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Reactions of carbamoylated amino enones with 3-substituted chromones for the preparation of 2-pyridones and chromeno[4,3-*b*]pyridine-2,5-diones

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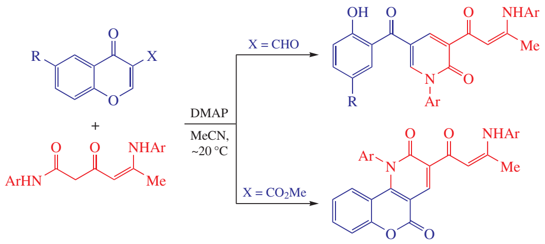
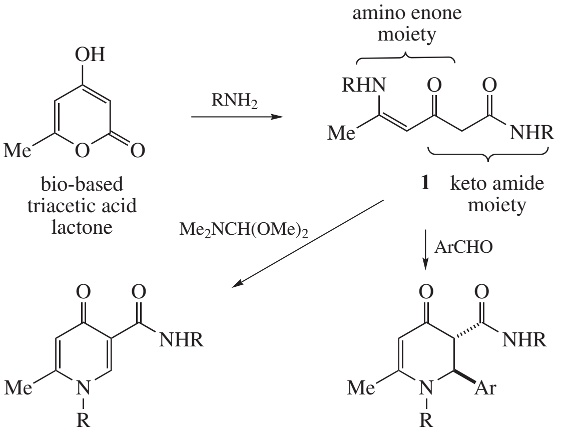
N-Aryl-5-arylamino-3-oxohex-4-enamides as 1,3-C,N-dinucleophiles react regioselectively with 3-formyl or 3-methoxycarbonyl chromones in the presence of DMAP in MeCN to form 2-pyridones (34–43%) or chromeno[4,3-*b*]pyridine-2,5-diones (54–73%) bearing the amino enone moiety.



The 2-pyridone moiety is a ubiquitous core structure unit in many bioactive molecules, natural compounds, dyes, and fluorescents.[1] One of the most convenient strategy for the synthesis of pyridones is based on various condensations of dicarbonyl substrates.[1,2(*a*)] When polycarbonyl compounds are used, pyridone conjugates and polycyclic pyridone derivatives can be accessed.[2(*b*)–(*f*)]

Pyrones and their benzoannelated derivatives may be regarded as latent polycarbonyl compounds which are of importance as highly reactive building blocks in the synthesis of medicines and modern materials.[3] Such compounds have several electrophilic centres and are prone to ring-opening transformations to produce various heterocycles.[4] In addition, pyrone derivatives have been paid a lot of attention as bioprivileged compounds as they can be produced from plant biomass and be used as potential platform molecules for organic synthesis.[5]

Triacetic acid lactone[6] belonging to pyrones is an available substrate that can be produced *via* either polyketide biosynthesis or the acid catalyzed deacetylation of dehydroacetic acid.[7] Very recently, we have modified triacetic acid lactone with amines and obtained highly reactive 5-amino-3-oxohex-4-enamides **1** containing both amino enone and keto amide moieties.[8(*a*)] This structural feature of compounds **1** allows one to consider them as valuable multifunctional building blocks. It has only been known that substrates of type **1** react as 1,5-C,N-dinucleophiles with dimethylformamide dimethyl acetal, leading to 4-pyridone-3-carboxamides,[8(*a*)] and with aromatic aldehydes to give dihydropyridones[8(*b*)] (Scheme 1).



Scheme 1

Since reactions of amino enones **1** with dielectrophiles have not been described previously, we suggested carrying out their reaction with chromones to combine two polycarbonyl moieties for the synthesis of multisubstituted heterocycles. 3-Formylchromones under the action of amino enones[9] or keto amides[10] are known to give multifunctionalized benzenes or 2-pyridones, respectively.

Herein, we report a ring-opening reaction of 3-substituted chromones with carbamoylated amino enones as 1,3-C,N-dinucleophiles to produce N-heterocyclic compounds, such as 2-pyridones and chromeno[4,3-*b*]pyridine-2,5-diones bearing the amino enone moiety.

We commenced our study by examining the reaction between amino enone **1a** and 3-formylchromone **2a** (Table 1, Scheme 2). We supposed that two products, dihydropyridone **3′** and 2-pyridone **3a**, can be formed as a result of the action of compound **1a** as a 1,5-C,N-dinucleophile without chromone ring opening and as a 1,3-C,N-dinucleophile followed by an ANRORC transformation of 3-formylchromone **2a**, respectively. In fact, this reaction afforded 2-pyridone **3a** whereas compound **3′** was not detected at all. This result can be explained by the formation of the more stable structure because of higher aromaticity of the 2-pyridone core and more effective conjugation of the amino enone group. Product **3a** is formed upon simple refluxing the reactants in MeCN without any catalysts for 4 h in a very low yield (Table 1, entry 1). Next, screening of bases in MeCN as a solvent showed that NEt_3, DBU, DABCO were less effective catalysts (entries 2–4) than 4-dimethylaminopyridine (DMAP) (1.2 equiv.), which provided

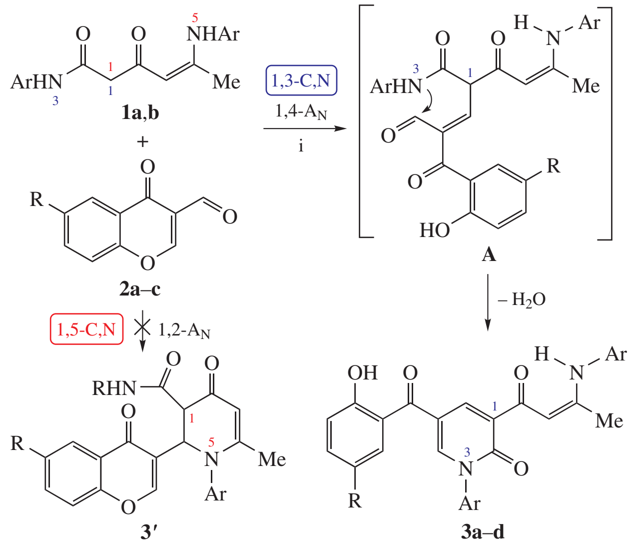
Table 1 The optimization of the reaction conditions[a] for the synthesis of pyridone **3a**.

Entry	Solvent	Base (equiv.)	*t*/h	Isolated yield of **3a** (%)
1	MeCN	–	4	8[b]
2	MeCN	NEt_3 (1.2)	24	2
3	MeCN	DBU (1.2)	24	15
4	MeCN	DABCO (1.2)	24	35
5	MeCN	DMAP (1.2)	24	43
6	dioxane	DMAP (1.2)	72	5
7	CH_2Cl_2	DMAP (1.2)	72	17
8	EtOH	DMAP (1.2)	72	11
9	MeCN	DMAP (1.2)	7	36[c]
10	MeCN	DMAP (0.1)	24	15
11	MeCN	DMAP (1.2)	24	35[d]
12	MeCN	DMAP (0.5)	24	42

[a] Unless otherwise noted, amino enone **1a** (100 mg, 0.34 mmol) and 3-formylchromone **2a** (71 mg, 0.41 mmol) were used at 20 °C in a solvent (2 ml). [b] The reaction was carried out under reflux. [c] The reaction was performed at 0 °C. [d] Amount of **2a** was 59 mg (0.34 mmol).

the best yield (43%) (entry 5).[†] Solvent screening with the use of DMAP as the catalyst of choice (1.2 equiv.) (entries 6–8) as well as changing temperature (entry 9) and the amounts of chromone **2a** or DMAP (entries 10–12) did not allow us to improve the yield of the product.

With the optimized conditions in hand, we probed the scope of the reaction with respect to both amino enones **1a**,**b** and 6-substituted 3-formylchromones **2a**–**c**. The substituents did not affect the formation of compounds **3** which were isolated in 34–43% yields. ^1H NMR spectra of 2-pyridones **3a**–**d** (DMSO-d_6) contain downfield characteristic singlets of the OH and NH protons involved in hydrogen bonding at δ 9.87–10.46 and 13.29–13.30 ppm, respectively. The protons of pyridone ring appeared as singlets at δ 8.63 and 9.18–9.23 ppm allowing products to be assigned to 2-pyridones **3** rather than dihydropyridones **3′**. Note also that, according to the published data,[8(*b*)] the ^1H NMR spectra of similar dihydropyridones (potential alternative products) contain characteristic doublets for the H-2 and H-3 protons of the dihydropyridone ring at δ 3.56–4.00 and 5.23–5.67 ppm with *J* 4.6–6.4 Hz (DMSO-d_6).



Amino enone	Ar	Chromone	R	Product	Yield (%)
1a	Ph	**2a**	H	**3a**	43
1a	Ph	**2b**	Cl	**3b**	36
1a	Ph	**2c**	Me	**3c**	37
1b	4-MeOC_6H_4	**2a**	H	**3d**	34

Scheme 2 *Reagents and conditions*: i, DMAP, MeCN, room temperature.

It is of notice that the formyl group in chromones **2** is synthetically equivalent to their C^2 atom. However, we believe that a more preferred mechanism for the formation of products **3** includes an initial Michael addition[9] (1,4-A$_N$) of the base-activated amino enone **1** at C^2 followed by ring opening to give intermediate **A** (see Scheme 2). Further intramolecular cyclization involving the amide and aldehyde groups after elimination of water leads to 2-pyridones **3**. The fact that the formation of dihydropyridones **3′** as a result of the attack at the aldehyde group (1,2-A$_N$) without chromone ring opening was not observed can be considered as an additional evidence of the 1,4-A$_N$ mechanism of this reaction.

Derivatives of chromone-3-carboxylic acid with the most electrophilic site at C^2 are known to be the valuable building blocks for organic synthesis,[11] however their reactivity towards keto amides has not been studied so far. We planned to obtain a series of novel 2-pyridone amino enone conjugates by the reaction of 3-(methoxycarbonyl)chromone **4** with amino enones **1** as 1,3-C,N-dinucleophiles (Scheme 3). To our delight, under the optimized conditions chromeno[4,3-*b*]pyridine-2,5-diones **5** were obtained as coloured solids in 54–73% yields. The structure of 5-amino-3-oxohex-4-enamides **1** has an influence on the coumarin formation. Amino enone **1b** bearing the electron donating group (Ar = 4-MeOC_6H_4) gave the product in the best yield. The reaction was found to be tolerant to steric hindrance of substrate **1**, and amino enone **1c** (Ar = 2-MeOC_6H_4) smoothly reacted with chromone **4** to produce coumarin **5c** in 54% yield (see Scheme 3).

We propose that compound **4** reacts with 5-amino-3-oxohex-4-enamides **1** to form polycarbonyl intermediate **B**, which undergoes cascade intramolecular cyclization into pyridocoumarins **5** (see Scheme 3). In opposition to the transformation of intermediate **A** (see Scheme 2), this route includes a nucleophilic

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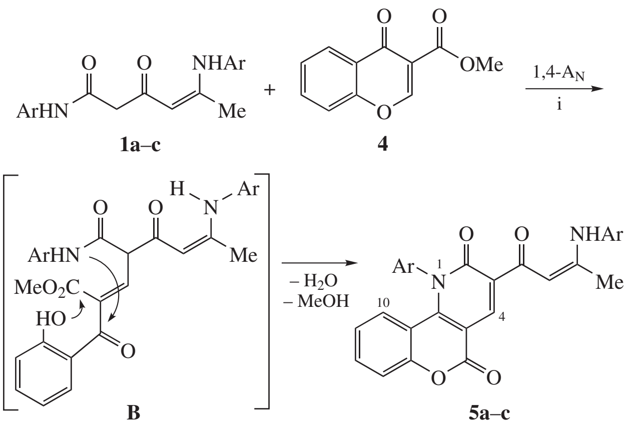
[†] *General procedure for the preparation of pyridones* **3** *and chromeno[4,3-*b*]pyridine-2,5-diones* **5**. A mixture of carbamoylated amino enone **1** (0.34 mmol) and chromone **2** or **4** (0.41 mmol) was stirred with DMAP (50 mg, 0.41 mmol) in dry MeCN (2 ml) for 24 h. Then the reaction mixture was left at 20 °C for 24 h, the product was filtered and washed with cold toluene.

*(Z)-5-(2-Hydroxybenzoyl)-1-phenyl-3-(3-phenylamino-1-oxobut-2-en-1-yl)pyridin-2(1*H*)-one* **3a**. Yield 43% (67 mg), yellow powder, mp 246–248 °C. IR (ATR, ν/cm^{-1}): 3192, 1652, 1565, 1531, 1486, 718. ^1H NMR (DMSO-d_6) δ: 2.13 (s, 3H, Me), 6.52 (s, 1H, =CH), 6.69 (td, 1H, Ar, *J* 7.5, 0.7 Hz), 6.72 (d, 1H, Ar, *J* 8.7 Hz), 7.12 (td, 1H, Ar, *J* 8.0, 1.6 Hz), 7.16–7.31 (m, 7H, Ph, Ar), 7.32 (d, 2H, H-2,6 Ph, *J* 8.0 Hz), 7.44 (dd, 2H, H-3,5 Ph, *J* 8.2, 7.6 Hz), 8.63 (s, 1H, pyridone), 9.18 (s, 1H, pyridone), 10.13 (s, 1H, OH), 13.29 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 20.0, 97.7, 115.3, 115.6, 117.1, 118.5, 124.1, 125.7, 127.0, 128.2, 128.4, 129.2, 129.3, 130.9, 131.4, 137.4, 137.9, 138.0, 154.3, 158.6, 160.9, 162.9, 182.5, 187.6. Found (%): C, 73.68; H, 4.73; N, 6.56. Calc. for $C_{28}H_{22}N_2O_4 \cdot 0.25H_2O$ (%): C, 73.91; H, 4.98; N, 6.16.

*(Z)-1-Phenyl-3-(3-phenylamino-1-oxobut-2-en-1-yl)-1*H*-chromeno[4,3-*b*]pyridine-2,5-dione* **5a**. Yield 65% (99 mg), yellow powder, mp 274–275 °C. IR (ATR, ν/cm^{-1}): 3051, 1738, 1673, 1526, 1279, 756. ^1H NMR (DMSO-d_6) δ: 2.14 (s, 3H, Me), 6.27 (dd, 1H, H-10, *J* 8.6, 1.3 Hz), 6.55 (s, 1H, =CH), 6.89 (ddd, 1H, H-9, *J* 8.6, 8.5, 1.3 Hz), 7.28 (tt, 1H, H-4 Ph, *J* 7.4, 1.0 Hz), 7.32 (d, 2H, H-2,6 Ph, *J* 7.6 Hz), 7.44 (dd, 2H, H-3,5 Ph, *J* 8.2, 7.6 Hz), 7.47 (dd, 1H, H-7, *J* 8.6, 1.3 Hz), 7.50–7.54 (m, 2H, Ph), 7.56 (ddd, 1H, H-8, *J* 8.6, 8.5, 1.3 Hz), 7.64–7.68 (m, 3H, Ph), 8.87 (s, 1H, H-4), 13.35 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 20.1, 97.7, 103.8, 113.1, 118.2, 123.7, 124.1, 125.8, 126.5, 128.7, 129.3, 129.7, 130.0, 133.3, 137.9, 139.2, 139.9, 148.0, 153.4, 159.0, 160.9, 163.4, 181.3. Found (%): C, 74.92; H, 4.48; N, 6.05. Calc. for $C_{28}H_{20}N_2O_4$ (%): C, 74.99; H, 4.50; N, 6.25.

For characteristics of products **3b**–**d**, **5b**,**c**, see Online Supplementary Materials.



Amino enone	Ar	Product	Yield (%)
1a	Ph	**5a**	65
1b	4-MeOC$_6$H$_4$	**5b**	73
1c	2-MeOC$_6$H$_4$	**5c**	54

Scheme 3 *Reagents and conditions*: i, DMAP, MeCN, room temperature.

attack of the OH and NHAr groups at the CO$_2$Me and C=O moieties, respectively. This mechanistic rationalization is in good agreement with the literature data since 3-methoxycarbonylchromone **4** can be considered as the synthetic equivalent of 3-formyl-4-hydroxycoumarin.[12]

^{1}H NMR spectra of coumarins **5a–c** (DMSO-d_6) contain characteristic downfield singlets for the NH proton involved in hydrogen bonding at 13.12–13.35 ppm and upfield doublet of doublets for the H-10 proton of the heterocyclic system at δ 6.27–6.50 ppm due to the shielding effect of the aromatic substituent at N^1 of chromeno[4,3-*b*]pyridine-2,5-dione system.[13]

In summary, we have developed a simple DMAP-promoted synthesis of 2-pyridones and chromeno[4,3-*b*]pyridine-2,5-diones bearing amino enone moieties based on the regioselective ring-opening reaction of 3-substituted chromones with carbamoylated amino enones. The structure of products formed depends on the nature of 3-positioned substituent in the chromone system. The use of 5-amino-3-oxohex-4-enamides as 1,3-C,N-dinucleophiles for the construction of heterocycles has been demonstrated. Since carbamoylated amino enones can be currently prepared from triacetic acid lactone, this work can be considered as a novel synthetic application of this bio-based molecule.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.041.

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