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Mendeleev Commun., 2023, **33**, 401–403

Mendeleev Communications

Revisited synthesis of fused diazepines from 3-(3-aryl-3-oxopropenyl)chromen-4-ones and binucleophilic amino enones in a three-step domino process

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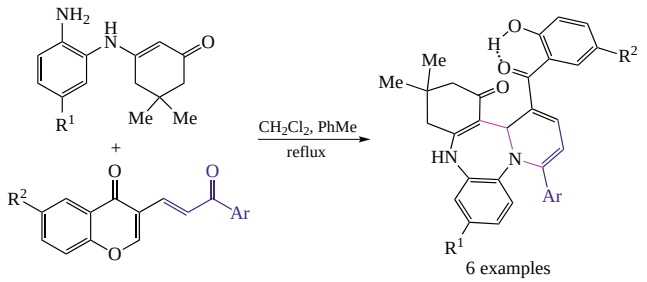
DOI: 10.1016/j.mencom.2023.04.032

The synthesis of tetracyclic 11,12,13,14b-tetrahydrodibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]diazepines was revisited *via* a catalyst-free three-step domino reaction involving a pyrone ring-opening/aza-Michael addition/intramolecular cyclization, the reactants having been *o*-arylenediamine–dimedone adducts and 3-(3-aryl-3-oxopropenyl)chromen-4-ones. The 3-positioned exocyclic α,β-enone fragment on the chromone moiety is involved in the cyclization into the final products at the last step of the process.



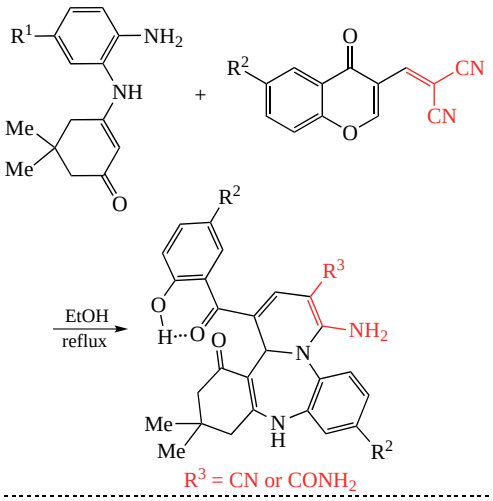
Keywords: 3-vinylchromones, binucleophilic amino enones, catalyst-free reactions, three-step domino reaction, dibenzo[*b*,*f*]pyrido-[1,2-*d*][1,4]diazepines, tetracyclic compounds, pyrido-fused compounds.

3-(3-Aryl-3-oxopropenyl)chromen-4-one has been demonstrated as a convenient synthon for constructing heterocyclic molecular scaffolds. Although 3-vinylchromones possess two electron-deficient olefinic double bonds, their chemical transformations have not received much attention.[1] They have been subjected to 1,3-dipolar cycloaddition with diazomethane[2] and nitrile oxides.[3] Organocatalytic [10 + 4] cycloadditions of 3-vinylchromones provide a diversity-oriented access to functionalized benzo[*a*]azulenes.[4] Brønsted acid-controlled Diels–Alder[5] and inverse-electron-demand Diels–Alder reactions of electron-deficient chromone-fused dienes have been used to construct xanthene and benzophenone derivatives.[6] Another chemical transformation is the regioselective epoxidation of α,β-unsaturated ketone moiety.[7] Other substrates, including *o*-phenylenediamines,[8] *o*-aminothiophenols,[9] and hydrazine hydrate[10] have been exploited as nucleophilic reagents in diverse heterocyclization of electron-deficient chromone-fused dienes. It should be noted that these reactions were carried out under harsh conditions in the presence of corrosive acids, and/or at high temperatures.

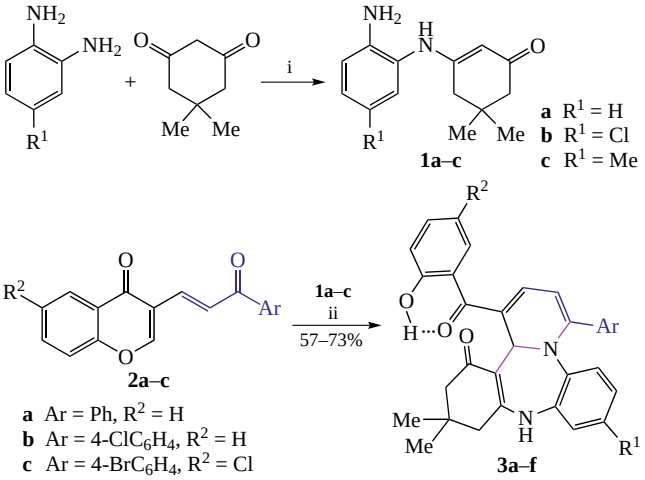
Among nucleophilic coupling reagents, amino enones are particularly fascinating for synthesizing nitrogen-containing heterocycles. In previous reports, the reactivity of 3-[(2-aminoaryl)amino]-5,5-dimethylcyclohex-2-en-1-ones as the binucleophilic amino enones towards electrophiles such as arylidenemalononitriles,[11] chromone-3-carboxaldehyde,[12] and Knoevenagel adduct obtained from malononitrile and 3-formylchromone[13] have been disclosed. Since the condensation of binucleophilic amino enones with these chromone-based electrophiles proceeds without acid catalysis, we decided to revisit the reaction of 3-[(2-aminoaryl)amino]-5,5-dimethylcyclohex-2-en-1-ones **1a–c** with 3-(3-aryl-3-oxopropenyl)chromen-4-ones **2a–c** in order to prepare novel compounds under mild conditions (Scheme 1). Recently,[13] we have reported the synthesis of tetracyclic pyrido-fused dibenzodiazepines using chromonyl malononitrile synthon *via* a catalyst-free domino reaction (see Scheme 1, top). The present work utilizes exocyclic α,β-unsaturated ketone substrates to synthesize fused diazepine ring systems. In our previous work, we applied alkenes having a Knoevenagel carbon–carbon double bond resulted in the introduction of a β-amino nitrile substituent on the six-membered heterocycle fused to the 1,4-diazepine moiety. In that method, the modification of tetracyclic pyrido-fused dibenzodiazepines was performed by introducing exocyclic α,β-unsaturated ketone substrates on electron-deficient chromone-fused dienes chromone moieties. In addition, a change in the reaction conditions was caused by changing the synthon so that EtOH could not be a suitable solvent for the formation of desired product.

We commenced our investigations by *in situ* synthesizing 3-[(2-aminoaryl)amino]-5,5-dimethylcyclohex-2-en-1-one **1a** from dimedone and *o*-phenylenediamine in boiling toluene (see Scheme 1, bottom). Afterwards, 3-(3-aryl-3-oxopropenyl)-chromen-4-one **2a** as a multifunctional synthon (prepared by the Wittig olefination of 3-formylchromone in EtOH) was added to the reaction mixture. After 1 h, a red spot was noticed on the TLC plate, and then the reaction mixture was stirred under reflux for 12 h. To our delight, the tetracyclic pyrido-fused dibenzodiazepine **3a** was obtained in 53% yield within 24 h. The structure of **3a** was identified by IR, mass, elemental analysis, ^{1}H and ^{13}C NMR spectra. Inspired by this initial result, we selected the one-pot sequential reaction of 3-[(2-aminoaryl)-amino]-5,5-dimethylcyclohex-2-en-1-one (1.0 equiv.) **1a** and 3-(3-aryl-3-oxopropenyl)chromen-4-one (1.0 equiv.) **2a** as the model reaction. The influence of different solvents such as CH_2Cl_2, DMF, MeCN, toluene, and THF was examined to optimize the reaction conditions. Dichloromethane was selected as the solvent of choice to chemoselectively obtain the products. Based on these results, the boiling CH_2Cl_2–toluene mixture at 80 °C was defined to be the optimal reaction condition.

Previous work:



This work:



Scheme 1 *Reagents and conditions*: i, PhMe, reflux, 3 h; ii, addition of **2a–c** in CH_2Cl_2 to *in situ* prepared **1a–c**, reflux, 12 h.

The mass spectrum of **3a** displayed a molecular ion peak at *m/z* = 488.21, which was compatible with a 1 : 1 adduct of **1a** and **2a** minus H_2O. In the IR spectrum of **3a**, the presence of NH, OH, and two C=O bonds indicated the most significant functional groups of the product. In the ^{1}H NMR spectrum of **3a**, two vicinal protons of the 6-membered heterocyclic ring gave a doublet of doublets (dd) and a doublet (d) signal, whose both the chemical shifts and the coupling constant values ($^3J_{HH}$ = 6.6 Hz, $^4J_{HH}$ = 1.9 Hz, 5.53 ppm, and $^3J_{HH}$ = 6.1 Hz, 6.66 ppm) revealed the structure of the dibenzo[*b*,*f*]-pyrido[1,2-*d*][1,4]diazepine **3a**. The coupling constant value $^4J_{HH}$ = 1.9 Hz is related to splitting one hydrogen of the six-membered ring with the 1,4-diazepine hydrogen. Also, two singlet signals at δ 9.55 and δ 10.00 ppm showed the protons of an NH and phenolic O–H, respectively. In the carbon spectrum, 32 particular resonances are consistent with the structure of the dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]diazepine **3a**.

Scheme 1 shows that available 3-formylchromone, *o*-phenylenediamine and phenacyl bromide derivatives are well tolerated allowing one to prepare other analogous products **3a–f** in satisfactory yields. Furthermore, our observations revealed that the reaction did not proceed for substrates bearing the nitro group as the R^2 substituent.

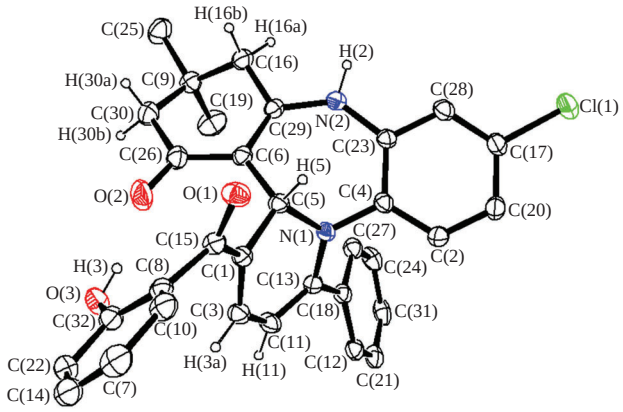
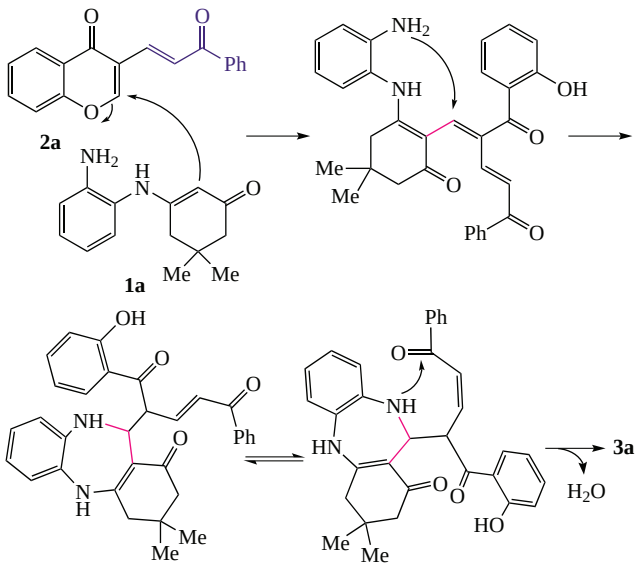


Figure 1 ORTEP diagram of **3e**.

The structure of **3e** was ultimately confirmed by single-crystal X-ray crystallographic analysis (Figure 1).†

The plausible mechanism of this reaction is presented in Scheme 2. The first step that leads to the open-chain intermediate is the nucleophilic attack of the amino enone on the pyrone ring. The selective aza-Michael addition, followed by intramolecular ring expansion, liberates the H_2O



Scheme 2

† *Crystal data for* **3e**. $C_{32}H_{26}ClN_2O_3$ (M = 1045.00), monoclinic, space group *P*21/*c*1 at 290 K, a = 23.001(5), b = 13.972(3) and c = 16.662(3) Å, α = 90.0°, β = 96.17(3)°, γ = 90.0°, V = 5323.6(19) Å^3, Z = 4, d_{calc} = 1.304 g cm^{-3}, μ(MoKα) = 0.18 mm^{-1}, F(000) = 2188. A total of 38981 reflections were collected (10247 independent reflections, R_{int} = 0.089) and used in the refinement, which converged to wR_2 = 0.1511, GOOF = 1.062 for all independent reflections [R_1 = 0.0714 was calculated for 6267 reflections with $I > 2\sigma(I)$].

The X-ray diffraction analysis was carried out on a Bruker APEX area-detector diffractometer (MoKα radiation, λ = 0.71073 Å, Mirrors monochromator). Collection, editing of data and refinement of the unit cell parameters, as well as accounting for absorption, were carried out using the MAR345 dtb Program (1.24-4, 2013), Automar software package (3.3a, 2015) programs. All calculations were performed using the SHELXT 2018/2 (Sheldrick, 2018); SHELXL2016/6 (Sheldrick, 2016) software. The structure was solved by the direct method and refined by the least squares method in the anisotropic thermal approximation for non-hydrogen atoms.

CCDC 2216002 contains the supplementary crystallographic data for this paper. These data can be obtained free of change from The Cambridge Crystallographic Data Center *via* http://www.ccdc.cam.ac.uk.

molecule and affords the final dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]-diazepine **3a**.

In conclusion, the versatile reactivity of 3-[(2-aminoaryl)-amino]-5,5-dimethylcyclohex-2-en-1-ones toward electron-deficient chromone-fused dienes has been described. The modification of tetracyclic pyrido-fused dibenzodiazepines has been performed by introducing exocyclic α,β-unsaturated ketone substrates on chromone moieties. This catalyst-free three-step domino reaction proceeds *via* pyrone ring-opening/aza-Michael addition/intramolecular cyclization without adding acid catalysts.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.04.032.

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Received: 28th October 2022; Com. 22/7034