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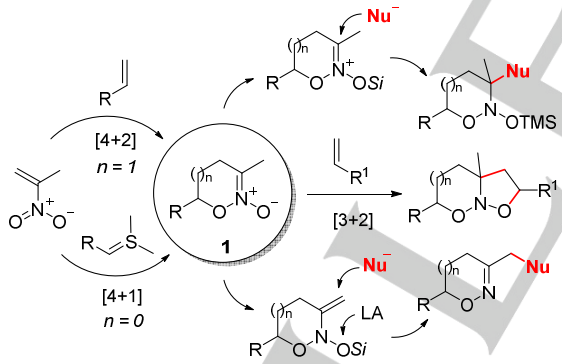
Tandem Deoxygenation/Halogenation of *N*-Oxides under Acylation Conditions: Scope and *In Situ* IR Spectroscopic Study

Roman S. Malykhin,[a],[b] Ivan S. Golovanov,[a] Sema L. Ioffe,[a] Alexey Yu. Sukhorukov[a],[c],[d],*

Abstract: Acylation of cyclic nitronates with acyl bromides produces 3-bromomethyl-substituted 5,6-dihydro-2*H*-1,2-oxazines *via* an unusual multi-stage process involving deoxygenation of *N*-oxide and the formation of Br_2. Low-temperature *in situ* ATR FT-IR monitoring and DFT calculations revealed α-halo-substituted *N,N*-bis(oxy)amines as key intermediates of the process. The developed method was successfully exploited in the stereoselective synthesis of pharmaceutically relevant molecules.

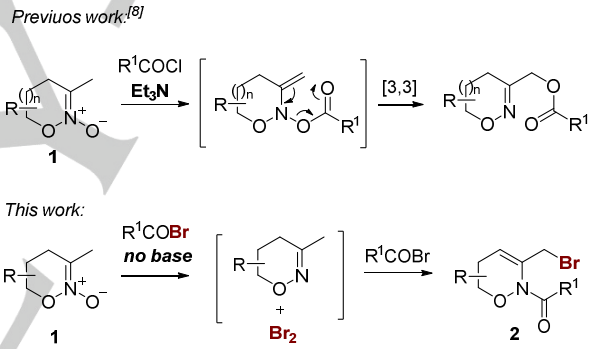
Introduction

Over the last two decades, cyclic nitronates **1** (1,2-oxazine-*N*-oxides and isoxazoline-*N*-oxides, Scheme 1) have gathered much attention from organic chemists community.[1] The availability of these heterocyclic *N*-oxides together with their versatile reactivity make them useful intermediates in the synthesis of stereochemically complex molecules.[2] Numerous total syntheses of natural alkaloids and pharmaceutically active molecules exploiting cyclic nitronates **1** have been developed by Denmark,[1d, 3] our group,[4] and other researchers.[5]



Scheme 1. Synthesis and chemistry of cyclic nitronates **1**

Chemical modifications of *N*-oxides of type **1** are usually performed via three major routes (Scheme 1): (a) TMSOTf-mediated nucleophilic addition to C=N bond;[6] (b) [3+2]-dipolar cycloaddition;[1a, 1d] (c) transformation into *N*-siloxyenamines followed by Lewis acid-mediated S_N'-substitution of TMSO-group.[7] Recently, we reported a novel functionalization of nitronates **1** exploiting tandem acylation/[3,3]-sigmatropic rearrangement process upon the action of R^1COCl with Et_3N (Scheme 2).[8] As a continuation of these studies, here we report that acylation of nitronates **1** in the absence of a base follows a completely different pathway leading to *N*-acylated bromides **2** via an unusual deoxygenation of the *N*-oxide moiety.

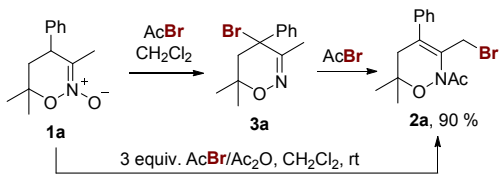


Scheme 2. Modifications of cyclic nitronates **1** via acylation

Results and Discussion

Optimization and substrate scope studies

During our studies on the acylation of model cyclic nitronate **1a** we unexpectedly discovered that its treatment with an excess of AcBr without Et_3N resulted in the formation of primary bromide **2a** in 41 % yield (Scheme 3). The yield of **2a** was increased up to 90 %, when AcBr/Ac_2O mixture was used as an acetylating agent.[9] In this reaction, tertiary bromide **3a** was detected as an intermediate, which could be isolated and subjected to acylation to give 2*H*-1,2-oxazine **2a** (*vide infra*).



Scheme 3. Acylation/rearrangement of model nitronate **1a** to bromide **2a**

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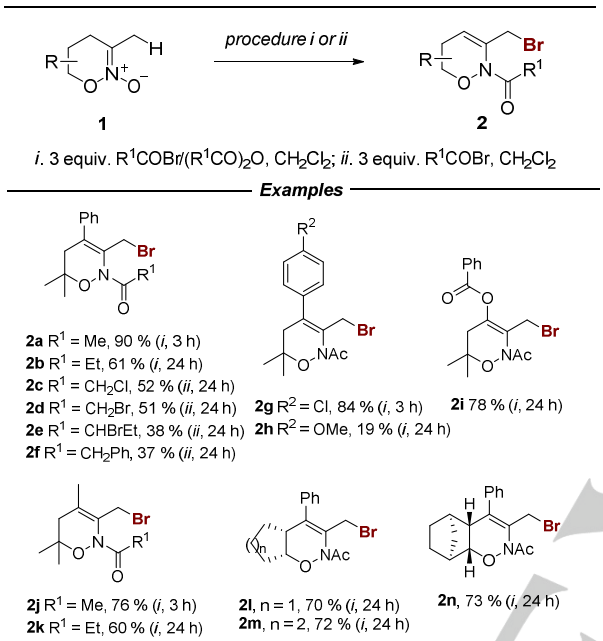
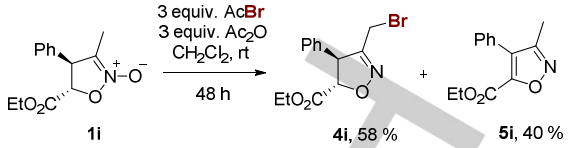
A series of six-membered cyclic nitronates **1** were converted into bromides **2** in good to high yields upon the action of an excess of acyl bromide/acyl anhydride system within 3-24 h (procedure *i* in Scheme 4). Electron-rich aromatic groups were not well-tolerated as can be seen from the example of synthesis of product **2h**. A complex mixture of indecipherable products was obtained in this experiment.



Scheme 4. One-pot synthesis of 3-bromomethyl-substituted 5,6-dihydro-2*H*-1,2-oxazines **2** from nitronates **1**

Different acyl bromides were involved in the reaction with nitronate **1a** to give corresponding products **2a**-**f**. In case when acid anhydride was not readily available, acylation was conducted with acyl bromide only (procedure *ii* in Scheme 4). Generally, the yields were lower with more bulky acyl bromides, which are likely to be less reactive in the acylation/[1,3]-rearrangement of bromide **3a**. Reaction of **1a** with pivaloyl bromide produced only tertiary bromide **3a** (64 %), which was not further pivaloylated. Products **2a**,**c**,**f** could be prepared by treatment of **3a** with corresponding acyl bromides and even chlorides, yet the overall yields were lower compared to the one-pot procedure.

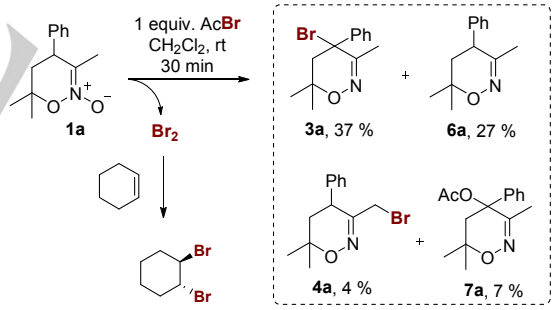
In contrast to six-membered cyclic nitronates, five-membered isoxazoline-*N*-oxide **1i** did not produce corresponding *N*-acylated 2,5-dihydroisoxazole under these conditions (Scheme 5). Instead, a mixture of primary bromide **4i** and isoxazole **5i** (likely resulting from the elimination of HBr from the corresponding 4-bromoisoxazoline) was obtained. Treatment of isolated **5i** with AcBr/Ac_2O did not result in any *N*-acylation product that can be explained by a lower nucleophilicity of the nitrogen atom in isoxazolines as compared to 1,2-oxazines.



Scheme 5. Acylation of isoxazoline-*N*-oxide **1i**

Mechanism studies

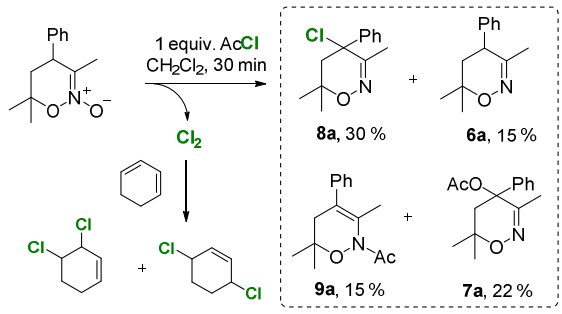
The multi-stage mechanism involved in the acylation of nitronates **1** was a subject of special studies. When model 1,2-oxazine-*N*-oxide **1a** was treated with 1 equivalent of AcBr, several products were detected after 30 minutes, namely tertiary and primary bromides **3a** and **4a**, 1,2-oxazine **6a**, and acetate **7a** (Scheme 6). Remarkably, product **6a** results from deoxygenation of initial nitronate **1a**. Moreover, a temporary appearance of brown color was observed upon mixing nitronate **1a** with AcBr indicating the formation of molecular bromine. This was unambiguously proved by the interception of Br_2 with cyclohexene to give *trans*-1,2-dibromocyclohexane. In the case of isoxazoline-*N*-oxide **1i**, the formation and consumption of bromine (λ_{max} 411 nm) along with the formation of deoxygenation product **6i** could be followed directly by UV-Vis spectroscopy (see Supporting information). In the reaction of nitronate **1a** with benzoyl iodide, the formation of 1,2-oxazine **6a** (43 %) and molecular iodine occurred (λ_{max} 504 nm, spectral yield ca. 70%) along with a complex mixture of other products.



Scheme 6. Deoxygenation of model nitronate **1a** upon acylation with AcBr

More strikingly, reaction with acetyl chloride afforded a mixture of tertiary chloride **8a**, 1,2-oxazine **6a**, the product of its *N*-acylation **9a** and acetate **7a** (Scheme 7). As an indication of the generation of molecular chlorine, isomeric dichlorocyclohexenes were formed, when reaction was carried out in the presence of 1,3-cyclohexadiene.

The initial nitronate **1a** does not oxidize halide anions as was demonstrated by its reaction with Bu_4NX. Therefore, it is likely, that dihalogen is produced from some reactive species generated upon acylation of nitronates **1**.



Scheme 7. Acylation of model nitronate **1a** with AcCl

In order to identify any intermediates, low temperature *in situ* ATR FT-IR monitoring of the acylation of nitronate **1a** reaction was performed (Figure 1).[10] At -65 °C, the formation of an intermediate (**I-1**) together with the consumption of both AcCl and nitronate was observed (ca. half of starting materials reacted before the equilibrium was established, Figure 1A). The position of ν(C=O) band at 1787 cm^{-1} suggests that acetyl is bounded to an electronwithdrawing group, that is consistent with either *N*-oxy,*N*-acyloxyiminium salt **A** or the covalently bonded nitrosoacetal **B** (Scheme 8).[11] No increase of electrical conductivity was observed in the course of intermediate **I-1** formation both in CH_2Cl_2 or CH_2Cl_2/CH_3CN (4 : 1) medium suggesting that **I-1** most likely has the covalent structure **B**. Warming up the reaction mixture resulted in a slow formation of products **6a** and **7a** (noticeable at -40 °C) along with the consumption of residual AcCl and nitronate **1a** (Figure 1B). At -15 °C, a fast decay of intermediate **I-1** to the reduced product **6a** and AcOH was observed.

Ionic and covalent intermediates **A** and **B** can co-exist in solution, and both of them can, in principle, undergo reduction with a halide anion (Scheme 8). Thus, a single electron transfer from X^- to the cation **A** would lead to radical **C**, which can suffer the N–O bond cleavage to give oxime derivative **6** and the acyloxy radical (path 1). However, the calculated activation barrier for an outer-shell electron transfer from Br^- to **A** is too high (+41.1 kcal/mol) for this process to take place with a reasonable rate (calculated at DFT-D3 m062x aug-cc-pVTZ, SMD (CH_2Cl_2) level of theory). Also, no products arising from fragmentation of acyloxy radicals were detected by GC-MS.

Intermediate **B** can transform into the reduced product **6** via two plausible pathways (Scheme 8). First is the attack of X^- on the halogen atom in **B** resulting in elimination of dihalogen and the acetate anion (path 2).[12] Another possible mechanism is a retro-ene reaction leading to product **6** and acyl hypohalide (path 3). In the experiment with cyclohexene as an intercepting agent (Scheme 6), trace amounts of 2-bromocyclohexyl acetate (formal product of AcOBr addition to the C,C-double bond) were detected by GC-MS. However, DFT calculations of the path 3 demonstrate that the elimination of acyl hypobromite is an endothermic process (+5.6 kcal/mol). Also, we were unable to locate the transition state for this pericyclic process using DFT methods. On the other hand, computations support path 2 with a reasonable calculated activation barrier of +19.4 kcal/mol (see Supporting information for the full energy profile).

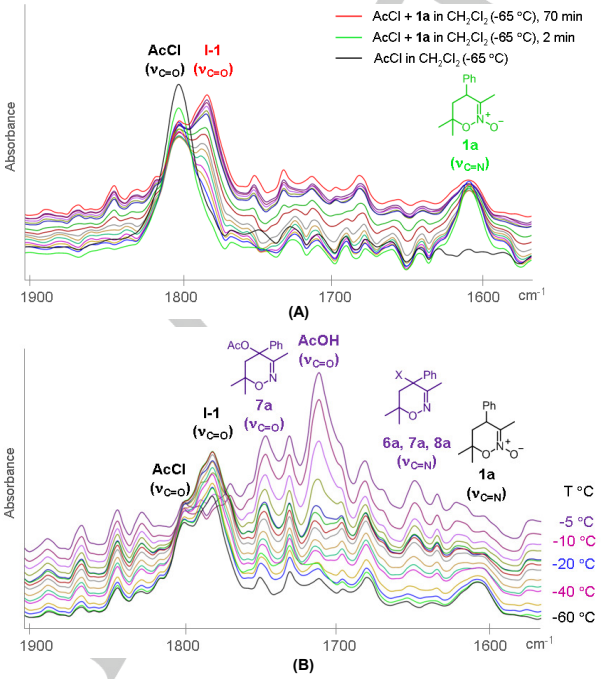
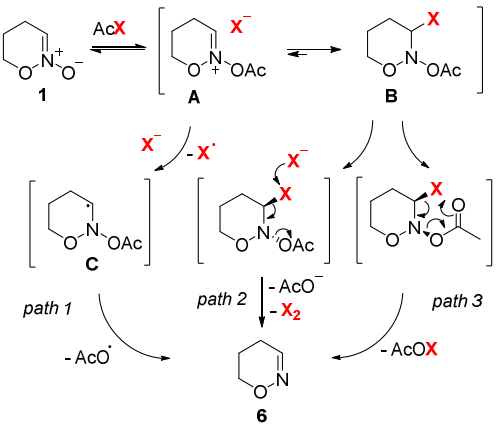
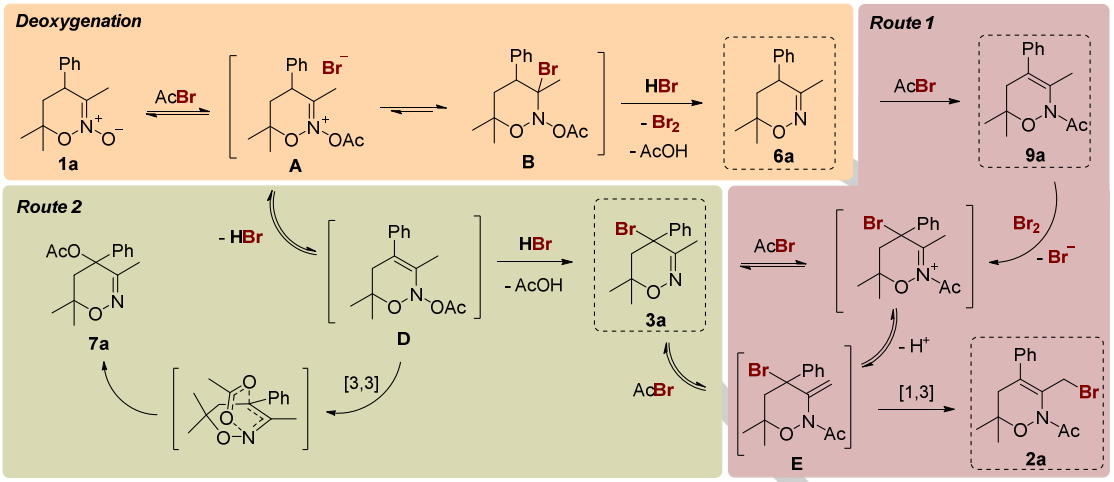


Figure 1. Low-temperature ATR FT-IR monitoring of acylation of nitronate **1a**. Conditions: **1a** (1 equiv.), AcCl (1 equiv.), 1,3-cyclohexadiene (1 equiv.), CH_2Cl_2. (A) Monitoring of the reaction progress at -65 °C. (B) Evolution of intermediate **I-1** upon warming up the reaction mixture



Scheme 8. Plausible mechanisms for deoxygenation of nitronates **1** upon acylation with acyl halides

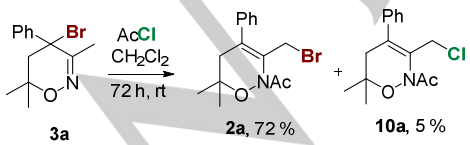


Scheme 9. Plausible mechanisms for the acylation of nitronate **1a** to bromide **2a**

The deoxygenated product **6a** is then acylated with AcBr to 2*H*-1,2-oxazine **9a**, which reacts with Br_2 to give transient enamide **E** (Scheme 9, route 1). The latter suffers a 1,3-halogen migration to afford final primary bromide **2a**. This mechanism was confirmed experimentally by the fast conversion of isolated intermediates **6a** and **9a** into bromide **2a** upon the action of Br_2 in the presence of AcBr/Ac_2O system (spectral yield of **2a**: 70 % and 90 % after 2 h, respectively).

However, the observed formation of non-acylated bromides **3a** and **4a** as intermediates cannot be explained by this mechanism. In the absence of AcBr, reaction of 1,2-oxazine **6a** with Br_2 to give **3a** and **4a** was found to be slow (ca. 50 % conversion after 3 h, **3a**/**4a** = 4 : 1). We, therefore, suggested an alternative mechanism for the formation of bromide **3a**, which involves deprotonation of intermediate **A** to give unstable enamine **D** followed by S_N' substitution of acetate for the bromide anion (Scheme 9, route 2). The generation of **D** is confirmed by the isolation of product **7a** resulting from its [3,3]-sigmatropic rearrangement.[8] Conversion of tertiary bromide **3a** into final product **2a** most likely occurs through acylation to enamide **E** and subsequent 1,3-halogen migration (Scheme 9, route 1).[13]

In the acylation of bromide **3a** with acetyl chloride, only trace amounts of primary chloride **10a** were formed indicating that the migration of bromine in **E** is an intramolecular process (Scheme 10).[14]



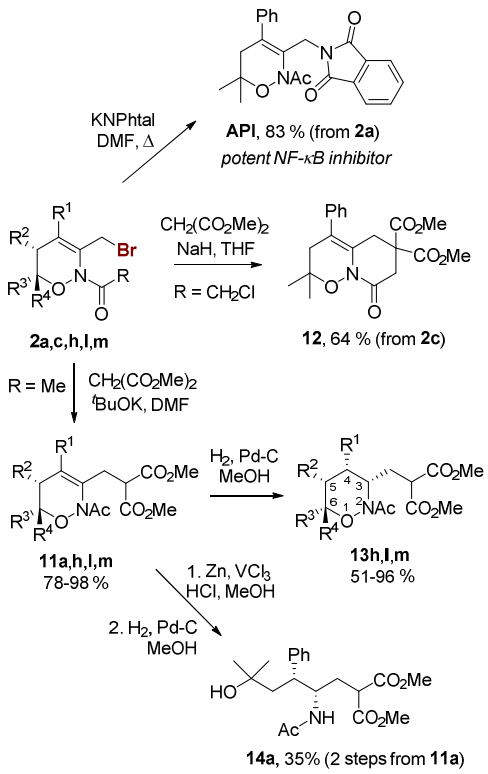
Scheme 10. Acylation of tertiary bromide **3a** with AcCl

Thus, our studies revealed that acylation of nitronates **1** into bromides **2** proceeds through a complicated multi-stage mechanism, which involves several competitive pathways leading to the final product.

Synthetic utility of 5,6-dihydro-2*H*-1,2-oxazines 2

Bromomethyl-substituted 5,6-dihydro-2*H*-1,2-oxazines **2** can be utilized as useful precursors to various pharmaceutically relevant molecules (Scheme 11). Thus, nucleophilic substitution of bromine in **2a** for phtalimide moiety provided a nuclear factor kappa B (NF-κB) inhibitor **API**,[15] which exhibits high potency against inflammatory bowel disease *in vivo* and against colon cancer *in vitro*. This synthesis is more efficient and straightforward (2 steps from **1a**, 75 % yield) as compared to the previous one (3 steps from **1a**, 52 % yield[16]), and it allows the preparation of **API** on multi-grams scale.

Bromides of type **2** were also exploited as precursors of derivatives of non-natural amino acids as shown in Scheme 11. Substitution of bromine in **2** for the malonate anion afforded products **11** in excellent yields. Same reaction with bromide **2c** bearing a chloroacetyl group produced fused bicyclic derivative **12**. Hydrogenation of 2*H*-1,2-oxazines **11h**,**l**,**m** over Pd-C gave saturated 1,2-oxazines **13** selectively as all-*cis*-isomers. N–O bond in oxazines **13** was surprisingly resistant toward further catalytic hydrogenation or action of strong reducing agents (Zn/AcOH, Na/Hg, $Mo(CO)_6$, $TiCl_3$, $TiCl_3$/$NaBH_4$). However, the open-chain γ-amino acid derivative **14a** was prepared by an inverted sequence of bonds reduction in **11a**: firstly the cleavage of N–O bond in **11a** was accomplished with VCl_3/Zn system followed by stereoselective hydrogenation of the C=C bond in the resulting enamine on the second stage. Thus, depending on the reagents used, 2*H*-1,2-oxazines **11** can serve as precursors to either open-chain or cyclic γ-amino acid derivatives[17] bearing up to four contiguous stereocenters.



Scheme 11. Synthetic utility of 5,6-dihydro-2*H*-1,2-oxazines **2** (**a** R = Me, R^1 = Ph, R^2 = H, R^3,R^4 = Me; **c** R = CH_2Cl, R^1 = Ph, R^2 = H, R^3,R^4 = Me; **h** R = Me, R^1 = 4-$MeOC_6H_4$-, R^2 = H; R^3,R^4 = Me; **l** R = Me, R^1 = Ph, R^2-R^3 = -$(CH_2)_3$-, R^4 = H; **m** R = Me, R^1 = Ph, R^2-R^3 = -$(CH_2)_4$-, R^4 = H)

Conclusions

In conclusion, we have demonstrated that acylation of cyclic nitronates with acyl bromides in the absence of a base produces 3-bromomethyl-substituted 5,6-dihydro-2*H*-1,2-oxazines. Mechanism studies revealed that this transformation involves deoxygenation of the *N*-oxide moiety with the formation of Br_2, followed by bromination and allylic rearrengement. The developed method was successfully exploited to access halo-substituted oxime and *N*-oxyenamide derivatives, which are useful building blocks in the synthesis of pharmaceutically relevant molecules.

Experimental section

All reactions were carried out in oven-dried (150°C) glassware. NMR spectra were recorded at room temperature with residual solvents peaks as an internal standard. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). HRMS were measured on electrospray ionization (ESI) instrument with a time-of-flight (TOF) detector. GC-MS was performed with the DB-1MS column 122-0132. Low-temperature FT-IR monitoring was conducted on an infrared spectrometer equipped with MCT detector and ATR-P-Ge-G30-150/50 probe with PIR 900/1000 fiber. Electrical conductivity was measured on a conductometer with a platinum 2-plate conductivity probe InLab720. Quantum-chemical calculations were performed with the Gaussian 16 Rev A.03 program (for details see Supporting information).

Column chromatography was performed using Kieselgel 40-60 μm 60A. Analytical thin-layer chromatography was performed on silica gel plates with QF-254. Visualization was accomplished with UV light and or solution of anisaldehyde/H_2SO_4 in ethanol. AcCl, AcBr, CH_2Cl_2 and THF were distilled from CaH_2; DMF was distilled from CaH_2 under reduced pressure. Hexane, pentane, diethyl ether, methyl *tert*-butyl ether, methanol and ethyl acetate were distilled without drying agents. Ac_2O, EtCOBr, $(EtCO)_2O$, HBr (48 % in water), cyclohexene, 1,3-cyclohexadiene, dimethyl malonate, potassium phtalimide, ^{t}BuOK, NaH (60 % in mineral oil), 5%-Pd/C, zinc dust, VCl_3 were commercial grade and were used as received. Acyl bromides,[18] benzoyl iodide,[19] were prepared according to previously published protocols. Previously described racemic nitronates **1** were prepared according to known procedures (see Supporting information for details).

General procedure for the acylation of nitronates 1 to *N*-acylated bromides 2 (procedures *i* and *ii*). To a stirred solution of nitronate (1 mmol) (with 3 mmol of carboxylic acid anhydride for procedure *i*) in CH_2Cl_2 (4.5 mL) was added acyl bromide (3 mmol) at rt. In most cases, an instantaneous appearance of dark red color of Br_2 was observed. The mixture was maintained at rt for time indicated in Scheme 4 and then transferred into a mixture of ethyl acetate (25 mL) and saturated aqueous solution of K_2CO_3 (25 mL). Aqueous phase was back-extracted with ethyl acetate (25 mL). Combined organic layers were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4) and evaporated. The residue was subjected to a column chromatography on silica gel.

1-(3-(Bromomethyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-2*H*-1,2-oxazin-2-yl)ethan-1-one (2a). Prepared according to procedure *i* from 438 mg (2 mmol) of nitronate **1a**, reaction time – 3 h. Yield: 581 mg (90 %). Oil. NMR spectra are in accordance with literature data.[16]

1-(3-(Bromomethyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-2*H*-1,2-oxazin-2-yl)propan-1-one (2b). Prepared according to procedure *i* from 109 mg (0.5 mmol) of nitronate **1a**, reaction time – 24 h. Yield: 103 mg (61 %). Mp = 46 – 49 °C (hexane-Et_2O). R_f = 0.41 (AcOEt/hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50 – 7.23 (m, 5H), 4.68 (s, 2H), 2.67 (q, *J* = 7.5 Hz, 2H), 2.40 (s, 2H), 1.39 (s, 6H), 1.22 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 173.7 (C), 138.5 (C), 132.1 (C), 128.8 (2 CH), 128.1 (2 CH), 127.9 (CH), 125.9 (C), 79.5 (C), 43.3 (CH_2), 28.5 (CH_2), 27.4 (CH_2), 25.7 (2 CH_3), 8.9 (CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{16}H_{21}BrNO_2^+$ 338.0750 and 340.0730; Found 338.0749 and 340.0728.

1-(3-(Bromomethyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-2*H*-1,2-oxazin-2-yl)-2-chloroethanone (2c). Prepared according to procedure *ii* from 219 mg (1.0 mmol) of nitronate **1a**, reaction time – 24 h. Yield: 184 mg (52 %). Mp = 106 – 109 °C. R_f = 0.33 (AcOEt/hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50 – 7.23 (m, 5H), 4.65 (s, 2H), 4.48 (s, 2H), 2.45 (s, 2H), 1.43 (s, 6H). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 164.8 (C), 137.8 (C), 131.3 (C), 128.8 (2 CH), 128.2 (CH), 127.9 (2 CH), 126.9 (C), 80.2 (C), 43.0 (CH_2), 42.3 (CH_2), 27.5 (CH_2), 25.6 (2 CH_3). Anal. Calcd for $C_{15}H_{17}BrClNO_2$: C, 50.23; H, 4.78; N, 3.91. Found: C, 50.23; H, 4.55; N, 3.85.

2-Bromo-1-(3-(bromomethyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-2*H*-1,2-oxazin-2-yl)ethanone (2d). Prepared according to procedure *ii* from 219 mg (1.0 mmol) of nitronate **1a**, reaction time – 24 h. Yield: 204 mg

(51 %). Mp = 98 – 101 °C (hexane-Et_2O). R_f = 0.62 (AcOEt/hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 – 7.20 (m, 5H), 4.63 (s, 2H), 4.24 (s, 2H), 2.45 (s, 2H), 1.43 (s, 6H). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 165.1 (C), 137.8 (C), 131.4 (C), 128.8 (2 CH), 128.2 (CH), 127.9 (2 CH), 127.3 (C), 80.3 (C), 43.1 (CH_2), 27.6 (CH_2), 27.5 (CH_2), 25.7 (2 CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}NO_2Br_2^+$: 401.9706; Found 401.9699.

2-Bromo-1-(3-(bromomethyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-2*H*-1,2-oxazin-2-yl)butan-1-one (2e). Prepared according to procedure *ii* from 55 mg (0.25 mmol) of nitronate **1a**, reaction time – 24 h. After column chromatography the product was crystallized from hexane-Et_2O mixture at -20 °C. Yield: 41 mg (38 %). Slightly pink crystals. Mp = 112 – 116 °C (hexane-Et_2O) with decomposition. R_f = 0.7 (AcOEt/hexane = 1 : 1). ^{1}H NMR (250 MHz, Chloroform-*d*) δ 7.46 – 7.17 (m, 5H), 4.99 (t, *J* = 7.2 Hz, 1H), 4.78 (d, *J* = 10.5 Hz, 1H), 4.53 (d, *J* = 10.5 Hz, 1H), 2.45 (s, 2H), 2.32 – 2.03 (m, 2H), 1.48 (s, 3H), 1.39 (s, 3H), 1.12 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (63 MHz, DEPT135, $CDCl_3$) δ 168.1 (C), 138.1 (C), 131.6 (C), 128.8 (2 CH), 128.1 (CH), 127.9 (2 CH), 127.7 (C), 80.4 (C), 46.0 (CH), 43.2 (CH_2), 28.8 (CH_2), 27.7 (CH_2), 26.1 and 25.6 (2 CH_3), 12.3 (CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{17}H_{22}Br_2NO_2^+$ 431.9992; Found 431.9983.

1-(3-(Bromomethyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-2*H*-1,2-oxazin-2-yl)-2-phenylethan-1-one (2f). Prepared according to procedure *ii* from 219 mg (1.0 mmol) of nitronate **1a**, reaction time – 24 h. After column chromatography the product was crystallized from hexane-Et_2O mixture at -20 °C. Yield: 149 mg (37 %). White solid. Mp = 89 – 94 °C (hexane-Et_2O) with decomposition. R_f = 0.41 (AcOEt/hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 – 7.25 (m, 10H), 4.68 (s, 2H), 3.99 (s, 2H), 2.42 (s, 2H), 1.38 (s, 6H). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 170.5 (C), 138.3 (C), 134.8 (C), 131.8 (C), 129.6 (2 CH), 128.7 (2 CH), 128.5 (2 CH), 128.0 (2 CH), 127.9 (CH), 126.9 (CH), 126.3 (C), 79.8 (C), 43.3 (CH_2), 41.2 (CH_2), 28.1 (CH_2), 25.6 (CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}BrNO_2^+$ 400.0907 and 402.0887; Found 400.0899 and 402.0881.

1-(3-(Bromomethyl)-4-(4-chlorophenyl)-6,6-dimethyl-5,6-dihydro-2*H*-1,2-oxazin-2-yl)ethan-1-one (2g). Prepared according to procedure *i* from 253 mg (1 mmol) of nitronate **1b**, reaction time – 3 h. Yield: 300 mg (84 %). Mp = 135 – 138 °C (hexane-Et_2O). NMR spectra are in accordance with literature data.[16]

1-(3-(Bromomethyl)-4-(4-methoxyphenyl)-6,6-dimethyl-5,6-dihydro-2*H*-1,2-oxazin-2-yl)ethan-1-one (2h). Prepared according to procedure *i* from 75 mg (0.3 mmol) of nitronate **1c**, reaction time – 24 h. Yield: 20 mg (19 %). Oil. NMR spectra are in accordance with literature data.[16]

2-Acetyl-3-(bromomethyl)-6,6-dimethyl-5,6-dihydro-2H-1,2-oxazin-4-yl benzoate (2i). Prepared according to procedure *i* from 100 mg (0.38 mmol) of nitronate **1d** with an exception that 6 equivalents of Ac_2O and 6 equivalents of AcBr were used, reaction time – 24 h. Yield: 109 mg (78 %). Oil. R_f = 0.26 (AcOEt/hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 7.7 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.51 (dd, *J* = 7.7, 7.6 Hz, 2H), 4.71 (s, 2H), 2.54 (s, 2H), 2.28 (s, 3H), 1.42 (s, 6H). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 170.1 (C), 164.1 (C), 137.3 (C), 134.1 (CH), 130.2 (2 CH), 128.8 (2 CH), 128.5 (C), 127.9 (C), 79.8 (C), 38.7 (CH_2), 25.5 (2 CH_3), 23.1 (CH_2), 22.2 (CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{16}H_{19}BrNO_4^+$ 368.0492 and 370.0472; Found 368.0490 and 370.0479.

1-(3-(Bromomethyl)-4,6,6-trimethyl-5,6-dihydro-2H-1,2-oxazin-2-yl)ethan-1-one (2j). Prepared according to procedure *i* from 100 mg (0.64 mmol) of nitronate **1e**, reaction time – 3 h. Yield: 127 mg (76 %). Mp = 82 – 84 °C (hexane-Et_2O). NMR spectra are in accordance with literature data.[16]

1-(3-(Bromomethyl)-4,6,6-trimethyl-5,6-dihydro-2H-1,2-oxazin-2-yl)propan-1-one (2k). Prepared according to procedure *i* from 157 mg (1.0 mmol) of nitronate **1e**, reaction time – 24 h. Yield: 164 mg (60 %). Oil. R_f = 0.39 (AcOEt/hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.73 (s, 2H), 2.57 (q, *J* = 7.5 Hz, 2H), 2.09 (s, 2H), 1.79 (s, 3H), 1.27 (s, 6H), 1.15 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 173.5 (C), 130.3 (C), 122.3 (C), 79.4 (C), 42.7 (CH_2), 27.0 (CH_2), 26.4 (CH_2), 25.7 (2 CH_3), 17.5 (CH_3), 8.9 (CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{11}H_{19}BrNO_2^+$ 276.0594 and 278.0574; Found 276.0592 and 278.0570.

***Rel*-1-((4aR*,7aR*)-3-(bromomethyl)-4-phenyl-5,6,7,7a-tetrahydrocyclopenta[e][1,2]oxazin-2(4aH)-yl)ethanone (2l).** Prepared according to procedure *i* from 239 mg (1.0 mmol) of nitronate **1f**, reaction time – 24 h. Yield: 235 mg (70 %). Oil. NMR spectra are in accordance with literature data.[16]

***Rel*-1-((4aR*,8aR*)-3-(bromomethyl)-4-phenyl-4a,5,6,7,8,8a-hexahydro-2H-benzo[e][1,2]oxazin-2-yl)ethanone (2m).** Prepared according to procedure *i* from 245 mg (1.0 mmol) of nitronate **1g**, reaction time – 24 h. Yield: 252 mg (72 %). Oil. NMR spectra are in accordance with literature data.[16]

***Rel*-1-((4aR*,5R*,8S*,8aR*)-3-(bromomethyl)-4-phenyl-4a,5,6,7,8,8a-hexahydro-2H-5,8-methanobenzo[e][1,2]oxazin-2-yl)ethan-1-one (2n)**. Prepared according to procedure *i* from 257 mg (1.0 mmol) of nitronate **1h**, reaction time – 24 h. Yield: 264 mg (73 %). Mp = 127 – 130 °C (hexane-Et_2O) with decomposition. NMR spectra are in accordance with literature data.[16]

4-Bromo-3,6,6-trimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazine (3a). To a stirred solution of nitronate **1a** (219 mg, 1.0 mmol) in CH_2Cl_2 (4.5 mL) was added pivaloyl bromide (500 mg, 3.0 mmol) at rt. An instantaneous appearance of dark brown color of Br_2 and warming-up of the reaction mixture was observed. The mixture was maintained at rt for 24 h and then transferred into a mixture of ethyl acetate (50 mL) and saturated aqueous solution of K_2CO_3 (50 mL). Aqueous phase was back-extracted with ethyl acetate (50 mL). Combined organic layers were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and evaporated. The residue was subjected to column chromatography on silica gel to give 181 mg (64 %) of **3a**, further elution provided also 56 mg (28 %) of **6a**. Oil. R_f = 0.56 (AcOEt/hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.41-7.25 (m, 3H), 2.82 (d, *J* = 15.8 Hz, 1H), 2.55 (d, *J* = 15.8 Hz, 1H), 2.11 (s, 3H), 1.51 and 1.23 (2 s, 3H and 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4 (C), 142.1 (C), 128.7 (2 CH), 128.1 (CH), 126.9 (2 CH), 74.2 (C), 58.9 (CH), 53.1 (CH_2), 28.6 (CH_3), 24.9 (CH_3) and 19.6 (CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}NOBr^+$ 282.0494 and 284.0468; Found 282.0488 and 284.0478.

3,6,6-Trimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazine (6a). To a stirred solution of nitronate **1a** (100 mg, 0.46 mmol) in CH_2Cl_2 (1 mL) was added a solution of benzoyl iodide (215 mg, 0.93 mmol) in CH_2Cl_2 (1 mL) at rt. An instantaneous appearance of dark brown color of I_2 and warming-up of the reaction mixture was observed. The mixture was maintained at rt for 3 h and then transferred into a mixture of ethyl acetate (50 mL) and aqueous solution of $Na_2S_2O_3$ (50 mL). Aqueous phase was back-extracted with ethyl acetate (25 mL). Combined organic layers were washed with saturated aqueous solution of K_2CO_3 (50 mL), water (50 mL), brine (50 mL), dried (Na_2SO_4) and evaporated. The residue was

subjected to column chromatography on silica gel to give 40 mg (43 %) of **6a** as a yellowish oil. R_f = 0.28 (AcOEt/hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.37-7.23 (m, 3H), 7.17 (d, *J* = 7.5 Hz, 2H), 3.31 (dd, *J* = 11.8, 7.9 Hz, 1H), 2.04 (dd, *J* = 13.5, 7.9 Hz, 1H), 1.90 (dd, *J* = 13.5, 11.8 Hz, 1H), 1.70 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 155.7 (C), 140.8 (C), 129.0 (2 CH), 128.2 (2 CH), 127.1 (CH), 73.6 (C), 41.2 (CH_2), 40.8 (CH), 28.6 (CH_3), 22.8 (CH_3), 20.00 (CH_3). FT-IR (KBr): 2975, 2926, 1663, 1493, 1454, 1370, 1271, 1145, 1127, 924, 857, 779, 758, 703, 619 cm^{-1}. ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{13}H_{18}NO^+$ 204.1383; Found 204.1389.

Acylation of nitronate 1i. To a stirred solution of nitronate **1i** (249 mg, 1.0 mmol) in CH_2Cl_2 (4.6 mL) was added acetic anhydride (0.283 mL, 3.0 mmol) followed by acetyl bromide (0.222 mL, 3.0 mmol) at rt. An instantaneous appearance of dark red color of Br_2 was observed. The mixture was maintained at rt for 48 h (color almost disappeared), and then transferred into a mixture of ethyl acetate (100 mL) and saturated aqueous solution of K_2CO_3 (100 mL). Aqueous phase was back-extracted with ethyl acetate (50 mL). Combined organic layers were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and evaporated. The residue was subjected to a column chromatography on silica gel to give 280 mg of chromatographically inseparable mixture of bromide **4i** (58 %) and isoxazole **5i** (40 %) as colorless oil. Isoxazole **5i** was separated from bromide **4i** by crystallization from hexane-Et_2O mixture.

Ethyl *rel*-(4S*,5S*)-3-(bromomethyl)-4-phenyl-4,5-dihydroisoxazole-5-carboxylate (4i). Oil. R_f = 0.43 (AcOEt/hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.47 – 7.33 (m, 3H), 7.24 (d, *J* = 8.2 Hz, 2H), 5.00 (d, *J* = 5.8 Hz, 1H), 4.86 (d, *J* = 5.8 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.24 (d, *J* = 11.1 Hz, 1H), 3.69 (d, *J* = 11.1 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 169.0 (C), 157.2 (C), 136.1 (C), 129.6 (2 CH), 128.7 (CH), 127.6 (2 CH), 86.5 (CH), 62.2 (CH_2), 57.6 (CH), 21.3 (CH_2), 14.1 (CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{13}H_{15}BrNO_3^+$ 312.0230 and 314.0210; Found 312.0229 and 314.0210.

Ethyl 3-methyl-4-phenylisoxazole-5-carboxylate (5i). White crystals. Mp = 68 – 71 °C (hexane-Et_2O). R_f = 0.43 (AcOEt/hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 – 7.33 (m, 5H, C_6H_5), 4.32 (q, *J* = 7.2 Hz, 2H, CH_2O), 2.29 (s, 3H, CH_3), 1.28 (t, *J* = 7.2 Hz, 3H, CH_3CH_2). ^{13}C NMR (75 MHz, DEPT135, HMBC, $CDCl_3$) δ 160.4 (C=N), 157.3 (C=O), 155.7 (C), 154.6 (C), 129.7, 128.7 and 128.3 (*o,m,p*-C_6H_5), 125.2 (*i*-C_6H_5), 61.9 (CH_2), 13.9 (CH_2CH_3), 10.6 (CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{13}H_{14}NO_3^+$ 232.0968; Found 232.0976.

Ethyl *rel*-(4S*,5S*)-3-methyl-4-phenyl-4,5-dihydroisoxazole-5-carboxylate (6i). To a stirred solution of nitronate **1i** (125 mg, 0.5 mmol) in CH_2Cl_2 (2.3 mL) at -25 °C was added acetic anhydride (0.141 mL, 1.5 mmol) followed by acetyl bromide (0.111 mL, 1.5 mmol). After keeping for 20 min at this temperature, the reaction mixture was transferred into a mixture of ethyl acetate (25 mL) and saturated aqueous solution of K_2CO_3 (25 mL). Aqueous phase was back-extracted with ethyl acetate (25 mL). Combined organic layers were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4) and evaporated. The residue was subjected to a column chromatography on silica gel to give 87 mg (75 %) of isoxazoline **6i** as white solid. Mp = 69 – 73 °C (MeOH). R_f = 0.31 (AcOEt/hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.46 – 7.30 (m, 3H), 7.23 (d, *J* = 7.8 Hz, 2H), 4.88 (d, *J* = 5.7 Hz, 1H), 4.50 (d, *J* = 5.7 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.89 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 170.0 (C), 157.1 (C), 137.0 (C), 129.4 (2 CH), 128.3 (CH), 127.6 (2 CH), 85.2 (CH), 61.9 (CH_2), 61.5 (CH), 14.1 (CH_3), 11.3 (CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}NO_3^+$ 234.1120; Found 234.1125.

Reaction of nitronate 1a with 1 equivalent of acetyl bromide. To a stirred solution of nitronate **1a** (109 mg, 0.5 mmol) in CH_2Cl_2 (2.3 mL) was added acetyl bromide (0.037 mL, 0.5 mmol) at rt. An instantaneous appearance of dark red color of Br_2 was observed. The mixture was maintained at rt for 20 minutes and then transferred into a mixture of ethyl acetate (25 mL) and saturated aqueous solution of K_2CO_3 (25 mL). Aqueous phase was back-extracted with ethyl acetate (25 mL). Combined organic layers were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4) and evaporated. Analysis of the residue by ^{1}H NMR with internal standard revealed the presence of tertiary bromide **3a** (37 %), primary bromide **4a**[20] (4 %), 1,2-oxazine **6a** (27 %) and acetate **7a**[8] (7 %).

Interception of molecular bromine in the acylation of nitronate 1a. To a stirred solution of nitronate **1a** (219 mg, 1.0 mmol) and cyclohexene (0.5 mL, 5.0 mmol) in CH_2Cl_2 (4.6 mL) was added acetyl bromide (0.148 mL, 2.0 mmol) at rt. The mixture was maintained at rt for 30 minutes and then transferred into a mixture of ethyl acetate (50 mL) and saturated aqueous solution of K_2CO_3 (50 mL). Aqueous phase was back-extracted with ethyl acetate (50 mL). Combined organic layers were washed with water (40 mL), brine (40 mL), dried (Na_2SO_4) and evaporated at 300 Torr. The residue was subjected to a column chromatography on silica gel, which provided 92 mg (38 % based on nitronate **1a**) of *trans*-1,2-dibromocyclohexane (colorless liquid, NMR and MS data are in agreement with literature data.[21]). In other fractions, mixtures of products **2a** (7 %), **6a** (32 %), **7a** (19 %), **9a** (13 %) and 3,6,6-trimethyl-4-phenyl-6*H*-1,2-oxazine[8] (11 %) were isolated.

1-(3,6,6-Trimethyl-4-phenyl-5,6-dihydro-2*H*-1,2-oxazin-2-yl)ethan-1-one (9a). Oil. R_f = 0.38 (AcOEt/hexane = 1 : 3). ^{1}H NMR (300 MHz, HSQC, HMBC, Chloroform-*d*) δ 7.35 (dd, *J* = 7.3, 7.1 Hz, 2H, *m*-C_6H_5), 7.28 (m, 1H, *p*-C_6H_5), 7.21 (d, *J* = 7.1 Hz, 2H, *m*-C_6H_5), 2.37 (s, 2H, CH_2), 2.26 (s, 3H, CH_3C=O), 2.15 (s, 3H, CH_3C=C), 1.38 (s, 6H, 2 CH_3). ^{13}C NMR (75 MHz, HSQC, HMBC, DEPT135, $CDCl_3$) δ 170.0 (C=O), 140.2 (*i*-C_6H_5), 130.9 (C=*C*-N), 128.7 (*o*-C_6H_5), 128.3 (*m*-C_6H_5), 127.0 (*p*-C_6H_5), 120.0 (*C*=C-N), 79.0 (C-O), 42.3 (CH_2), 25.6 (2 CH_3), 22.5 (CH_3C=O), 17.6 (CH_3C=C). FT-IR (KBr): 2975, 2930, 2856, 1677, 1442, 1378, 1344, 1291, 1267, 1145, 868, 764, 701, 619 cm^{-1}. ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{15}H_{20}NO_2^+$ 246.1489; Found 246.1491.

Interception of molecular chlorine in the acylation of nitronate 1a. To a stirred solution of nitronate **1a** (249 mg, 1.14 mmol) and 1,3-cyclohexadiene (0.54 mL, 5.7 mmol) in CH_2Cl_2 (5.2 mL) was added acetyl chloride (0.16 mL, 2.28 mmol) at rt. The mixture was maintained at rt for 30 minutes and then transferred into a mixture of methyl *tert*-butyl ether (50 mL) and saturated aqueous solution of K_2CO_3 (50 mL). Aqueous phase was back-extracted with methyl *tert*-butyl ether (50 mL). Combined organic layers were washed with water (40 mL), brine (40 mL), dried (Na_2SO_4) and evaporated at 300 Torr. The residue was subjected to a column chromatography on silica gel. Elution with hexane provided 12 mg (7% based on **1a**) of a mixture of *cis*/*trans* isomers of 3,6-dichlorocyclohex-1-ene and 3,4-dichlorocyclohex-1-ene (liquid, NMR and GC-MS data are in agreement with literature data.[22]). Further elution with hexane/AcOEt mixtures (20 : 1 → 10 : 1 → 5 : 1) provided 80 mg (30 %) of tertiary chloride **8a**,[8] 42 mg (15 %) of *N*-acylated derivative **9a**, 66 mg (22 %) of acetate **7a**, and 35 mg (15%) of 1,2-oxazine **6a**.

Acylation of tertiary bromide 3a with AcCl and AcBr. To a stirred solution of bromide **3a** (0.14 g, 0.5 mmol) in CH_2Cl_2 (2.3 mL) was added acetyl chloride (0.071 mL, 1.0 mmol) at rt. ^{1}H NMR analysis after 1 h and 3 h revealed the absence of **10a** (yield of bromide **2a**: 20 % and 25 %, respectively). The mixture was kept for 72 h, and then concentrated in vacuum. The residue was subjected to a column chromatography on silica gel to give 0.123 g of an inseparable mixture containing bromide **2a**

(0.116 g, 72 %) and chloride **10a** (0.007 g, 5 %). Acylation of tertiary bromide **3a** with a mixture of AcBr (1 equiv.) and Ac_2O (1 equiv.) afforded 71 % of primary bromide **2a** after 24 h.

Parallel synthesis of 1-(3-(chloromethyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-2*H*-1,2-oxazin-2-yl)ethan-1-one (10a). To a solution of 3-(chloromethyl)-6,6-dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazine[20] (25 mg, 0.105 mmol) in CH_2Cl_2 (0.5 mL) was added Ac_2O (11 µL, 0.116 mmol) followed by AcCl (7.5 µL, 0.105 mmol). The mixture was kept for 72 h, and then volatiles were removed in vacuum. The residue was subjected to a column chromatography on silica gel to give 18 mg (61 %) of chloride **10a** as colorless oil. R_f = 0.34 (AcOEt/hexane = 1 : 3). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.55 – 7.12 (m, 5H), 4.73 (t, *J* = 1.0 Hz, 2H), 2.44 (s, 2H), 2.31 (s, 3H), 1.41 (s, 6H). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 170.1 (C), 138.2 (C), 131.7 (C), 128.7 (2 CH), 128.3 (2 CH), 127.9 (CH), 126.1 (C), 79.6 (C), 43.0 (CH_2), 40.3 (CH_2), 25.6 (2 CH_3), 22.3 (CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{15}H_{19}ClNO_2^+$ 280.1099 and 282.1070; Found 280.1105 and 282.1071. Same reaction conducted with AcBr instead of AcCl (reaction time – 24 h) gave a mixture of chloride **10a** (spectral yield: 67 %) and bromide **2a** (spectral yield: 18 %).

Low-temperature monitoring of the interaction of nitronate 1a with AcCl. A solution of AcCl and 1,3-cyclohexadiene in CH_2Cl_2 (7.25 mL) was placed in a round-bottom 4-necked flack equipped with an ATR(Ge) FT-IR probe, platinum electrode, argon inlet, rubber septum and magnetic stirring bar. The mixture was cooled to -65 °C under argon atmosphere, and FT-IR spectra and conductivity were measured. A solution of nitronate **1a** in CH_2Cl_2 (0.75 mL) was slowly added *via* a syringe. Reaction progress was monitored by measuring FT-IR spectra (5 minutes intervals) and conductivity (30 seconds intervals). After 75 min, no significant changes in spectra were detected. The reaction mixture was slowly warmed up to 0 °C and FT-IR spectra/conductivity were measured with 5 °C intervals. Results are shown in Figure 1 and in the Supporting information.

2-((2-Acetyl-6,6-dimethyl-4-phenyl-5,6-dihydro-2H-1,2-oxazin-3-yl)methyl)isoindoline-1,3-dione (APl). To a stirred solution of bromide **2a** (0.32 g, 1.0 mmol) in DMF (2.3 mL) was added potassium phtalimide (0.278 g, 1.5 mmol). The mixture was stirred at 30-40 °C for 2 h and then transferred into a mixture of Et_2O (50 mL) and water (50 mL). Aqueous phase was back-extracted with Et_2O (100 mL). Combined organic layers were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and evaporated. The residue was subjected to a column chromatography on silica gel to give 0.32 g (83 %) of **APl** as a white solid. Mp = 137 – 139 °C (with decomposition). NMR spectra are in accordance with published data.[16]

Dimethyl 2-((2-acetyl-6,6-dimethyl-4-phenyl-5,6-dihydro-2*H*-1,2-oxazin-3-yl)methyl)malonate (11a) (typical procedure for the synthesis of malonates 11). To a stirred solution of dimethyl malonate (0.63 mL, 5.48 mmol) in DMF (4.5 mL) was added potassium *tert*-butoxide (0.614 g, 5.48 mmol) at 0 °C under inert atmosphere. After stirring for 5 minutes, a solution of bromide **2a** (1.48 g, 4.57 mmol) in DMF (7.0 mL) was added. The mixture was stirred at 30-40 °C for 3 h and then transferred into a mixture of AcOEt (100 mL) and water (100 mL). Aqueous phase was back-extracted with ethyl acetate (100 mL). Combined organic layers were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and evaporated. The residue was subjected to a column chromatography on silica gel to give 1.34 g (78 %) of malonate **11a** as colorless oil, which solidified upon standing. Mp 61 – 64 °C (Lit.[16] 64 – 69 °C). NMR spectra are in accordance with published data.[16]

Dimethyl 2-((2-acetyl-4-(4-methoxyphenyl)-6,6-dimethyl-5,6-dihydro-2*H*-1,2-oxazin-3-yl)methyl)malonate (11h). Prepared from bromide **2h** (0.5 mmol, 0.177 g) according to the procedure used for the synthesis of **11a**. Yield: 0.178 g (88 %). Mp 95 – 96 °C (Et_2O-pentane) (Lit.[4c] 90 – 92 °C). NMR spectra are in accordance with published data.[4c]

Dimethyl *rel*-2-(((4aR*,7aR*)-2-acetyl-4-phenyl-2,4a,5,6,7,7a-hexahydrocyclopenta[e][1,2]oxazin-3-yl)methyl)malonate (11l). Prepared from bromide **2l** (1.41 g, 4.2 mmol) according to the procedure used for the synthesis of **11a**. Yield: 1.59 g (98 %). Oil. R_f = 0.47 (AcOEt/hexane = 1 : 1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42 – 7.12 (m, 5H), 4.45 (t, *J* = 5.1 Hz, 1H), 3.73 (s, 3H), 3.63 (s and m, 4H), 3.36 (ddd, *J* = 15.0, 5.1, 2.5 Hz, 1H), 2.91 (dd, *J* = 15.0, 10.1 Hz, 1H), 2.56 – 2.39 (m, 1H), 2.23 (s, 3H), 2.19 – 2.08 (m, 1H), 1.91 – 1.59 (m, 3H), 1.49 – 1.34 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.7 (C), 169.3 (C), 169.2 (C), 138.7 (C), 131.2 (C), 129.2 (C), 128.8 (2 CH), 128.5 (2 CH), 127.3 (CH), 84.7 (CH), 52.5 and 52.4 (2 CH_3), 49.6 (CH), 44.9 (CH), 31.3 (2 CH_2), 29.0 (CH_2), 23.2 (CH_2), 22.1 (CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{21}H_{26}NO_6^+$ 388.1755; Found 388.1768.

Dimethyl *rel*-2-(((4aR*,8aR*)-2-acetyl-4-phenyl-4a,5,6,7,8,8a-hexahydro-2H-benzo[e][1,2]oxazin-3-yl)methyl)malonate (11m). Prepared from bromide **2m** (1.51 g, 4.32 mmol) according to the procedure used for the synthesis of **11a**. Yield: 1.49 g (86 %). White foam. R_f = 0.41 (AcOEt/hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.38 – 7.22 (m, 3H), 7.14 (d, 2H, *J* = 6.6 Hz), 4.19 (m, 1H), 3.75 (s, 3H), 3.65 (dd, *J* = 9.7, 5.7 Hz, 1H), 3.61 (s, 3H), 3.34 (ddd, *J* = 15.0, 5.7, 2.1 Hz, 1H), 2.95 (dd, *J* = 15.0, 9.7 Hz, 1H), 2.26 (s, 3H), 2.22 – 2.07 (m, 2H), 1.80 – 1.44 (m, 5H), 1.42 – 1.25 (m, 1H), 1.19 – 1.04 (m, 1H). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 171.5 (C), 169.4 (C), 169.2 (C), 138.4 (C), 130.6 (C), 129.1 (2 CH), 128.4 (C), 128.3 (2 CH), 127.1 (CH), 79.6 (CH), 52.4 and 52.3 (2 CH_3), 49.8 (CH), 40.2 (CH), 29.5 (CH_2), 29.5 (CH_2), 27.3 (CH_2), 24.5 (CH_2), 22.6 (CH_3), 20.8 (CH_2). ESI-HRMS m/z: $[M+Na]^+$ Calcd for $C_{22}H_{27}NO_6Na^+$ 424.1731; Found 424.1737.

Dimethyl 2,2-dimethyl-8-oxo-4-phenyl-3,5,7,8-tetrahydropyrido[1,2-b][1,2]oxazine-6,6(2*H*)-dicarboxylate (12). To a stirred solution of dimethyl malonate (11.5 µL, 0.1 mmol) in anhydrous THF (0.4 mL) was added NaH (12 mg, 60 % in mineral oil, 0.3 mmol) at 0 °C under inert atmosphere. After stirring for 5 minutes, a solution of dihalide **2c** (30 mg, 0.08 mmol) in anhydrous THF (0.2 mL) was added. The mixture was stirred at rt for 3 h and then transferred into a mixture of AcOEt (10 mL) and water (10 mL). Aqueous phase was back-extracted with ethyl acetate (10 mL). Combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated. The residue was subjected to a column chromatography on silica gel to give 19 mg (64 %) of bicyclic derivative **12** as yellowish oil. R_f = 0.23 (AcOEt/hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45 – 7.30 (m, 3H), 7.17 (d, *J* = 6.6 Hz, 2H), 3.71 (s, 6H), 3.08 (s, 2H), 3.03 (s, 2H), 2.41 (s, 2H), 1.39 (s, 6H). ^{13}C NMR (75 MHz, DEPT135, $CDCl_3$) δ 169.5 (2 C), 160.6 (C), 138.8 (C), 128.6 (4 CH), 127.4 (CH), 125.9 (C), 116.7 (C), 78.0 (C), 53.2 (2 CH_3), 52.1 (C), 41.9 (CH_2), 37.9 (CH_2), 31.5 (CH_2), 25.1 (2 CH_3). ESI-HRMS m/z: $[M+H]^+$ Calcd for $C_{20}H_{24}NO_6^+$ 374.1598; Found 374.1590.

General procedure for hydrogenation of 2*H*-1,2-oxazines 11 to saturated 1,2-oxazines 13. To a solution of 2*H*-1,2-oxazine **11** (0.5 mmol) in methanol (5 mL) in a vial was added 5%-Pd/C (0.15 g). The vial was placed to a steel autoclave which was flushed and filled with hydrogen to a pressure of 40 bar. The autoclave was heated to 40-50 °C and the mixture was stirred at this temperature for the indicated time period. Then the autoclave was cooled to r.t., slowly depressurized and the catalyst was removed by filtration. The filtrate was concentrated in vacuum, and the residue was subjected to a column chromatography on silica gel to give the corresponding saturated 1,2-oxazine **13**.

Dimethyl *rel*-2-(((3S*,4R*)-2-acetyl-4-(4-methoxyphenyl)-6,6-dimethyl-1,2-oxazinan-3-yl)methyl)malonate (13h). Prepared from 165 mg (0.41 mmol) of 2*H*-1,2-oxazine **11h** according to the general procedure, reaction time – 4 h. Yield: 165 mg (96 %). White crystals. Mp = 77 – 80 °C. R_f = 0.14 (AcOEt/hexane = 1 : 1). ^{1}H NMR (500 MHz, COSY, HSQC, $CDCl_3$): δ = 1.31 and 1.40 (2 s, 6 H, 2 CH_3), 1.62 (m, 2 H, CH_2CH(CO_2CH_3)$_2$ and HC-5), 2.05 (s, 3 H, CH_3C(O)), 2.16 (m, 2 H, CH_2CH(CO_2CH_3)$_2$ and HC-5), 3.17 (dd, *J* = 9.4, 4.9 Hz, 1 H, CH$_2$C*H*(CO_2CH_3)$_2$), 3.31 (ddd, *J* = 14.0, 4.2, 4.0 Hz, 1 H, H_{ax}C-4), 3.62 (s, 6 H, 2 CO_2CH_3), 3.76 (s, 3 H, OCH_3), 4.92 (ddd, *J* = 11.9, 4.2, 4.0 Hz, 1 H, H_{eq}C-3), 6.84 (d, *J* = 8.5 Hz, 2 H, *o*-$C_6H_4OCH_3$), 7.11 (d, *J* = 8.5 Hz, 2 H, *m*-$C_6H_4OCH_3$). ^{13}C NMR (125 MHz, HSQC, $CDCl_3$): δ = 20.1 (CH_3C(O)), 21.9 and 28.7 (2 CH_3), 24.0 (CH_2CH(CO_2CH_3)$_2$), 35.1 (C-5), 37.2 (C-4), 48.4 (CH$_2$CH(CO_2CH_3)$_2$), 51.2 (C-3), 52.5 (2 CO_2CH_3), 55.2 (OCH_3), 80.0 (C-6), 114.1 (*o*-$C_6H_4OCH_3$), 128.3 (*m*-$C_6H_4OCH_3$), 131.5 (*p*-$C_6H_4OCH_3$), 158.5 (=C-O), 168.9 and 169.7 (N-C=O and 2 CO_2CH_3). Anal. Calcd for $C_{21}H_{29}NO_7$: H, 7.17; C, 61.90; N, 3.44. Found: H, 7.36; C, 61.92; N, 3.52.

Dimethyl *rel*-2-(((3S*,4R*,4aR*,7aR*)-2-acetyl-4-phenyloctahydrocyclopenta[e][1,2]oxazin-3-yl)methyl)malonate (13l). Prepared from 155 mg (0.4 mmol) 2*H*-1,2-oxazine **11l** according to the general procedure, reaction time – 2 h. Yield: 79 mg (51 %). White solid. Mp = 117 – 120 °C. R_f = 0.19 (AcOEt/hexane = 1 : 1). ^{1}H NMR (500 MHz, COSY, HSQC, $CDCl_3$): δ = 1.73, 1.88, 1.97 and 2.13 (4 m, 1 H, 3 H, 1 H and 1 H, -CH_2-CH_2-CH_2-), 2.18 (s, 3 H, CH_3C(O)), 2.22 (ddd, *J* = 13.8, 8.7, 2.3 Hz, 1 H, CH_2CH(CO_2CH_3)$_2$), 2.35 (ddd, *J* = 13.8, 12.0, 4.8 Hz, 1 H, CH_2CH(CO_2CH_3)$_2$), 2.42 (m, 1 H, H_{eq}C-5), 3.34 (dd, *J* = 8.7, 4.8 Hz, 1 H, CH$_2$C*H*(CO_2CH_3)$_2$), 3.54 (dd, *J* = 5.2, 5.1 Hz, 1 H, H_{ax}C-4), 3.68 and 3.70 (2 c, 6 H, 2 CO_2CH_3), 4.31 (m, 1 H, HC-6), 5.03 (ddd, *J* = 12.0, 5.2, 2.3 Hz, 1 H, H_{eq}C-3), 7.21-7.40 (m, 5 H, *o*,*m*,*p*-C_6H_5). ^{13}C NMR (125 MHz, HSQC, $CDCl_3$): δ = 19.9 (CH_3C(O)), 23.4, 26.9, 27.0 and 30.4 (-CH_2-CH_2-CH_2- and CH_2CH(CO_2CH_3)$_2$), 41.8 (C-5), 43.2 (C-4), 49.5 (CH$_2$CH(CO_2CH_3)$_2$), 51.0 (C-3), 52.6 (2 CO_2CH_3), 87.1 (C-6), 126.8, 128.1 and 128.5 (*o*,*m*,*p*-C_6H_5), 139.2 (*i*-C_6H_5), 169.1 and 169.7 (N-C=O and 2 CO_2CH_3). Characteristic 2D NOESY correlations: HC-4/HC-6, HC-3/HC-4, HC-4/HC-5, CH_2CH(CO_2CH_3)$_2$/*o*-C_6H_5. Anal. Calcd for $C_{21}H_{27}NO_6$: H, 6.99; C, 64.77; N, 3.60. Found: H, 7.23; C, 64.41; N, 3.61.

Dimethyl *rel*-2-(((3S*,4R*,4aR*,8aR*)-2-acetyl-4-phenyloctahydro-2H-benzo[e][1,2]oxazin-3-yl)methyl)malonate (13m). Prepared from 155 mg (0.39 mmol) of 2*H*-1,2-oxazine **11m** according to the general procedure, reaction time – 2 h. Yield: 97 mg (62 %). White solid. Mp = 150 – 153 °C. R_f = 0.20 (AcOEt/hexane = 1 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15-1.29 and 1.57-1.96 (4 m, 8 H, -CH_2-CH_2-CH_2-CH_2-), 2.18 (s and m, 4 H, CH_3C(O) and H_{eq}C-5), 2.42 (ddd, *J* = 14.0, 9.2, 2.6 Hz, 1 H, CH_2CH(CO_2CH_3)$_2$), 2.54 (ddd, *J* = 14.0, 11.2, 5.3 Hz, 1 H, CH_2CH(CO_2CH_3)$_2$), 3.28 (dd, *J* = 4.6, 4.6 Hz, 1 H, H_{ax}C-4), 3.49 (dd, *J* = 9.2, 5.3 Hz, 1 H, CH$_2$C*H*(CO_2CH_3)$_2$), 3.72 and 3.75 (2 s, 6 H, 2 CO_2CH_3), 3.97 (m, 1 H, H_{ax}C-6), 5.17 (ddd, *J* = 11.2, 4.6, 2.6 Hz, 1 H, H_{eq}C-3), 7.25-7.42 (m, 5 H, *o*,*m*,*p*-C_6H_5). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$): δ = 20.0 (CH_3C(O)), 21.1, 24.1, 25.8, 28.8 and 30.6 (-CH_2-CH_2-CH_2-CH_2- and CH_2CH(CO_2CH_3)$_2$), 37.9 (C-5), 46.2 (C-4), 49.7 (CH$_2$CH(CO_2CH_3)$_2$), 50.3 (C-3), 52.7 (2 CO_2CH_3), 83.4 (C-6), 126.6, 128.0 and 128.5 (*o*,*m*,*p*-C_6H_5), 137.8 (*i*-C_6H_5), 169.4, 169.7 and 169.9 (N-C=O and 2 CO_2CH_3). Anal. Calcd for $C_{22}H_{29}NO_6$: H, 7.25; C, 65.49; N, 3.47. Found: H, 7.53; C, 65.18; N, 3.60.

***Rel*-dimethyl *rel*-2-((2S*,3R*)-2-acetamido-5-hydroxy-5-methyl-3-phenylhexyl)malonate (14a).** To a stirred solution of 2*H*-1,2-oxazine **11a** (170 mg, 0.45 mmol) in a mixture of methanol (10 mL) and water (3.5 mL) were successively added VCl_3 (560 mg, 2.27 mmol), zinc dust (150 mg, 2.27 mmol) and concentrated hydrochloric acid (0.9 mL). The mixture was intensively stirred for 3.5 h, and then transferred into a mixture of AcOEt (100 mL) and water (100 mL). Aqueous phase was back-extracted with ethyl acetate (2×50 mL). Combined organic layers were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and evaporated. The residue was subjected to a column chromatography on silica gel to give 131 mg (77 %) of dimethyl (*E*)-2-(2-acetamido-5-hydroxy-5-methyl-3-phenylhex-2-en-1-yl)malonate as a yellowish oil, which solidified upon standing [Mp = 118 – 120 °C. R_f = 0.09 (AcOEt/hexane = 1 : 1). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.83 (s, 1H), 7.43 – 7.10 (m, 5H), 3.73 (s, 6H), 3.65 (t, *J* = 8.1 Hz, 1H), 3.16 (d, *J* = 8.0 Hz, 2H), 2.63 (s, 2H), 2.30 (br, 1H), 2.09 (s, 3H), 1.18 (s, 6H). ^{13}C NMR (75 MHz, JMOD, $CDCl_3$) δ 169.6 and 169.3 (3 C), 142.2 (C), 132.9 and 129.7 (2 C), 128.9, 128.3 and 126.6 (5 CH), 74.5 (C), 52.4 and 50.0 (2 CH_3 and CH), 47.5 (CH_2), 30.3 (2 CH_3), 28.8 (CH_2), 23.8 (CH_3). ESI-HRMS m/z: [M+H]$^+$ Calcd for $C_{20}H_{28}NO_6^+$ 378.1911; Found 378.1912]. A portion of product (0.065 g, 0.17 mmol) was dissolved in methanol (2.5 ml); the solution was placed in a vial and 5%-Pd/C (0.065 g) was added. The vial was placed to a steel autoclave which was flushed and filled with hydrogen to a pressure of 80 bar. The autoclave was heated to 70-80 °C and the mixture was stirred at this temperature for 4 h. Then the autoclave was cooled to r.t., slowly depressurized and the catalyst was removed by filtration. The filtrate was concentrated in vacuum, and the residue was subjected to a column chromatography on silica gel to give 29 mg (45 %) of *N*-acylated amine **14a** as a colorless oil. R_f = 0.14 (AcOEt). ^{1}H NMR (500 MHz, 250 MHz, COSY, HSQC, Chloroform-*d*) δ 7.36 – 7.16 (m, 5H, C_6H_5), 5.46 (d, *J* = 9.6 Hz, 1H, NH), 4.49 (dddd, *J* = 11.1, 9.6, 4.1, 3.1 Hz, 1H, CH-N), 3.70 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.36 (t, *J* = 7.0 Hz, 1H, C*H*-CO_2), 3.02 – 2.75 (br s, 1H, OH), 3.07 (ddd, *J* = 7.1, 5.5, 4.1 Hz, 1H, C*H*-Ph), 2.17 (ddd, *J* = 14.3, 7.0, 3.1 Hz, 1H, CH_2CH-N), 2.02 (dd, *J* = 14.8, 7.1 Hz, 1H, CH_2CHPh), 1.94 (s, 3H, CH_3CO), 1.78 (dd, *J* = 14.8, 5.5 Hz, 1H, CH_2CHPh), 1.64 (ddd, *J* = 14.3, 11.1, 7.0 Hz, 1H, CH_2CH-N), 1.19 and 1.13 (2 s, 3H and 3H). ^{13}C NMR (125 MHz, 63 MHz, HSQC, $CDCl_3$) δ 170.8, 170.2 and 169.4 (3 C=O), 141.6 (*i*-C_6H_5), 128.7 and 127.0 (*o*,*m*,*p*-C_6H_5), 70.7 (C-O), 52.8 and 52.7 (2 CH_3O), 51.7 (CH-N), 49.2 (*C*H-CO_2), 46.1 (*C*H-Ph), 44.5 (*C*H_2CHPh), 32.7 (*C*H_2CH-N), 31.9 and 28.2 (2 CH_3), 23.3 (CH_3CO). ESI-HRMS m/z: [M+Na]$^+$ Calcd for $C_{20}H_{29}NO_6Na^+$ 402.1887; Found 402.1885.

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[10] Acetyl chloride (not bromide) was used to reduce the rate of acylation. Reaction was performed in the presence of 1,3-cyclohexadiene to intercept molecular chlorine, which can react with the material of optic probe.

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[13] Reaction of **3a** with HBr did not produce the isomeric primary bromide **4a** demonstrating that reaction proceeds through initial acylation (not protonation) of the nitrogen atom.

[14] No chloride **10a** was observed after 1 h and 3 h suggesting that slow Cl/Br exchange takes place after **2a** is formed. Unlike bromide **3a**, tertiary chloride **8a** was unreactive towards AcBr.

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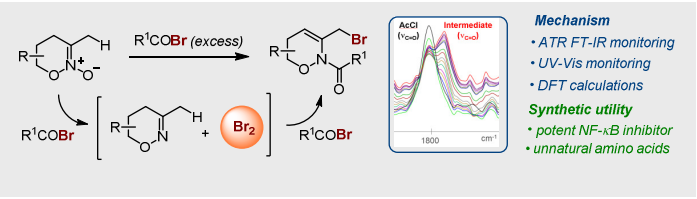

Unusual acylation of 1,2-oxazine-*N*-oxides with acyl bromides produces 3-bromomethyl-substituted 2*H*-1,2-oxazines *via* the formation of molecular bromine as intermediate. The developed process was successfully exploited in the stereoselective synthesis of pharmaceutically relevant molecules.

Acylation of *N*-oxides

*Roman S. Malykhin, Ivan S. Golovanov, Sema L. Ioffe, Alexey Yu. Sukhorukov**

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Tandem Deoxygenation/Halogenation of *N*-Oxides under Acylation Conditions: Scope and *In Situ* IR Spectroscopic Study