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Dedication ((optional))

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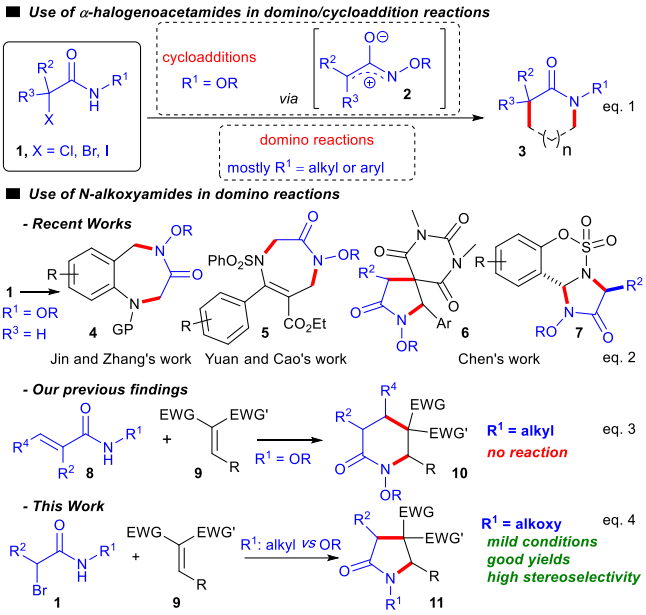
Abstract: The main objective of the present work is to better delineate the positive impact of *N*-alkoxy versus *N*-alkyl moieties in domino reactions. The key role of the metallic counterion of the basic reagent *via* a templating effect has been established, giving an insight over the superiority of *N*-alkoxy α-bromoacetamides compared to their *N*-alkyl analogues. The former demonstrated enhanced reactivity and efficiency, thus requiring milder conditions and leading to a wider scope of γ-lactams in good to excellent yields ranging from 67 to 98%. Overall, this study contributes to the emerging point of view that *N*-alkoxy nitrogenated compounds are useful building blocks with powerful but still under-developed synthetic potential, in particular in domino reactions.

Introduction

α-Haloacetamides are readily accessible and versatile building blocks used in a wide range of organic reactions.[1] This interest lies in their ability to act both as a C-electrophile thanks to the halogenated carbon-atom and as an aza-nucleophile. Going one step forward, the underlying 1,3-dipole character of α-haloacetamides has been recently exploited with properly chosen partners in various domino reactions or concerted processes, thus emphasizing their synthetic potential.[2] In this context the behaviour of α-haloacetamides **1** appears to be closely dependent on the general substitution pattern surrounding the carbonyl function (R^2 and R^3 substituents) but more importantly on the nature of the R^1-N substituent (Scheme 1, eq. 1). Thus, as a rule of thumb, one can state that *N*-alkoxyhaloamides **1** (R^1 = OR, R^2 and/or $R^3 \neq H$) are typically engaged in (3 + *m*) cycloadditions *via* the transient formation of azaoxyallyl cations **2**,[3] while *N*-alkylhaloamides are mostly implied in domino reactions.[2] However, some very recent investigations have shown that *N*-alkoxyhaloamides **1** (R^1 = OR) can also be useful players in these reactions (Scheme 1, eq. 2).[4] For example, the efficient access to 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones **4** has been reported by Jin, Zhang and co-workers by reaction with *N*-(2-chloromethyl)aryl amides.[5] Likewise, a domino aza-Michael/S_N2 cyclization leading to 1,4-diazepinone derivatives **5** was developed by Yuan, Cao and co-workers starting from 1-azadienes.[6] Chen and co-workers have documented another facet of a domino aza-Michael/S_N2 reaction allowing access to spirobarbiturate-pyrrolidinones **6**.[7]



Scheme 1. α-Haloacetamides **1** in domino/cycloaddition reactions.

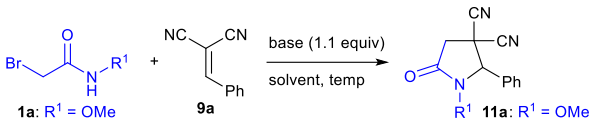
A common statement of these three contributions was the importance of *N*-alkoxyamides as crucial reaction partners as proven by an absence of reactivity when employing *N*-benzylhaloamide derivatives in control experiments. Prior to these studies, Chen and co-workers had pioneered the use of *N*-alkoxyhaloamides **1** in the regio- and diastereoselective synthesis of 4-imidazolidinones **7** by a domino aza-Mannich addition/intramolecular S_N2 reaction.[8] The authors elegantly proved that the reaction did not occur *via* the azaoxyallyl cation pathway, thus allowing the use of *N*-alkylhaloamide substrates, albeit with reduced efficiency compared to their *N*-alkoxy counterparts. We recently observed such differences, during the development of the domino addition of acrylamides **8** to Michael

acceptors **9** providing a new approach to functionalize piperidones **10**, *i.e.* δ-valerolactams (Scheme 1, eq. 3).[9] Good yields of the desired products were obtained from *N*-alkoxyacrylamides **8** (R^1 = alkoxy) but no reaction was observed when *N*-alkylacrylamides (R^1 = alkyl) were employed. These first observations prompted us to re-examine some of our earlier works on the synthesis of γ-lactams **11**,[10] employing this time *N*-alkoxyhaloamides **1** compared to the original *N*-alkyl congeners (Scheme 1, eq. 4). In the literature, little is known on *N*-alkyl-*versus* *N*-alkoxyamide reactivity in aza-Michael addition and related domino reactions.[11,12] Beside these synthetic objectives, this study also intends to better delineate the influence of the *N*-alkoxy substituent in this type of transformation, and, one step further, to refine our general understanding of the "*N-alkoxy effect*" in organic synthesis.

Results and Discussion

As mentioned above, the main goal of this study is to compare, and, to some extent, evaluate the reactivity of bromoamides **1** bearing a *N*-methoxy (**1a**) *versus* a *N*-alkyl (**1b**,**c**) substituent. On that purpose, we first compared the reactivity of *N*-benzylbromoacetamide **1b** versus *N*-methoxybromoamide[13] **1a** in the presence of a highly electrophilic Michael acceptor **9a** bearing two nitrile groups (Scheme 2). While we had previously shown[10a] that under the promotion of a strong base such as NaH in THF at room temperature *N*-benzylbromoacetamide **1b** behave satisfactorily to afford the corresponding lactam **11b** in an acceptable 63% yield (entry 1, Table 1), we observed no reaction in the present study when employing a weaker base like K_2CO_3, either at rt or in refluxing acetonitrile (entries 2 and 3, Table 1).[9,13] These sets of reaction conditions were next comparatively applied to *N*-methoxybromoamide **1a**, and remarkably an opposite trend was observed. While use of NaH in THF at rt resulted in total decomposition of the amide **1a** (entry 4, Table 1), a promising benchmark yield of 30% for the desired product **11a** was obtained by using K_2CO_3 in refluxing acetonitrile (entry 5, Table 1). To our delight this result could be greatly improved at ambient temperature, where decomposition pathways were completely suppressed at the benefit of a fast and clean conversion to the desired lactam **11a** (1 h, 98% yield, entry 6, Table 1). The use of K_2CO_3 in various solvents (entries 7-9, Table 1) or other organic or mineral bases in CH_3CN (entries 10-14, Table 1) proved to be less efficient.[14] This preliminary set of results confirms that important benefits arise from the use of *N*-alkoxy carboxamides while providing useful information on their intrinsic properties. Beside its doubtless synthetic utility opening an improved route to the class of γ-lactams, this study clearly indicates that *N*-alkoxycarboxamides are by far more reactive than their *N*-alkyl analogues, but at the same time less robust especially in the presence of strong bases. Then, we turned our attention to the *N*-methylbromoacetamide **1c** to evaluate the impact of steric hindrance. This structural variation of the ambivalent carboxamide partner (R = Me) enabled considerable reactivity enhancement in comparison with the *N*-benzyl reference substrate (lactam **11c** 59% yield, 29 h, entry 15 *versus* 2 Table 1), which nevertheless remained much below that of *N*-methoxybromoacetamide **1a** (compare entries 6 and 15, Table 1).

Table 1. Comparison and optimization of the reaction conditions



1a: R^1 = OMe
1b: R^1 = Bn
1c: R^1 = Me

9a

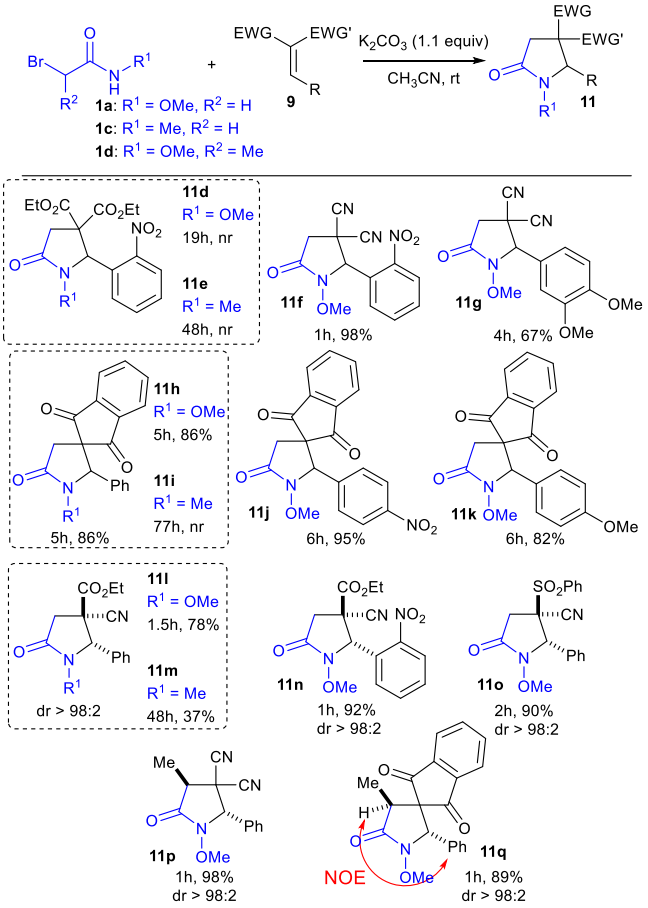
11a: R^1 = OMe
11b: R^1 = Bn
11c: R^1 = Me

Entry[a]	R^1	Base	Solvent	Temp (°C)	Yield (%)[b]
1	Bn	NaH	THF	0 to rt	63[c]
2	Bn	K_2CO_3	CH_3CN	rt	nr[d]
3	Bn	K_2CO_3	CH_3CN	reflux	nr[d]
4	OMe	NaH	THF	0 to rt	dec[e]
5	OMe	K_2CO_3	CH_3CN	reflux	30
6	OMe	K_2CO_3	CH_3CN	rt	98[f]
7	OMe	K_2CO_3	CH_2Cl_2	rt	74
8	OMe	K_2CO_3	EtOH	rt	nr[d]
9	OMe	K_2CO_3	THF	rt	85
10	OMe	Na_2CO_3	CH_3CN	rt	97
11	OMe	Cs_2CO_3	CH_3CN	rt	77
12	OMe	Et_3N	CH_3CN	rt	85
13	OMe	DBU	CH_3CN	rt	68
14	OMe	PhONa	CH_3CN	rt	72
15	Me	K_2CO_3	CH_3CN	rt	59[g]

[a] Reaction conditions: bromoacetamide **1a-c** (0.25 mmol, 1 equiv), Michael acceptor **9a** (0.3 mmol, 1.2 equiv), and base (0.275 mmol, 1.1 equiv) in 2 mL of solvent for 1 h. [b] Isolated yield. [c] See reference 10a. [d] nr: no reaction. [e] *dec*: decomposition of the *N*-methoxy bromoacetamide **1a**. [f] For the standard procedure of the domino reaction, see the Experimental Section and SI. [g] Stirred at rt for 29h.

With the optimal conditions in hand (see the Experimental Section and SI), we further delineated the scope of *N*-methoxybromoamide **1a** with various Michael acceptors (Scheme 2). We began with two additional dicyano derivatives, which gave the corresponding lactams **11f** and **11g** in good to excellent yields (98% and 67%, respectively), thereby confirming the excellent reactivity of this substrate class in our methodology. Conversely, a much less electrophilic Michael acceptor with two ester groups was left untouched (Scheme 2), thereby revealing the structural requirements necessary to achieve the desired reactivity. Not surprisingly, an excellent reactivity was restored when switching to Michael acceptors derived from indane-1,3-dione, with no major impact of the electronic identity (electron-rich or poor) of the aromatic ring on the reaction course (**11h**: 5h, 86%, **11j**: 6h, 95% and **11k**: 6h, 82%, Scheme 2). Likewise, the use of unsymmetrical and rather electrophilic Michael acceptors with cyano ester and cyano sulfone subunits gave the corresponding lactams in good yields along with, remarkably, a high control of the two contiguous stereocenters (**11l**: 1.5 h, 78% yield, **11n**: 1 h, 92% yield, **11o**: 1 h, 90% yield Scheme 2).[15] To continue assessing the *N*-alkoxy effect, the more reactive *N*-alkylated derivatives, *i.e.* *N*-

methylbromoacetamide **1c**, was next evaluated in a set of domino reactions employing the same conditions. First of all, the examination of the least reactive pairs of reactants to form **11e** (with diester derivatives as the Michael acceptor), resulted in no reaction as expected (*vide supra*). Conversely, with more reactive Michael acceptors like those derived from indanedione or having both cyano and ester substituents, the addition reactions of *N*-methylbromoamide **1c** was possible, albeit with an anticipated limited efficiency and scope compared to the *N*-methoxy analogs as previously observed (see entry 15 in Table 1). For instance, γ-lactam **11i**, with an 1,3-indandione framework, was not formed while compound **11m** was isolated in a low 37% yield.

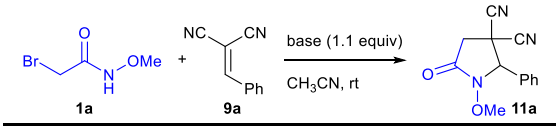


Scheme 2. Comparison and substrate scope for bromoamides **1a**,**c**,**d** and Michael acceptors **9**.

Overall, it is obvious that the reaction course is closely related to the reactivity of the alkene domino partners. The weakest *gem*-diactivated electrophiles impose harsher experimental conditions not compatible with *N*-methoxy bromoamide **1a** and, hence, only *N*-alkylated amides can be used, albeit with limited efficiency (see entry 1, Table 1). Except these few exceptions, *N*-alkoxyamides are obviously more potent domino partners. Indeed, in comparison to *N*-methylamide, the *N*-methoxy congener perform greatly in almost all circumstances under mild conditions which emphasizes the great utility of the *N*-methoxybromoacetamide. The fundamental importance of an alkoxy effect[8,9,11,12] in the aza-Michael-initiated domino reactions studied is thus demonstrated. Finally, when engaging the more challenging α-mono-substituted *N*-methylbromoamide **1d** likely to follow a competitive azaoxyallyl cation pathway, we were delighted to isolate the highly substituted lactams **11p** and **11q** in good yields and excellent diastereoisomeric ratio of 98:2 (Scheme 2), thereby confirming the aptitude of these building blocks for a domino reactivity.[16]

In order to better understand the role of the *N*-alkoxy group, the impact of both pK_a(BH$^+$) and counter-cation of the base were next examined on our model substrates **1a** and **9a** (Table 2). A close relationship could be observed between the conversion and pK_a(BH$^+$) for potassium bases (entries 1-4, Table 2). In comparison to $KHCO_3$, AcOK and HCO_2K, the weakly basic KF promoted higher conversion possibly due to its higher solubility in CH_3CN (entry 5, Table 2).[17] Surprisingly, a significant difference was observed when Na^+ bases were evaluated, with only Na_2CO_3 affording the desired product albeit in extended time (entries 6-8, Table 2). Moreover, no reaction occurred with Li_2CO_3 even if its pK_a(BH$^+$) is close to the other carbonated bases used in this study (entries 9 *vs* 1 and 6 9, Table 2). Obviously, these results would not be fully supported neither by the pK_a(BH$^+$) values and/or solubility effects nor by the α-effect[18] or related influences long-questioned in the chemistry of *N*-alkoxyamine derivatives.[19]

Table 2. Impact of the pK_a(BH$^+$) and the counterion.

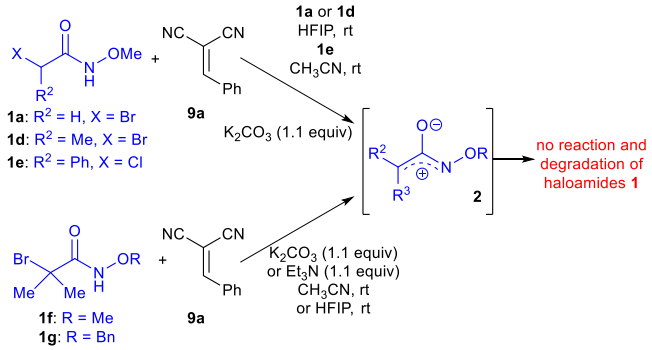


Entry[a]	Base	pK_a(BH$^+$)[b]	Time (h)	Conversion (%)[c]
1	K_2CO_3	10.3	1	100
2	$KHCO_3$	6.4	45	90
3	AcOK	4.8	45	71
4	$KHCO_2$	3.8	45	45
5	KF	3.2	45	86
6	Na_2CO_3	10.3	24	100
7	$NaHCO_2$	3.8	45	nr[d]
8	NaF	3.2	45	nr[d]
9	Li_2CO_3	10.3	45	nr[d]

[a] Reaction conditions: *N*-methoxybromoamide **1a** (0.25 mmol, 1 equiv), Michael acceptor **9a** (0.3 mmol, 1.2 equiv), and base (0.275 mmol, 1.1 equiv) in 2 mL of solvent for 1 h. [b] pK_a(BH$^+$) values of the conjugated acid in water. [c] Determined by ^{1}H NMR of the crude mixture. [d] nr: no reaction

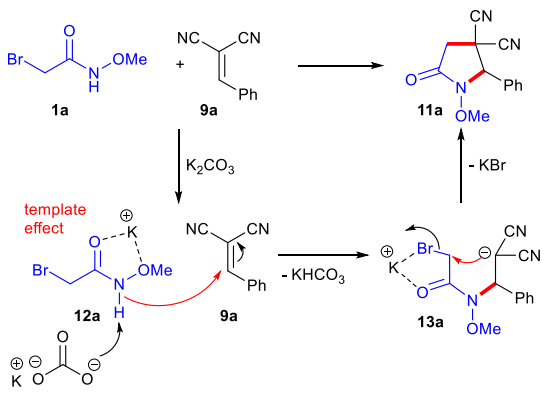
In that context, we sought to ascertain that, in our conditions, the reaction was proceeding either *via* a domino pathway or through an azaoxyallyl cation. Different research groups have established that the formation of an azaoxyallyl cation was very unlikely in the transformations of unsubstituted *N*-alkoxybromoamide such as **1a** (R^2 = H and X = Br, Scheme 3).[20] Interestingly, by replacing

CH_3CN with hexafluoro-2-propanol (HFIP), a solvent favoring the formation of an azaoxyallyl cation, only decomposition of the bromoamide was observed with no lactam formation. Applying the same conditions to the mono substituted α-methylbromoamide **1d** (R^2 = Me and X = Br, Scheme 3), resulted in the total decomposition of the starting amide. More interestingly, α-phenyl-α-chloroacetamide **1e**, known to evolve through the formation of an azaoxyallyl cation such as **2** even in CH_3CN (R^2 = Ph and X = Cl, Scheme 3),[21] also decomposed entirely. Moreover, the same result was observed when α,α-disubstituted-α-bromoacetamides **1f** and **1g**, well known to form azaoxyallyl cations, were engaged in our reaction conditions. We thus assume that no dipole formation occurs in our case or, if so, the azaoxyallyl cation **2** does not react and undergoes fast decomposition.[22]



Scheme 3. Support experiments for the postulated mechanism.

Based on all the gathered observations above, a tentative mechanism for the domino process is proposed (Scheme 4). First, formation of a bidentate chelate **12a** involving both oxygens of the alkoxyamide **1a** would increase the *N*-H acidity. Such a templating effect, not possible with alkylamides, and likely gradually disfavored with the decrease in the size of the metallic cation, $K^+ \rightarrow Na^+ \rightarrow Li^+$, would account for the observed differences in reactivity. Finally, a concomitant deprotonation/aza-Michael addition would generate intermediate **13a** that undergoes ring-closure through intramolecular S_N2 alkylation. As the scheme 4 shows, the possibility of another K^+ -based templating effect to assist the latter step is also considered.[23]



Scheme 4. Proposed mechanism.

Conclusion

In the context of our long-standing interest in domino reactions between bromoacetamides and *gem*-diactivated alkenes to produce elaborated γ-lactams, the contribution of a *N*-alkoxy group was evaluated. We have demonstrated that, with very few exceptions the superiority of the *N*-alkoxycarboxamides is clear. This advantage manifests by an exquisite reactivity under mild experimental conditions not applicable to *N*-alkylcarboxamides. Therefore, the referred lactams are produced with clear enhanced efficiency and wider scope with respect to our original approach combining *N*-alkylamides and a strong base. Control experiments have also established that the metallic counterion of the basic reagent plays an important role, presumably by orchestrating templating effects. Overall, this study contributes to shed light on *N*-alkoxy nitrogenated compounds as useful building blocks with greater synthetic possibilities than their traditional *N*-alkyl analogues. New advances in this field of research are expected in a near future. The results of our ongoing research to exploit the benefits of *N*-alkoxy groups in domino reactions will be published in due course.

Experimental Section

General Information. All commercially available starting materials have been used without further purification. Acetonitrile (MeCN) was distilled under argon over CaH_2. Melting points (Mp) were determined with a SMP10 capillary melting point apparatus (Stuart) and are uncorrected. FT-IR spectra were recorded with a Perkin-Elmer Frontier. The NMR spectra were recorded on a 300 UltraShield instrument (Bruker) from solutions in $CDCl_3$-d, CD_3CN-d3 or DMSO-d6 at 300 MHz (1H) and 75 MHz (13C), respectively, and chemical shifts (δ) are expressed in ppm. High-resolution mass spectra (HRMS) were performed on a 6530 Q-TOF (Agilent System) apparatus and the electrospray ionization (ESI)-MS was measured in positive ionization mode (ESI+) by using Agilent Jet Stream spectrometer. Thin layer chromatography (TLC) was performed using silica gel analytical plates (F254) of 0.25 mm thickness. The detection on TLC plates was performed by UV light at 254 or 365 nm or using a potassium permanganate staining. All the Michael acceptors **9** and α-haloacetamides **1** were synthesized using known procedures. In the case of diastereomeric mixtures, the diastereomeric ratios were determined on the ^1H NMR of the crude product, the yields given are global yields.

Procedure for the synthesis of γ-lactams. Michael acceptor derivative **9** (0.3 mmol, 1.2 equiv) and the bromoacetamide derivative **1** (0.25 mmol, 1 equiv) were dissolved in acetonitrile, and potassium carbonate (0.275 mmol, 1.1 equiv) was added in one portion. The mixture was stirred at room temperature until complete consumption of the bromoacetamide **1** (monitored by TLC). The reaction mixture was filtered through celite 545 pad via a glass filter. The resulting filtrate was concentrated and the residue was purified by flash chromatography (Cy/EtOAc 10:1 to 1:10) to afford the desired domino product **11**.

1-methoxy-5-oxo-2-phenylpyrrolidine-3,3-dicarbonitrile **11a**. This compound was obtained in 98% yield (119 mg, starting from 0.5 mmol of bromoacetamide derivative) after stirring at rt for 1h as a white solid. R_f = 0.3 (Cy/EtOAc, 50/50), Mp = 136-138 °C. IR (ν_{max} / cm^{-1}): 1260, 1749, 2258, 2950, 2990. ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (d, *J* = 17 Hz, 1H), 3.22 (d, *J* =17 Hz, 1H), 3.87 (s, 3H), 5.21 (s, 1H), 7.41-7.42 (m, 2H), 7.49-7.61 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.3, 37.1, 63.7, 66.8, 112.0, 113.8, 127.7 (2C), 129.5 (2C), 130.3, 131.1, 165.8. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{13}H_{12}N_3O_2$ 242,0924; found 242.0913.

1-methyl-5-oxo-2-phenylpyrrolidine-3,3-dicarbonitrile **11c**. This compound was obtained in 59% yield (66 mg, starting from 0.5 mmol of bromoacetamide derivative) after stirring at rt for 29h as a yellow solid. R_f = 0.3 (Cy/EtOAc, 50/50), Mp = 150-152 °C. IR (ν_{max} / cm^{-1}): 1703, 2258, 2926, 2988, 2992. ^1H NMR (300 MHz, $CDCl_3$) δ 2.84 (s, 3H), 3.19 (d, *J* = 17 Hz, 1H), 3.28 (d, *J* = 17 Hz, 1H), 5.04 (s, 1H), 7.29-7.37 (m, 2H), 7.50-7.59 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.3, 36.1, 39.9, 69.9, 112.2, 114.4, 127.3 (2C), 129.8 (2C), 131.0, 131.1, 167.8. Unfortunately, this compound proved to be unstable whatever the HRMS conditions used.

HRMS (ESI$^+$) m/z: [M+K]$^+$ Calcd for $C_{12}H_{10}N_2OK$ (loss of HCN fragment) 237.0425; found 237.0801.

1-methoxy-2-(2-nitrophenyl)-5-oxopyrrolidine-3,3-dicarbonitrile **11f**. This compound was obtained in 98% yield (70 mg) after stirring at rt for 1h as a yellow oil. R_f = 0.35 (Cy/EtOAc, 50/50). IR (ν_{max} / cm^{-1}): 705, 1342, 1525, 1728, 2258, 2946, 3002. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.08 (d, *J* = 17.3 Hz, 1H), 3.31 (d, *J* = 17.3 Hz, 1H), 3.89 (s, 3H), 6.17 (s, 1H), 7.34 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.75 (td, *J* = 7.8, 1.5 Hz, 1H), 7.84 (td, *J* = 7.6, 1.5 Hz, 1H), 8.39 (dd, *J* = 8.2, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.9, 36.7, 62.7, 63.6, 111.9, 114.3, 126.9, 127.4, 127.7, 131.9, 135.2, 148.2, 163.2. HRMS (ESI$^+$) m/z: [M+H]$^+$ Calcd for $C_{13}H_{11}N_4O_4$ 287.0762, found 287.0775.

2-(3,4-dimethoxyphenyl)-1-methoxy-5-oxopyrrolidine-3,3-dicarbonitrile **11g**. This compound was obtained in 67% yield (51 mg) after stirring at rt for 4h as a yellow solid. R_f = 0.35 (Cy/EtOAc, 50/50), Mp = 131-133 °C. IR (ν_{max} / cm^{-1}): 1262, 1517, 1731, 2256, 2840, 2941. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (d, *J* = 17.2 Hz, 1H), 3.21 (d, *J* = 17.2 Hz, 1H), 3.85 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 5.15 (s, 1H), 6.88 (s, 1H), 6.97 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.4, 37.3, 56.0, 56.1, 63.6, 67.1, 110.2, 111.5, 112.0, 113.7, 120.4, 121.9, 149.7, 151.2, 165.3. HRMS (ESI$^+$) m/z: [M+H]$^+$ Calcd for $C_{15}H_{16}N_3O_4$ 302.1141, found 302.1147.

1'-methoxy-2'-phenylspiro[indene-2,3'-pyrrolidine]-1,3,5'-trione **11h**. This compound was obtained in 86% yield (138 mg, starting from 0.5 mmol of bromoacetamide derivative) after stirring at rt for 5h as a yellow solid. R_f = 0.3 (Cy/EtOAc, 50/50), Mp = 149-151 °C. IR (ν_{max} / cm^{-1}): 1259, 1701, 2937, 2990. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 (s, 2H), 3.84 (s, 3H), 5.04 (s, 1H), 7.06-7.24 (m, 5H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.81 (t, *J* = 7.4 Hz, 1H), 7.98 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.1, 56.1, 62.7, 67.1, 123.4, 123.6, 127.5 (2C), 128.4 (2C), 129.1, 132.7, 136.1, 136.6, 141.2, 142.2, 169.9, 197.5, 198.7. HRMS (ESI$^+$) m/z: [M+H]$^+$ Calcd for $C_{19}H_{16}NO_4$ 322.1079, found 322.1093.

1'-methoxy-2'-(4-nitrophenyl)spiro[indene-2,3'-pyrrolidine]-1,3,5'-trione **11j**. This compound was obtained in 95% yield (87 mg) after stirring at rt for 6h as a yellow solid. R_f = 0.35 (Cy/EtOAc, 50/50), Mp = 134-136 °C. IR (ν_{max} / cm^{-1}): 1216, 1375, 1469, 1650. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (s, 2H), 3.84 (s, 3H), 5.17 (s, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.80 (td, *J* = 7.4, 1.3 Hz, 1H), 7.88 (td, *J* = 7.4, 1.3 Hz, 1H), 7.98-8.10 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.8, 55.3, 62.7, 65.5, 123.6 (2C), 123.7, 123.9, 128.6 (2C), 136.7, 137.1, 140.5, 141.0, 141.8, 148.2, 169.3, 196.9, 198.2. HRMS (ESI$^+$) m/z: [M+H]$^+$ Calcd for $C_{19}H_{15}N_2O_6$ 367.0930, found 367.0933.

1'-methoxy-2'-(4-methoxyphenyl)spiro[indene-2,3'-pyrrolidine]-1,3,5'-trione **11k**. This compound was obtained in 83% yield (73 mg) after stirring at rt for 6h as a brown solid. R_f = 0.32 (Cy/EtOAc, 50/50), Mp = 148-151 °C. IR (ν_{max} / cm^{-1}): 759, 1100, 1250, 1500, 1710. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (s, 2H), 3.67 (s, 3H), 3.76 (s, 3H), 4.95 (s, 1H), 6.66 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.72 (td, *J* = 7.4, 1.3 Hz, 1H), 7.78 (td, *J* = 7.4, 1.4 Hz, 1H), 7.94 (d, *J* = 7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.2, 55.2, 56.3, 62.8, 66.7, 113.8 (2C), 123.5, 123.6, 124.4, 128.9 (2C), 136.0, 136.6, 141.3, 142.3, 159.9, 169.8, 197.7, 198.9. HRMS (ESI$^+$) m/z: [M+H]$^+$ Calcd for $C_{20}H_{18}NO_5$ 352. 1184, found 352.1197.

ethyl 3-cyano-1-methoxy-5-oxo-2-phenylpyrrolidine-3-carboxylate **11l**. This compound was obtained in 78% yield (113 mg, starting from 0.5 mmol of bromoacetamide derivative) after stirring at rt for 1.5h as a yellow solid. R_f = 0.3 (Cy/EtOAc, 50/50), Mp = 65-67 °C. IR (ν_{max} / cm^{-1}): 727, 1244, 1279, 1752, 2258, 2952, 3001. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 3.07 (d, *J* = 18 Hz, 1H), 3.17 (d, *J* = 18 Hz, 1H), 3.79 (s, 3H), 4.32-4.40 (m, 2H), 5.20 (s, 1H), 7.33-7.54 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 36.5, 46.7, 63.1, 64.4, 65.7, 115.7, 127.7 (2C), 129.0 (2C), 130.2, 132.6, 165.8, 166.9. HRMS (ESI$^+$) m/z: [M+H]$^+$ Calcd for $C_{15}H_{17}N_2O_4$ 289.1188, found 289.1185.

Ethyl 3-cyano-1-methyl-5-oxo-2-phenylpyrrolidine-3-carboxylate **11m**. This compound was obtained in 37% yield (33 mg, starting from 0.5 mmol of bromoacetamide derivative) after stirring at rt for 48h as a colorless oil. R_f=0.2 (Cy/EtOAc, 6/4). IR (ν_{max}/cm^{-1}): 1703, 1743, 2300, 2928. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.1 Hz, 3H), 2.77 (d, *J* = 0.9 Hz, 3H), 2.96-3.27 (m, 2H), 4.25-4.46 (m, 2H), 5.01 (s, 1H), 7.18-7.32 (m, 2H), 7.48 (dd, J = 5.2, 2.0 Hz, 3H).^{13}C NMR (75 MHz, CDCl3) δ 14.0, 29.1, 39.3, 48.8, 64.3, 68.9, 116.1, 127.4(2C), 129.4(2C), 130.1, 133.6, 166.7, 169.7. HRMS (ESI+) m/z [M+H]$^+$ Calcd for $C_{15}H_{16}N_2O_3$ 273.1160, found 273.1185.

ethyl 3-cyano-1-methoxy-2-(2-nitrophenyl)-5-oxopyrrolidine-3-carboxylate **11n**. This compound was obtained in 92% yield (31 mg, starting from 0.1 mmol of bromoacetamide derivative) after stirring at rt for 1h as a brown oil. R_f = 0.3 (Cy/EtOAc, 50/50). IR (ν_{max} / cm^{-1}): 755, 1088, 1342, 1525, 1728. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.2 Hz, 3H), 2.99 (d, *J* = 17.4 Hz, 1H), 3.08 (d, *J* = 17.3 Hz, 1H), 3.82 (s, 3H), 4.40-4.50 (m, 2H), 6.05 (s, 1H), 7.49 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.65 (td, *J* = 7.7, 1.6 Hz, 1H), 7.80 (td, *J* = 7.7, 1.6 Hz, 1H), 8.28 (dd, *J* = 8.3, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 36.8, 45.3, 61.0, 62.5, 64.7, 115.8, 126.4, 128.3, 130.2, 131.0, 134.9, 148.3, 164.4, 166.8. HRMS (ESI$^+$) m/z: [M+H]$^+$ Calcd for $C_{15}H_{16}N_3O_6$ 334.1039, found 334.1045.

1-methoxy-5-oxo-2-phenyl-3-(phenylsulfonyl)pyrrolidine-3-carbonitrile **11o**. This compound was obtained in 90% yield (41 mg, starting from 0.125 mmol of bromoacetamide derivative) after stirring at rt for 2h as a brown solid. R_f = 0.3 (Cy/EtOAc, 50/50), Mp = 101-103 °C. IR (ν_{max} / cm^{-1}): 1160, 1352, 1756, 2258, 2990. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.96 (d, *J* = 18.1 Hz, 1H), 3.12 (d, *J* = 18.0 Hz, 1H), 3.82 (s, 3H), 5.54 (s, 1H), 7.21-7.25 (m, 2H), 7.41-7.48 (m, 3H), 7.70 (t, *J* = 15.7 Hz, 2H), 7.82-7.86 (m, 1H), 8.02-8.14 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.2, 61.9, 62.9, 63.1, 114.1, 127.4 (2C), 129.3 (2C), 129.9 (2C), 130.4, 131.1 (2C), 132.55, 132.8, 136.3, 163.3. HRMS (ESI$^+$) m/z: [M+H]$^+$ Calcd for $C_{18}H_{17}N_2O_4S$ 357.0909, found 357.0919.

1-methoxy-4-methyl-5-oxo-2-phenylpyrrolidine-3,3-dicarbonitrile **11p**. This compound was obtained in 98% yield (25 mg, starting from 0.1 mmol of bromoacetamide derivative) after stirring at rt for 1h as a white solid. R_f = 0.33 (Cy/EtOAc, 50/50), Mp = 97-99 °C. IR (ν_{max} / cm^{-1}): 705, 1050, 1342 1525, 1729. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (d, *J* = 7.3 Hz, 3H), 3.09 (q, *J* = 7.2 Hz, 1H), 3.86 (s, 3H), 5.28 (s, 1H), 7.28-7.37 (m, 2H), 7.46-7.55 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 40.6, 41.1, 63.6, 65.3, 111.5, 112.5, 127.4 (2C), 129.6 (2C), 129.8, 130.9, 166.9. HRMS (ESI$^+$) m/z: [M+H]$^+$ Calcd for $C_{14}H_{14}N_3O_2$ 256.1086, found 256.1086.

1'-methoxy-4'-methyl-2'-phenylspiro[indene-2,3'-pyrrolidine]-1,3,5'-trione **11q**. This compound was obtained in 89% yield (33 mg, starting from 0.1 mmol of bromoacetamide derivative) after stirring at rt for 1h as a yellow solid. R_f = 0.33 (Cy/EtOAc, 50/50), Mp = 99-101 °C. IR (ν_{max} / cm^{-1}): 674, 1048, 1252, 1289, 1701, 1739. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, *J* = 7.4 Hz, 3H), 3.18 (q, *J* = 7.4 Hz, 1H), 3.86 (s, 3H), 5.01 (s, 1H), 6.90-7.08 (m, 2H), 7.27-7.31 (m, 3H), 7.73-7.98 (m, 3H), 8.00-8.09 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 38.1, 59.5, 62.7, 64.4, 123.7, 123.9, 127.2 (2C), 128.8 (2C), 129.2, 133.6, 136.4, 136.6, 141.4, 142.3, 170.5, 196.8, 198.5. HRMS (ESI$^+$) m/z: [M+H]$^+$ Calcd for $C_{20}H_{18}NO_4$ 336.1236, found 336.1238.

Supporting Information Summary

Experimental procedure and all spectroscopic data are provided in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: domino reactions • *N*-alkoxyacrylamides • stereoselective synthesis • γ-lactams • reactivity

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[14] The use of more equivalents of carbonated bases, 1.2 up to 2.4 equiv, led either to a decrease in the yields or decomposition with the higher loadings.

[15] Only one diastereoisomer was observed on the ^{1}H NMR of the crude product. The *trans* relationship between the phenyl groups and the ester or sulfonyl groups were reasoned from our previous related works, see references [10a,c].

[16] The stereoselective outcome is the same, but with a higher *trans* selectivity, than Chen's team reference [7]. The *trans* relationship was ascertained by NOE experiments, see SI.

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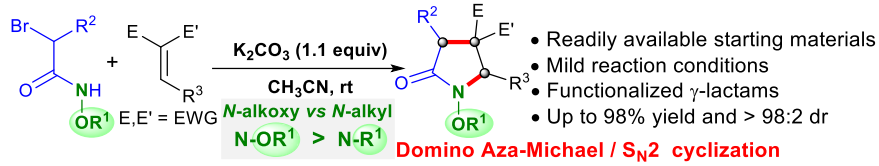

The superiority of still under-exploited *N*-alkoxy versus *N*-alkyl α-bromoacetamides in domino reactions is demonstrated and the possible reasons of this benefit discussed. The enhanced reactivity of the former allows milder conditions and higher efficiency leading to good yields and diastereoselectivity to functionalized γ-lactams