Decarboxylative Knoevenagel-Type Reactions on Tetronamides: Synthesis of 5-Ylidene-4-Amino-2(5*H*)-Furanones

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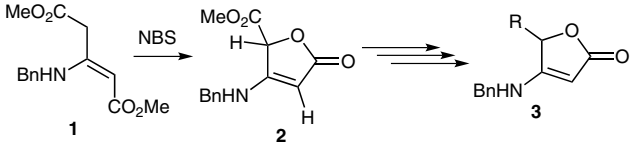
Abstract: A detailed account regarding the synthesis of 5-ylidene-2(5*H*)-furanones is given. The key step is a decarboxylative Knoevenagel-type reaction of tetronamides with various α-functionalized aldehydes. The synthesis of protected basidalin is presented.

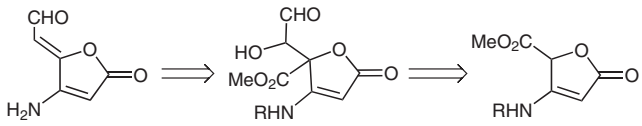
Key words: Knoevenagel–Doebner reaction, β-enaminoesters, tetronamides, 4-amino-2(5*H*)-furanones, basidalin

Amino-2(5*H*)-furanones, commonly referred to as tetronamides, are important intermediates in the synthesis of natural products,[1] and they are also of interest in the pharmaceutical and agrochemical arenas.[2] Most methods reported for the preparation of substituted tetronamides are based on the nucleophilicity of the enamine function.[3] A sequence involving condensation of primary or secondary amines with tetronic acid followed by alkylation or aldolization using, most generally, *tert*-butyllithium as a base furnishes 5-substituted tetronamides.[4] We have described a novel *N*-bromosuccinimide (NBS)[5]-promoted cyclization of enaminoesters[6] **1** to 4-amino-5-carboxymethyl-2(5*H*)-furanones **2** and subsequent C5-alkylation to prepare 5-substituted tetronamides **3** in an overall three-step approach (Scheme 1).[7]



Scheme 1

In our continuing efforts to develop efficient C5 modifications of tetronamides, we were interested in the possibility of preparing 5-ylidene-4-amino-2(5*H*)-furanones **6**. Though the synthesis of these heterocyclic derivatives have been described (most often obtained as unexpected products through thermal rearrangements of azido- or isoxazoloquinones),[8] no direct methylene insertion onto the C5 position of tetronamides has been reported. Moreover, this structural framework is found in basidalin, a natural product isolated from the mushroom *Leucoagaricus naucina*. This natural product exhibits antibacterial and antitumor activities, and its structure was elucidated in 1983 by X-ray diffraction analysis.[9] To the best of our knowledge only the synthesis of the non-natural *E* isomer has been described.[10] Thiobasidalin, the thiolactone analogue of basidalin, has been synthesized by Stachel and co-workers.[11] Therefore, it was of interest to evaluate the preparation of basidalin by means of a process that would make use of glyoxal derivatives and the pivotal tetronamide **2** as reaction partners in a Knoevenagel–Doebner-type reaction (Scheme 2).[12]



Scheme 2

Though the Knoevenagel–Doebner reaction has been extensively used in organic synthesis, only few examples have been documented with α-functionalized aldehydes such as dialkyl acetals of aldehydes in aldose chemistry.[13] Most generally, the reaction involves aromatic aldehydes, giving access to cinnamic acid derivatives.[14] The classical Knoevenagel–Doebner reaction is carried out in a solvent such as pyridine, catalyzed by secondary amines, commonly piperidine.[15] The List group has demonstrated that aliphatic aldehydes react effectively using DMAP as catalyst,[16] while Zhenyuan and Wannian demonstrated that β-alanine and DBU catalyzes the reaction with aromatic aldehydes.[17] Recently, the group of Sandhu published a solvent-free Doebner–Knoevenagel reaction between aromatic and heteroaromatic aldehydes and malonic acid with alum [$KAl(SO_4)_2 \cdot 12H_2O$] as catalyst.[18] Kallikat Augustine's group used *gem*-dibromomethylarenes as analogues of aldehydes with malonic acid in the synthesis of cinnamic acid derivatives.[19] Some examples of microwave-assisted Knoevenagel–Doebner reactions of aromatic aldehydes have also been described.[20] Bifunctional polymeric catalysts have been successfully used in the stereoselective synthesis of (*E*)-cinnamates,[21] and a synthesis of β-keto esters starting from β-ketoacids has been described by Taddei.[22]

We report herein the decarboxylative Knoevenagel-type reaction of conjugated diester precursors, such as butenolide ester **2**, and an approach to the synthesis of basiladin.

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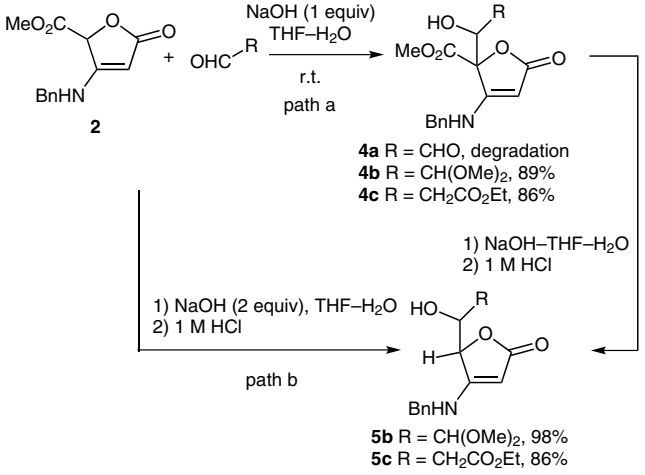
The choice of the aldehyde was crucial since it has to deliver the conjugate formyl function of basidalin in a few steps. We thus first considered the use of glyoxal in the presence of NaOH, K_2CO_3, or LiHMDS to promote the deprotonation of tetronamide **2**, but only decomposition of the starting material was observed.

We thus turned our attention to the use of dimethoxyacetaldehyde and ethyl glyoxylate. By treating tetronamide **2** with one equivalent of NaOH in wet THF, we isolated the expected aldol products **4b**,**c** in good yields. A further treatment of compounds **4b** and **4c** with one equivalent of NaOH followed by an acidic quench led quantitatively to the formation of products **5b** and **5c**, respectively (path a, Scheme 3). More interestingly, the same reactions performed in the presence of two equivalents of NaOH followed by an acidic quench led directly to the decarboxylated products **5b** and **5c** as mixtures of two diastereoisomers in 50:50 and 70:30 ratios, respectively (path b, Scheme 3).

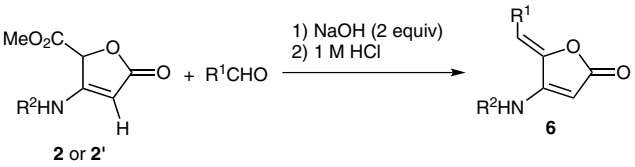


Scheme 3 Knoevenagel-type reactions

To our surprise, all standard acidic conditions examined to deprotect the acetal function or to eliminate the hydroxyl group of **5b**,**c** were unsuccessful. Both acetal and alcohol functions were stable in the presence of trifluoroacetic acid, 6 M HCl, or aqueous toluenesulfonic acid. Furthermore, compounds **5b** and **5c** could not be dehydrated using trifluoroacetic anhydride in presence of base, as has been reported in the synthesis of pulvinic acids.[23] Instead, we observed selective trifluoroacetylation on C3 as previously described.[3a]

To our satisfaction, the reaction of **2** with other aldehydes led to more useful products (Table 1). Indeed, when the reaction was conducted with dimeric glycolaldehyde, we observed the formation of the expected decarboxylated Knoevenagel-type product **6d** in 67% yield (Table 1, entry 1). Starting with the *para*-methoxybenzyl-protected compound **2′** (R^2 = PMB) significantly increased the yield of product **6e** to 79% (Table 1, entry 2). In contrast, a lower yield, associated with difficulties to purification, was

Table 1 Synthesis of Compounds **6**



Entry	R^1	R^2	Product	*Z*/*E* of **6**	Yield (%)
1	CH_2OH	Bn	**6d**	92:8	67
2	CH_2OH	PMB	**6e**	>95:5	79
3	CH_2OH	H	**6f**	>95:5	35[a]
4	Ph	Bn	**6g**	>95:5	79
5	Me	Bn	**6h**	90:10	49
6	$Me(CH_2)_{10}$	Bn	**6i**	>95:5	54
7	Et_2CO	Bn	**6j**	–	0

[a] Evaluated by ^{1}H NMR analysis of the crude product mixture.

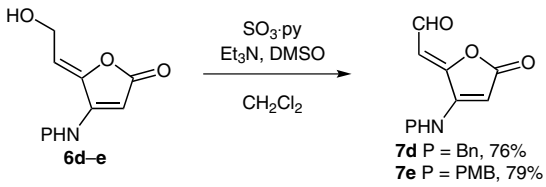
observed starting from unprotected tetronamide **2** (R^2 = H, Table 1, entry 3).

Aromatic or aliphatic aldehydes such as benzaldehyde (Table 1, entry 4), acetaldehyde (Table 1, entry 5), and dodecanal (Table 1, entry 6) were also productive in this novel decarboxylative Knoevenagel reaction. In all cases the *Z* diastereoisomers **6d**–**i** were formed with excellent stereoselectivities. The assignment of the *Z* or *E* configuration of the double bond was achieved by ^{1}H NMR analysis of the chemical shifts of the NH proton of both stereoisomers of compound **6d** (vide infra), as the NH proton is deshielded in the *E* isomer appearing around 10 ppm; whereas the proton of the *Z* isomer presents standard chemical shift around 6 ppm.[24]

The reaction of **2** with a ketone such as pentan-3-one gave neither the Knoevenagel–Doebner nor the aldol products but the decarboxylated tetronamide **8** in quantitative yield.[25]

Concerning the mechanism of this novel one-pot decarboxylative Knoevenagel-type reaction, it is interesting to note that the first step should be a classical condensation leading to aldol adduct **4**. The second step is the saponification of the ester group; whereas the slower dehydration–decarboxylation is only promoted by the acidic medium (aq HCl) during the third step. As the formation of aldols **5d**–**i** was not observed, we speculate that the decarboxylation is concomitant with dehydration.[26] We propose an asynchronous concerted mechanism in which a positive charge is developed, induced by the departure of the alcohol function. This E_1-like mechanism can explain why the reactions with dimethoxyacetaldehyde and ethyl glyoxylate (Scheme 3), in which the development of such positive charge α to an electron-withdrawing group is strongly disfavored, yield adducts **4** and why there is a discrepancy

between the diastereoselectivities observed for the formation of aldols **4** and alkenes **6**.



Scheme 4 Synthesis of protected (*Z*)-basidalin

Pyridinium chlorochromate oxidation of the allylic alcohol **6f** did not lead to the expected basidalin. This could be due to overoxidation of the unprotected nitrogen atom in compound **6f**. On the other hand, oxidation of **6d** and **6e** with SO_3·pyridine[27] gave the corresponding aldehydes **7d** and **7e** in good yields (Scheme 4). Attempts to remove the *p*-methoxybenzyl group were conducted on aldehyde **7e** using ceric ammonium nitrate,[28] DDQ,[29] and TFA.[30] However, although the formation of *p*-methoxybenzaldehyde was observed, basidalin could not be isolated from the mixture.

In conclusion, we have described a methodology wherein C5 ester-substituted tetronamide **2** can be employed as malonate equivalent in the Knoevenagel–Doebner reaction for the synthesis of 5-ylidene-4-amino-2(5*H*)-furanones. The process is mild, efficient, and practical. Some insights into the mechanism of the reaction and an application to the synthesis of two protected basidalin derivatives are presented.

General Procedure for the Preparation of Compounds 6
To a solution of tetronamide **2** (0.88 mmol) in THF (10 mL) was added NaOH (0.07 g; 1.76 mmol) in H_2O (1 mL), followed by the aldehyde (0.88 mmol), and the mixture was stirred for 30 min. Then, 10% HCl was added, and the solution was stirred overnight. The mixture was then extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography to afford compounds **6d–i**.

Compound 6d
IR (NaCl): ν = 3616, 3321, 1739, 1614 cm^{-1}. ^1H NMR (250 MHz, MeOD): δ = 4.31 (d, *J* = 3.0 Hz, 2 H), 4.32 (d, *J* = 7.0 Hz, 2 H), 4.73 (s, 1 H), 5.72 (t, *J* = 7.0 Hz 1 H), 7.21–7.34 (m, 5 H, Ph). ^{13}C NMR (62.5 MHz, MeOD): δ = 49.0, 56.6, 82.0, 107.7, 128.1, 128.3, 129.4, 138.1, 145.6, 160.3, 172.7. HRMS: *m/z* $[M + Na]^+$ calcd for $C_{13}H_{13}NO_3$: 254.0787; found: 254.0789.

Compound 6e
^1H NMR (250 MHz, $CDCl_3$): δ = 3.94 (s, 3 H), 4.26 (d, *J* = 3.0 Hz, 2 H), 4.48 (d, *J* = 6.0 Hz, 2 H), 4.93 (s, 1 H), 5.30 (t, *J* = 6.0 Hz 1 H), 6,90 (d, *J* = 7.0 Hz, 2 H), 7,22 (d, *J* = 7.0 Hz, 2 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 53.8, 56.0, 56.6, 82.0, 107.7, 114.3, 127.0, 127.5, 160.0, 145.6, 160.4, 172.6. HRMS: *m/z* $[M + Na]^+$ calcd for $C_{14}H_{15}NO_4$: 284.0893; found: 284.0896.

General Procedure for the Preparation of Compounds 7d,e
To a solution of 5-ylidene-4-amino-2(5*H*)-furanones **6d**,**e** (0.32 mmol) in CH_2Cl_2 (2 mL) was successively added SO_3·pyridine (65 mg, 0.38 mmol), DMSO (0.4 mL), and Et_3N (0.4 mL), and the mixture was stirred for 4 h. The organic phase was then washed with H_2O (2 × 2 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography to afford the (*Z*)-3-(benzylamino)-[5-oxo-(5*H*)-furan-2-ylidene]acetaldehyde (**7d**) {or (*Z*)-3-(*p*-methoxybenzylamino)-[5-oxo-(5*H*)-furan-2-ylidene]acetaldehyde (**7e**)}.

Compound 7d
IR (NaCl): ν = 3317, 1753, 1739, 1636, 1615 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 4.41 (d, *J* = 5.5 Hz, 2 H), 4.98 (s, 1 H), 5.68 (d, *J* = 7.5 Hz, 1 H), 5.84–5.87 (s, NH), 7.29–7.42 (m, 5 H, Ph), 10.10 (d, *J* = 7.5 Hz, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 49.7, 84.5, 102.2, 127.8, 128.7, 129.4, 135.3, 157.5, 158.3, 167.7, 189.3. HRMS: *m/z* $[M + Na]^+$ calcd for $C_{13}H_{11}NO_3$: 252.0631; found: 252.0633.

Compound 7e
^1H NMR (250 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 4.33 (d, *J* = 5.5 Hz, 2 H), 5.00 (s, 1 H), 5.30 (s, NH), 5.58 (d, *J* = 7.5 Hz, 1 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 10.13 (d, *J* = 7.5 Hz, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 49.0, 55.4, 84.3, 102.2, 114.5, 127.0, 129.0, 129.2, 159.9, 157.1, 158.1, 167.5, 189.0. HRMS: *m/z* $[M + Na]^+$ calcd for $C_{14}H_{13}NO_4$: 282.0736; found: 282.0736.

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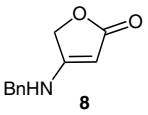

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Figure 1

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