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Domino conversions of allyl tetronates and 4-allyloxycoumarins to all-*trans* 1,3,4,5-tetrasubstituted γ-butyrolactams

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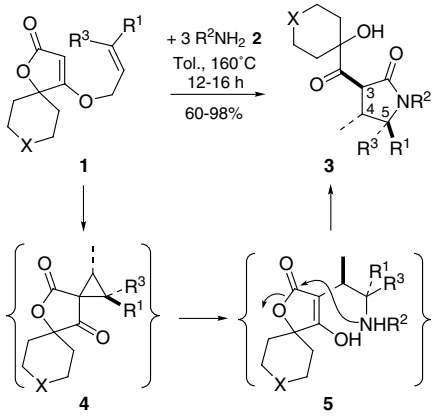
Abstract—All-*trans* 1,3,4,5-tetrasubstituted γ-butyrolactams **3** and **7** are readily available in one-pot from allyl tetronates or 4-allyloxycoumarins and amines via a four-step domino Claisen–Conia ring-opening transamidation reaction.

We have recently[1] found a thermal four-step domino conversion of an allyl tetronate **1a**[2] in the presence of allylamine into a 1,3,4,5-tetrasubstituted γ-butyrolactam **3a**. This sequence seems to be rather general for 5,5-disubstituted tetronates, which furnish in good to excellent yields predominantly, if not exclusively, the all-trans isomers. In accordance with earlier findings[1,3] for the mechanism of [2,3]-sigmatropic rearrangements of **1**, it comprises consecutive Claisen and Conia rearrangements, the opening of the intermediate spirocyclopropanes **4** by the amine to give 3-(β-amino)alkyltetronic acids **5** and a final lactone → lactam transamidation[4] to **3** (Scheme 1, Table 1). This contrasts with the reaction of similar 2-acylcyclopropane-carboxylates with amines as reported by Lhommet and co-workers where the amine group in the intermediates analogous to **5** reacts with the keto/enol rather than the ester carbonyl moiety yielding 3-alkoxycarbonyldihydropyrrols.[5] Ring-opening of **4** takes place selectively at the carbon atom bearing residues R^1 larger than C_2H_5 (e.g., **4e**). Only for $R^1 = C_2H_5$ were mixtures of tetrasubstituted lactams found, which result from attack of the amine on both tertiary carbon atoms of the 3-ring. This and the formation of the 4,5-*trans* configured lactams **3** suggest that the amine attacks **4** at a relatively advanced stage of ring-opening with a good deal of carbenium ion character of the carbon atom bearing R^1. Reacting stable derivatives of **4** with amines at room temperature normally furnishes the syn diastereomers of **5**.[1]



Scheme 1. Four-step domino synthesis of all-*trans*-γ-lactams **3** from allyl tetronates **1** and amines **2**.

Bohlmann et al.[7] reported that 4-allyloxycoumarins like **6** when heated in *N*,*N*-diethylaniline also undergo [2,3]-rearrangements via spirocyclopropanes followed by ring-closure to give furocoumarins at sufficiently high temperatures. Hence, reaction of **6** with amines should produce 3-(*o*-hydroxy)phenacyllactams **7** in analogy to the synthesis of **3** from **1**. While the reaction of **6** with butyl- and benzylamine in toluene at 160 °C actually led to the formation of the expected lactams **7**,[8] *exo*-benzylidenelactam **10a**[9] was found upon reaction of **6a** ($R^1 = R^3 = Me$) with an excess of allylamine. This can be rationalized by assuming a cascade extended by three steps: formation of an *N*-allylimine **8**, tautomerization of the latter to give **9** and an eventual β-elimination of a vinylimine to leave *E*-configured product **10** (Scheme 2, Table 2).

Keywords: Domino reactions; Lactams; Rearrangements; Tetronates; Coumarins; Microwaves.
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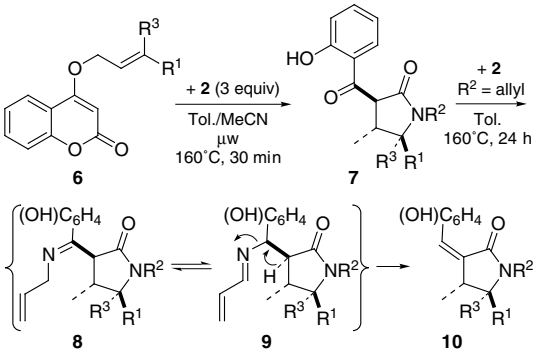
Table 1. γ-Lactams **3**[6] from allyl tetronates **1** and amines **2**

	R^1	R^2	R^3	X	Yield (%)
3a	Ph	$CH_2CH{=}CH_2$	H	CH_2	94
3b	Ph	*i*-Bu	H	CH_2	72[a]
3c	Ph	Bu	H	CH_2	84
3d	Ph	$CH_2CH{=}CH_2$	H	O	71
3e	Pr	Bu	H	CH_2	65[a]
3f	CH_3	$CH_2(CH_2)_2OC_2H_5$	CH_3	CH_2	89

[a] Containing 10% of the 3,4-*cis* isomer as to NMR.



Scheme 2. γ-Lactams **7/10** from 4-allyloxycoumarins **6** and amines **2**.

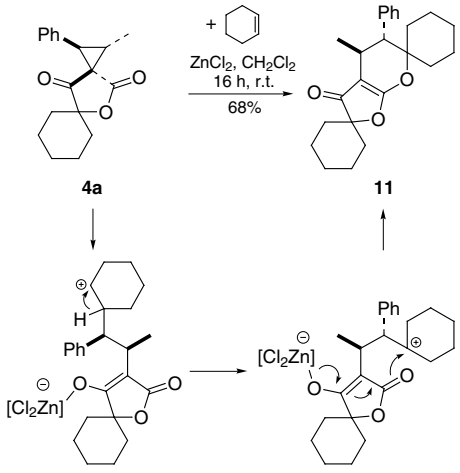
Table 2. γ-Lactams **7/10** from 4-allyloxycoumarins **6** and amines **2**

	R^1	R^2	R^3	Yield (%)
7a	Me	CH_2 $CH{=}CH_2$	Me	58[a]
7b	Ph	$CH_2CH{=}CH_2$	H	53[a]
7c	Me	Bn	Me	51[a]
7d	Me	Bu	Me	62[a]
7e	Ph	Bu	H	60[a]
10a	Me	$CH_2CH{=}CH_2$	Me	40[b]

[a] PhMe/MeCN (9:1), microwave, 160 °C, 30 min.
[b] PhMe, 160 °C, 24 h.

Better stabilization of positive partial charges next to the phenyl ring in **7/9** when compared to the saturated six-membered ring in **3** explains the different outcome in the tetronate and coumarin series. However, lactams **7** were obtained in every case, including derivatives with R^2 = allyl, when the reaction was carried out in toluene/acetonitrile under microwave irradiation at 160 °C for 30 min. These conditions strongly favour the initial pericyclic steps over imine formation and elimination.[10]

Only amines seem capable of attacking both the 3-ring and the lactone ring of intermediates **4** and **5** in a nucleophilic manner. In contrast, reaction of diastereopure 3-spirocyclopropyl-dihydrofurane-2,4-dione **4a**[3] with the soft nucleophile cyclohexene under $ZnCl_2$ catalysis furnished the furo[2,3-*b*]-pyran-3-one **11** as the sole product of a formal [5+1] cycloaddition in 68% yield.[11] Mechanistically, we assume an initial 'electrophilically assisted' ring-opening of **4a** by the alkene attacking the phenyl-bearing cationoid carbon atom. The resulting secondary cation rearranges to a tertiary one, which gets eventually trapped by the ester enolate oxygen atom producing **11** with the trans configuration of residues Me and Ph preserved ($^3J_{HH}$ = 11.2 Hz). Interestingly, tertiary alcohols as conceivable products of a Prins-type reaction of cyclohexene with the keto carbonyl group of **4a** were not observed (Scheme 3).



Scheme 3. Furo[2,3-*b*]pyran-3-one **11** from tandem ring-opening/recyclization of **4a** with cyclohexene.

In summation, a regio- and stereoselective one-pot synthesis of densely substituted γ-butyrolactams from 5, 5-disubstituted allyl tetronates or from 4-allyloxycoumarins has been developed.

Acknowledgement

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References and notes

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