Formal [3+2]-Cycloaddition-Based Approach Using Ethoxymethylene Malonate Derivatives: Novel and Expedient Access to Functionalized *N*-Acyliminium Precursors

Moussa Saber,[a] Sébastien Comesse,*[a] Vincent Dalla,*[a] Adam Daïch,*[a] Morgane Sanselme,[b] Pierre Netchitaïlo[a]

[a] Laboratoire de Chimie, URCOM, EA 3221, CNRS-INC3M FR3038, UFR des Sciences et Techniques, Université du Havre, BP: 540, 25 Rue Philipe Lebon, 76058 Le Havre Cedex, France
Fax +33(02)32744391; E-mail: sebastien.comesse@univ-lehavre.fr; E-mail: vincent.dalla@univ-lehavre.fr; E-mail: adam.daich@univ-lehavre.fr

[b] UPRES-EA 3233, IRCOF, Université de Rouen, 1 Rue Tesnière, 76821 Mont-Saint-Aignan Cedex, France

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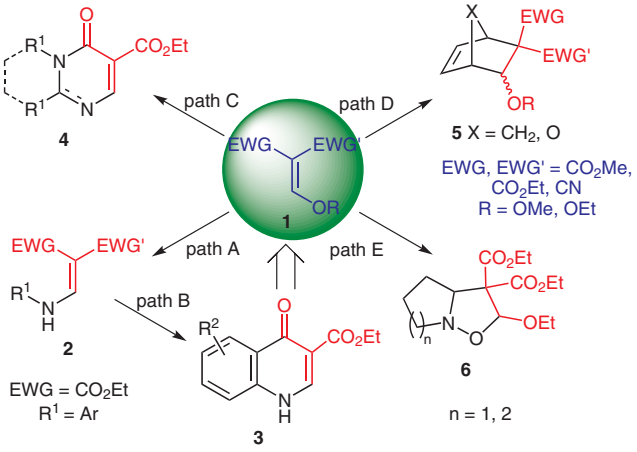
Abstract: Combination of a base, ethoxymethylene malonates, and α-bromoacetamides was used to reach structurally diverse α-alkoxy-γ-lactams via a direct aza-MIRC sequence in excellent yields. Subsequent acidic treatment allowed the formed pyrrolo [2,1-*a*]isoquinoline alkaloid core to be isolated in high yield.

Key words: [3+2] annulation, aza-heterocycle, tandem reaction, α-alkoxy-γ-lactams, *N*-acyliminium, α-amidoalkylation

Commercially available diethyl ethoxymethylene malonate (DEEM), ethyl ethoxymethylene cyanoacetate, and ethoxymethylene malononitrile (**1**) are powerful tools for the synthesis of cyclic and heterocyclic frameworks.[1] The presence of two electron-withdrawing groups (EWG) within these structures makes them versatile useful building blocks in organic synthesis. Importantly, their reactivity can be classified according to three main modes as: (1) biselectrophiles (Scheme 1, paths A–C), (2) dienophiles/dipolarophiles (Scheme 1, paths D and E) and (3) 1,2-dipoles (Scheme 2, equation 1). The seminal developments of dialkyl alkoxymethylene malonates and their derivatives have mainly focused on reactions with primary anilines to typically provide enamines **2** through substitution of the alkoxy group (Scheme 1, path A). Under thermal conditions, the aza-Michael addition is commonly followed by a cyclization step onto one of the ester functions (EWG) to furnish the corresponding 4-quinolones **3** (path B).[2] Many variants of such tandem aza-Michael addition–intramolecular acylation using various 1,3-bisnucleophiles are known. In these cases, both cyclic and acyclic amidine and aminal-type reactants forming pyrimidin-4-ones **4** as typified in path C,[3] ureas,[4] and their sulfonyl analogues $H_2N(SO_2)NHR$[5] were investigated. Similar sequences using also 1,2-bisnucleophiles such as hydrazines[6] and hydroxylamines[7] have also been developed. Alternatively, ethoxymethylene derivatives can be employed as dienophiles in Diels–Alder reactions leading to bicyclo- or oxabicyclohexenes **5** (path D)[8], while 1,3-dipolar cycloadditions with oximes allow an efficient access to bicyclic systems **6** (path E).[9] Complementary to these approaches, the 1,2-dipolar potential of DEEM has also been exploited for the efficient preparation of highly functionalized 3-arylidene-(or alkenylidene)tetrahydrofurans of type **7** using a three-component reaction involving a palladium-mediated cyclization (Scheme 2, eq. 1).[10] In this context, we wish to present herein a new aspect of the latter reactivity mode that expands the scope of the commercially available ethoxymethylene derivatives **1** and provides an expedient and innovative entry into a novel variety of α-alkoxy-γ-lactam scaffolds **9** as remarkable *N*-acyliminium precursors (Scheme 2, eq. 2).[11]

This work complements a related [3+2] annulation of allylsilanes and chlorosulfonyl isocyanate recently developed by Woerpel and co-workers.[12]



Scheme 1 Use of ethoxymethylene derivatives **1** in the synthesis of the corresponding enaminones **2** and various heterocyclic compounds **3–6**

Over the last decade, we have investigated several aspects in the chemistry of *N*-acyliminium ions, including the main heterocyclization process, the catalytic intermolecular and intramolecular α-amidoalkylations as well as the preparation of potential drug candidates.[13]

Another ongoing program in our group focuses on the development of new tandem and domino processes for the synthesis of heterocyclic systems containing one or more nitrogen atom(s).[14] In this paper, we describe our preliminary findings in a merging of both aspects for an unprec-

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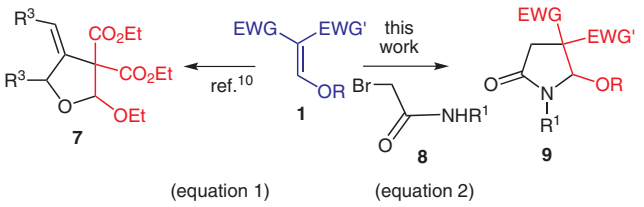


Scheme 2 1,2-Dipolar properties of ethoxymethylene derivatives **1** in the synthesis of heterocyclic compounds

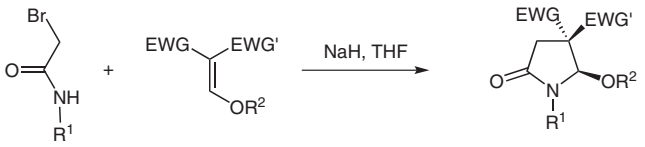
edented and expedient approach to *N*-acyliminium ion precursors and their use in the straightforward synthesis of tricyclic core of the bioactive alkaloid crispine A. Our strategy builds on our previously developed formal [3+2] cycloaddition using benzylidene malonates and α-bromoacetamides of type **8**.[14b] In the present work, the Michael acceptor components have been switched to alkoxymethylene malonate derivatives **1** without alteration of the aza-MIRC reactivity, providing us with an efficient and expedient access to substituted γ-lactams **9**.

In this sense, a first set of reactions was settled starting from either dimethyl methoxymethylene malonate (DMMM) or DEEM of type **1** and α-bromoacetamides **8a–d** using NaH as base in THF at room temperature. We were delighted to observe that side products potentially arising from ethoxide displacement were never observed, with only the expected α-alkoxy-γ-lactams **9a–d** being obtained in high yields ranging from 88% up to 95% (Table 1, entries 1–4).[15] Switching the Michael acceptor structure from malonates to cyanoacetates did not alter the efficacy of the tandem process and the desired ethoxy lactams **9e–h** were also isolated in good yields and excellent diastereoselectivities along (entries 5–8). The *syn* relationship between the ethoxy group and the nitrile function in these adducts was confirmed by a single X-ray analysis performed onto adduct **9h** (Figure 1)[16] and stands in agreement with our previous work in this area.[14b] Unfortunately, the above conditions were shown to be less efficient in the case of ethoxymethylene malononitrile (**1d**), and under these conditions, the aminal **9i** was isolated in an unsatisfying 48% yield (entry 9) probably due to competitive polymerization of the starting material **1d**. After further screening of the reaction conditions (base, solvent), K_2CO_3 in refluxing acetonitrile (entry 10) appeared to be the best combination to provide the expected system **9i** in a very good yield of 89% after purification.[17]

Having established the capacity of ethoxymethylene malonate derivatives **1**, with α-bromoacetamides **8** and a base, to provide an unusual aza-MIRC cascade process in forming substituted α-alkoxy-γ-lactams as remarkable *N*-acyliminium precursors, we next sought to outline the utility of this approach in polyazaheterocyclic synthesis.

In fact, heterocyclic systems bearing azabicyclo[4.3.0]nonane skeleton are of great biological importance since they are found in a wide range of bioactive natural products and therefore, the formation of this framework has been, and continues to be, of interest.

Table 1 Conditions for the Synthesis of α-Alkoxy-γ-lactams **9a–i**



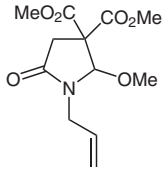
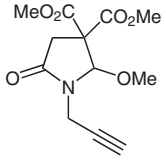
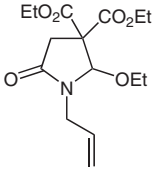
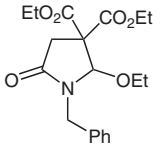
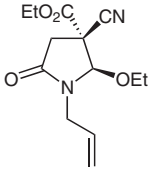
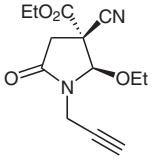
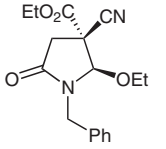
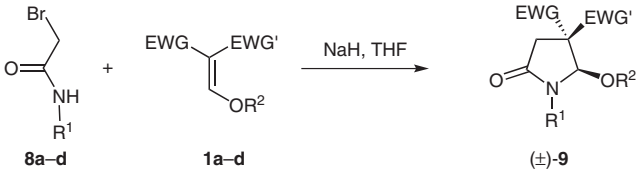
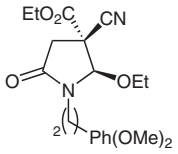
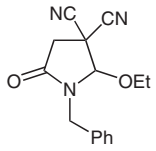
Entry	Amide **8** (R^1)[a]	Michael acceptor **1** (R^2)	γ-Lactam product **9**[b]	Yield (%)[c]	dr[f]
1[d]	**8a** (All)	**1a** (Me)	 **9a**	93	–
2[d]	**8b** (Propar)	**1a** (Me)	 **9b**	91	–
3[d]	**8a** (All)	**1b** (Et)	 **9c**	95	–
4[d]	**8c** (Bn)	**1b** (Et)	 **9d**	88	–
5[d]	**8a** (All)	**1c** (Et)	 **9e**	95	>95:5
6[d]	**8b** (Propar)	**1c** (Et)	 **9f**	90	>95:5
7[d]	**8c** (Bn)	**1c** (Et)	 **9g**	89	>95:5

Table 1 Conditions for the Synthesis of α-Alkoxy-γ-lactams **9a–i** (continued)



8a–d **1a–d** (±)-**9**

Entry	Amide **8** (R^1)[a]	Michael acceptor **1** (R^2)	γ-Lactam product **9**[b]	Yield (%)[c]	dr[f]
8[d]	**8d** (DMPE)	**1c** (Et)	 **9h**	90	>95:5
9[d]	**8c** (Bn)	**1d** (Et)	 **9i**	48	–
10[e]				89	–

[a] For abbreviations used for alkyl and arylalkyl groups, see (**a**) All: allyl, (**b**) Propar: propargyl, (**c**) Bn: benzyl, and (**d**) DMPE: 3,4-dimethoxyphenylethyl.
[b] For EWG and EWG′ groups see directly the structure in column 4.
[c] Isolated yields.
[d] Conditions: NaH, THF, 0 °C, 3 h.
[e] Alternative method: K_2CO_3, MeCN, reflux, 2 h.
[f] Determined by ^{1}H NMR on the crude mixture.

The alkaloid (+)-crispine A (**11**), isolated in 2002 by Zhao and co-workers from *Carduus crispus*,[18] exhibits important activity against notably some human cancer lines, and constitutes a prototypical example of such interesting azabicyclo[4.3.0]nonanes. Therefore, methods enabling a simple access to its tricyclic core and analogous thereof continue to be stimulating and to date, some racemic and enantioselective syntheses have been published.[19] In order to highlight the interest of our novel *N*,*O*-acetal system as *N*-acyliminium ion precursors, we turned our attention to the two-steps synthesis of this tricyclic skeleton by means

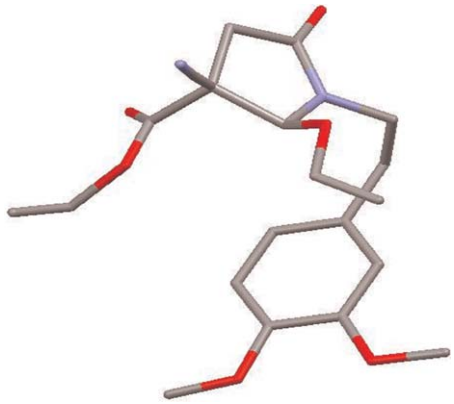
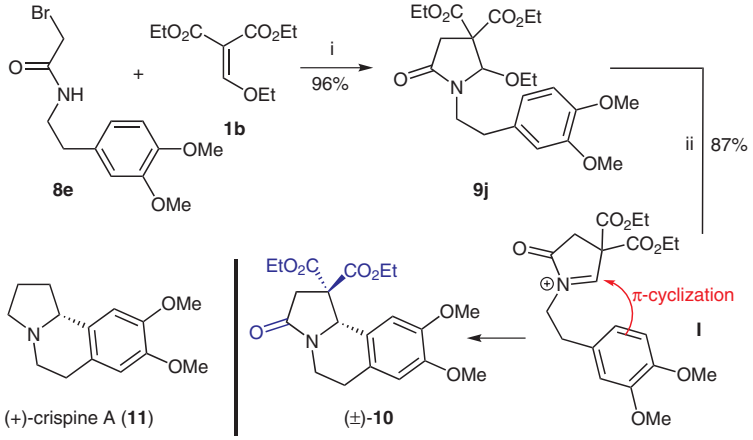


Figure 1 Stick model plot of hydroxy lactam **9h**; for clarity, hydrogen atoms are omitted

of an intramolecular α-amidoalkylation reaction subsequent to the *N*,*O*-acetal formation. Our tandem aza-MIRC strategy using commercially available DEEM (**1b**) was successfully applied to the known *N*-(3,4-dimethoxyphenethyl)-α-bromoacetamide **8e** providing the α-alkoxy-γ-lactam **9j** in an excellent yield of 96% (Scheme 3).

With a quaternary center equipped with two electron-withdrawing groups resident to the *N*,*O*-acetalic carbon, this novel substrate class a priori **9j** seems sterically and electronically unsuitable for *N*-acyliminium ion chemistry. Therefore, the reactivity of the representative compound **9j** for the intramolecular α-amidoalkylation reaction was originally believed to be challenging, and prompted us to first use a large excess of trifluoroacetic acid as *N*-acyliminium promoter. *N*,*O*-Acetal **9j** was indeed subjected to 7 equivalents of TFA in refluxing acetonitrile overnight, and we were delighted to isolate the targeted tricyclic system **10** via the probable intermediacy of the cationic species **I** in a good yield of 87% (Scheme 3). The reaction was further optimized by gradually reducing the charge of Brønsted acid (TFA) which fell down to 3 equivalents[20] without loss of the efficacy. Interestingly, with 2 equivalents of TFA only the corresponding α-hydroxylactam, not presented in Scheme 3,



Scheme 3 *Reagents and conditions*: (i) NaH, THF, 0 °C, 3 h; (ii) TFA, MeCN, reflux, overnight.

was isolated after the reaction workup in nearly quantitative yield.

In conclusion, we have investigated a new field in the chemistry of alkoxymethylene derivatives by showcasing their ability to provide an alternative access to novel and densely functionalized α-alkoxy-γ-lactams. This was operated through a formal [3+2] cycloaddition with diversely functionalized α-bromoacetamides. These species bearing two electron-withdrawing groups were isolated in both high yields and diastereoselectivities. The value of these new *N*-acyliminium ion precursors was demonstrated with the synthesis of the azatriheterocyclic scaffold of crispine A with an overall yield of 83% in two steps starting from commercially available DEEM. Finally, we are currently exploring the scope of this tandem process for the access to more challenging *N*,*O*-acetals. The investigation of both intramolecular and intermolecular catalytic α-amidoalkylations of this novel *N*,*O*-acetals class is also under way in our group and the results will be published in due time.

Acknowledgment

We are grateful to the University of Le Havre for the aid 'ATER position', attributed to M.S. and to our colleague M.-J. Tranchant for technical assistance.

References and Notes

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(15) **Typical Procedure for the Preparation of 9a–j**
The required alkoxymethylene derivative **1a–d** (1.0 mmol) and *N*-alkyl-α-bromoacetamide (**8a–e**, 1.1 mmol) were dissolved in freshly distilled THF (10 mL) at 0 °C. NaH (48 mg, 60% suspension in mineral oil, 1.2 mmol) was then added in small portions, and the mixture was stirred for 3 h. The reaction was carefully quenched by addition of a sat. aq NH_4Cl solution (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), the organic layers were combined, dried over $MgSO_4$, and evaporated. The residue was then chromatographed on silica gel and provided the desired α-alkoxy-γ-lactams **9a–j**.
Physical Data for 9j
This product was isolated as colorless oil; yield 96% (EtOAc–cyclohexane, 30:70). IR (KBr): 3419, 1965 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.0 Hz, 3 H), 1.22–1.23 (m, 6 H), 2.61 (d, *J* = 17.7 Hz, 1 H), 2.82 (m, 2 H), 3.19–3.29 (m, 1 H), 3.42 (d, *J* = 17.7 Hz, 1 H), 3.64 (q, *J* = 7.0 Hz, 2 H), 3.75–3.81 (m, 1 H), 3.84 (s, 3 H), 3.86 (s, 3 H), 4.10–4.32 (m, 4 H), 5.42 (s, 1 H), 6.73–6.81 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.2, 15.5, 33.8, 36.5, 42.8, 56.0, 56.1, 59.9, 62.4, 62.5, 67.3, 91.7, 111.5, 112.2, 120.7, 131.5, 147.9, 149.2, 166.7, 169.3, 171.4 ppm.

(16) Full crystallographic data have been deposited at the Cambridge Crystallographic Data Centre; CCDC reference number 777319 for product **9h**. Copies of the data can be obtained free of charge at the following address: http://www.ccdc.cam.ac.uk.

(17) **Optimized Procedure for the Preparation of Compounds 9a–i**
Starting from ethoxymethylene malononitrile (**1d**, 270 mg, 2.2 mmol) and *N*-alkyl-α-bromoacetamide (**8c**, 1 mmol) were dissolved in freshly distilled MeCN (10 mL). K_2CO_3 (166 mg, 1.2 mmol) was then added, and the mixture was stirred for 2 h under reflux. The reaction was filtered through a small pad of Celite 545 using CH_2Cl_2, and the organic layer was evaporated. The residue was then purified by chromatography on silica gel column and provided the desired α-alkoxy-γ-lactam.
Physical Data for Compound 9i
This product was isolated as colorless oil; yield 89% (EtOAc–cyclohexane, 20:80). IR (KBr): 2982, 2257, 1723 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 6.9 Hz, 3 H), 3.02 (d, *J* = 16.8 Hz, 1 H), 3.17 (d, *J* = 16.8 Hz, 1 H), 3.49 (dq, *J* = 15.2, 7.0 Hz, 1 H), 3.74 (dq, *J* = 15.2, 7.0 Hz, 1 H), 3.94 (d, *J* = 14.9 Hz, 1 H), 4.82 (s, 1 H), 4.94 (d, *J* = 14.9 Hz, 1 H), 7.12–7.15 (m, 2 H), 7.21–7.29 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 35.0, 38.7, 44.8, 67.8, 90.4, 111.7, 113.4, 128.2, 128.6, 129.2, 134.0, 167.0 ppm.

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(20) **Synthesis of Diethyl 8,9-Dimethoxy-3-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-1,1 (10*bH*)-dicarboxylate (10)**

TFA (0.23 mL, 3 mmol) was added dropwise at r.t. to a solution of α-alkoxy-γ-lactam **9j** (438 mg, 1 mmol) in freshly distilled MeCN (10 mL). The mixture was refluxing overnight, cooled to 0 °C and then carefully hydrolyzed with a sat. solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), the organic layers were combined, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on silica gel column to provide **10**.

Physical Data for Compound **10**

This product was isolated as colorless crystals; mp 157–159 °C (recrystallized from Et_2O); yield 87% (EtOAc–cyclohexane, 30:70). IR (KBr): 1728, 1691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.0 Hz, 3 H), 1.36 (t, *J* = 7.0 Hz, 3 H), 2.60 (d, *J* = 16.4 Hz, 1 H), 2.79–3.03 (m, 3 H), 3.05 (d, *J* = 16.4 Hz, 1 H), 3.62–3.84 (m, 2 H), 3.84 (s, 6 H), 4.29–4.50 (m, 3 H), 5.54 (s, 1 H), 6.57 (s, 1 H), 7.30 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 14.3, 28.6, 37.8, 40.1, 60.9, 62.0, 26.6, 110.8, 110.5, 123.6, 127.9, 147.7, 148.4, 168.9, 169.8, 170.7 ppm.