyl. These now give the scaffold designer a simple route to fused ring pyrimidinones (Scheme 3).[8] Some examples of the fused-ring scaffold syntheses are presented in Table 2.

Curiously, the tetrahydrothiopyran-3-one *S*,*S*-dioxide ring **14** gave a good yield of fused-ring pyrimidine under the standard Biginelli conditions, while the acyclic version of that reaction with α-phenylsulfonylacetophenone **16** failed completely to provide a pyrimidine scaffold. The successful reaction of this sulfonyl-activated methylene ring compound in providing a fused-ring pyrimidine is interesting given the failure to obtain fused-ring pyrimidines from β-ketolactones such as tetronic acid **17**.[9]



The product of this reaction is, in fact, a mixture of spiro-fused pyrimidines **18** having the R-substituents oriented *cis* to each other, the result of adding two units of aldehyde to the reactive methylene.

This suggested that we could manufacture additional scaffolds for our library synthesis program using ring structures containing a β-dicarbonyl system activating a central methylene. Accordingly, we applied our conditions to cyclopentane-1,3-dione **19** and dimethylbarbituric acid **21** (Scheme 4). The results of these spiro-fused ring syntheses are included in Table 2; the stereochemistry of the aryl rings is assigned cis based on the work of Byk.[9]



Scheme 3. Cyclic ketones to fused ring pyrimidines.

Table 2. Preparation of fused-ring scaffolds[a]

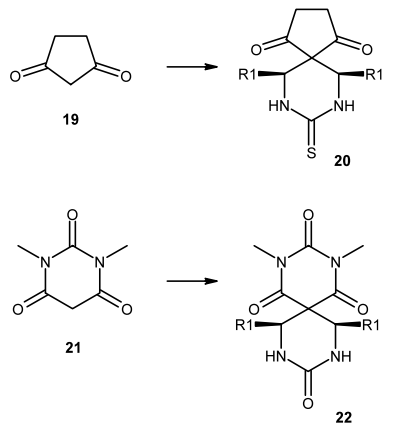
Entry	R_1	Ring	Yield (%)[b]	Acid cat.
1	Ph	α-Tetralone	75	HCl
2	Ph	1-Indanone	90	HCl
3	H	β-Tetralone	50[c]	HCl
4	Ph	β-Tetralone	80	HCl
5	Ph	THP *S*,*S*-dioxide	64	HCl
6	Ph	α-PSA	NR	HCl
7	Ph	*N*,*N*′-DMB	90[d]	HCl
8	4-ClPh	CPD	39[d]	HCl

[a] Ph = phenyl. THP *S*,*S*-dioxide = tetrahydrothiopyran-3-one *S*,*S*-dioxide. α-PSA = α-phenylsulfonylacetophenone. *N*,*N*′-DMB = *N*,*N*′-dimethylbarbituric acid. CPD = cyclopentan-1,3-dione.

[b] Yields are isolated yields. All reactions were carried out in ethanol under reflux for 24 h unless otherwise noted. All compounds were characterized by high field ^{1}H NMR (400 MHz), ^{13}C NMR, IR and mass spectroscopy.

[c] Note: example 3 accounts for the first time the use of diethoxymethane as a formaldehyde equivalent in a Biginelli-type reaction.

[d] The ratio of diketone, urea and aldehyde was 1:1:2.



Scheme 4. Spriro-fused heterocycles.

In summary we have expanded the synthetic scope of the multicomponent Biginelli reaction to include α-ketoacids other than oxalacetic acid,[5b] as well as additional cyclic ketones; in addition, we have expanded on the spiroheterocycles prepared using a four-component condensation reaction where the aldehyde is utilized twice in the reaction. The novel carboxylic acid scaffolds make useful functional coupling partners in amidation reactions with diverse amines providing focused, drug-like library components.

Acknowledgements

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10. A typical experimental follows for the preparation of dihydropyrimidines using methanesulfonic acid catalyst (Table 1, entry 7): *4-(4-nitrophenyl)-2-oxo-5-phenyl-1,2,3,4-tetrahydropyrimidine-6-carboxylic acid*: To a solution of urea (1.3 g, 23 mmol) in hot EtOH (30 mL) was added 4-nitrobenzaldehyde (3.4 g, 23 mmol) followed by phenylpyruvic acid (2.5 g, 15 mmol) and methanesulfonic acid (0.1 mL). The mixture was heated to reflux for 24 h, after which a white precipitate was observed. The reaction was cooled to ambient room temperature and the product isolated by filtering through a Büchner funnel and washing with ethyl ether to give the product as a white crystalline powder (3.2 g, 63% yield). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.3 (d, J = 0.62 Hz, 1H), 8.12 (d, J = 8.9 Hz, 2H), 7.68 (s, 1H), 7.38 (d, J = 8.9 Hz, 2H), 7.15 (m, 3H), 7.0 (dd, J = 8.2, 1.9 Hz, 2H), 5.3 (d, J = 2.7 Hz, 1H), 3.5 (bs, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 164.5, 152.8, 150.4, 147.6, 137.0, 129.3, 128.9, 128.5, 127.8, 127.5, 124.4, 117.2, 60.2; IR (KBr) 3980, 1717, 1612 cm^{-1}.
11. Experimental using pyrrolidinium tosylate catalyst (Table 1, entry 9): *5-(4-hydroxyphenyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-6-carboxylic acid*: To a solution of urea (1.6 g, 26 mmol) in hot EtOH (45 mL) was added the benzaldehyde (2.6 mL, 26 mmol), 4-hydroxyphenylpyruvic acid (3.0 g, 17 mmol) and the pyrrolidinium tosylate (0.58 g, 2.4 mmol). The mixture was heated under reflux for 24 h. The reaction was cooled to ambient room temperature and then reduced in volume on a rotary evaporator to a viscous oil. The oil was taken up in a 1:1 mixture of THF and ethyl acetate (100 mL)

and was washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and reduced in vacuo to provide 4.4 g (85% yield) of the desired product as a tan crystalline powder. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.9 (s, 1H), 7.45 (s, 1H), 7.15–7.30 (m, 3H), 7.12 (d, $J=7.0$ Hz, 2H), 6.8 (d, $J=8.2$ Hz, 2H), 6.54 (d, $J=8.2$ Hz, 2H), 4.98 (d, $J=2.7$ Hz, 1H); ^{13}C (DMSO-d_6, 100 MHz) δ 164.2, 162.8, 156.4, 152.5, 142.6, 129.6, 128.4, 127.5, 126.8, 125.3, 118.4, 114.5, 60.1; IR (KBr) 1680, 1611, 1512 cm^{-1}.