Access to $\beta$-Alkylated $\gamma$-Functionalized Ketones via Conjugate Additions to Arylideneisoxazol-5-ones and Mo(CO)$_6$-Mediated Reductive Cascade Reactions

Antonio Macchia, Francesco F. Summa, Guglielmo Monaco, Andreas Eitzinger, Armin R. Olfal, Antonia Di Mola, and Antonio Massa*

ABSTRACT: 1,4-Conjugate addition of ((chloromethyl)sulfonyl)benzene to arylideneisoxazol-5-ones, followed by one-pot, N-selective trapping in the presence of electrophiles, was investigated. This strategy led to the synthesis of new, stable N-protected isoxazol-5-ones in good yields and high diasterelectivity. The study of the reactivity of obtained products in the presence of the Mo(CO)$_6$/H$_2$O system allowed the development of a cascade reaction leading to novel methyl ketones in high yields and unchanged dr bearing an uncommon chloromethinearylsulfonyl end group.

INTRODUCTION

1,4-Conjugate addition of nucleophiles carrying a leaving group (LG) in the $\alpha$-position like ((chloromethyl)sulfonyl)benzene (PhSO$_2$CH$_2$Cl) is particularly useful in the development of effective cyclopropanation reactions, while the isolation of the respective Michael adducts has been rarely accomplished. The presence of the LG drives the reactivity of this pro-nucleophile in several other domino reactions as typically in vicarious nucleophilic substitutions (VNS reactions) at electron-deficient arenes or in the formation of oxiranes (Darzens condensation) when combined with carbonyl compounds. In our recent study, we were able to tune the reactivity of ((chloromethyl)sulfonyl)benzene in the addition to carbonyls with the introduction of a further electrophilic cyano group as in 2-acetylbenzonitriles, which competed with chloride displacement of the alkoxide intermediate, leading to the formation of isindolin-1-ones instead of oxiranes.

Isoxazol-5-ones are heterocyclic compounds, which are straightforwardly obtained by condensation of hydroxylamine with readily available $\beta$-ketoesters. This class of heterocycles gains increasing interest because of the wide range of biological properties as anti-cancer, anti-microbial, anti-obesity, and anti-inflammatory agents or as functional materials in non-linear optical and luminescent probes (see Figure 1 for selected examples). In addition, the rather labile nature of the N–O bond combined with the unique properties of the isoxazole ring enables the synthesis of numerous classes of diverse acyclic and cyclic compounds under several reaction conditions.

Figure 1. Selected isoxazol-5-ones showing biological and optical properties.

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Isoxazol-5-ones are characterized by relatively high acidity at C-4 ($pK_a 4 - 6$), and the resulting carbanions find a wide use as nucleophiles, which can also be used in condensation reactions with aldehydes to generate electrophilic arylidene-isoxazol-5-ones (Scheme 1).

Michael reactions of arylideneisoxazol-5-ones suffer, however, from a relatively limited scope. Tautomerism and scarce stability of the adducts are the main drawbacks (Scheme 1). Non-isolated Michael adducts have been directly transformed into acyclic ketones or alkynes by nitrosative cleavage of the $N-O$ bond in the presence of FeSO$_4$/NaNO$_2$ into diverse heterocyclic compounds using molybdenum reagents or as part of domino reactions in the presence of multifunctional nucleophiles, leading to spirocyclic compounds. On the other hand, when a reactive electrophilic component was included at the end of 1,4-conjugate addition of malonate diesters to arylideneisoxazol-5-ones, the selective N-trapping of the adduct was achieved in high efficiency, preserving the isoxazol-5-one architecture. The obtained products showed high stability and were easily purified by standard techniques, while any attempt to purify or isolate the unprotected Michael adducts led to failures.

As part of our research interest in the development of new reactions involving multifunctional electrophiles and nucleophiles, in the present work, we have investigated Michael reactions of arylideneisoxazol-5-ones with ((chloromethyl)sulfonyl)benzene and subsequent trapping with electrophiles. Intrigued by this possible dualism (see the scheme of Table 1), in a first set of reactions, we investigated the reactivity of the carbanion of ((chloromethyl)sulfonyl)benzene quantitatively generated by reaction with KO$_2$Bu (1 equiv), with 3-methyl-4-benzylideneisoxazol-5-ones in anhydrous acetonitrile. Complete conversion was detected at $-20 ^\circ C$ after 4 h of reaction time by thin-layer chromatography (TLC) (Table 1, entry 2), while at rt, we observed a series of unknown decomposition products (entry 1). $^1$H NMR spectroscopic analysis of the reaction mixture, obtained under the conditions of entry 2, in CD$_3$CN was inconclusive because the formation of a precipitate affected the spectra. After the evaporation of the solvent, $^1$H NMR analysis in CDCl$_3$ gave somewhat better indications, highlighting the disappearance of 2, the presence of signals compatible with the protonated Michael adduct of I-3a, and the lack of the cyclopropyl moiety (Table 1, entry 2). However, every attempt to purify the crude by chromatography led to decomposition together with the isolation of the starting materials, probably due to retro-Michael reaction occurring on silica gel. Therefore, we investigated the possibility to obtain stable products by the addition of chloroform, leading to cyclopropane formation. On the other hand, the N-selective trapping of the enamine form of the adducts by an electrophile E–X should preserve the structure of the chloromethinephenylsulfonyl end group (Scheme 1).

### RESULTS AND DISCUSSION

**Conjugate Additions of ((Chloromethyl)sulfonyl)benzene to Arylideneisoxazol-5-ones and Subsequent Trapping with Electrophiles.**

Intrigued by this possible dualism (see the scheme of Table 1), in a first set of reactions, we investigated the reactivity of the carbanion of ((chloromethyl)sulfonyl)benzene 1 (PhSO$_2$CH$_2$Cl) quantitatively generated by reaction with KO$_2$Bu (1 equiv), with 3-methyl-4-benzylideneisoxazol-5-ones 2 in anhydrous acetonitrile. Complete conversion was detected at $-20 ^\circ C$ after 4 h of reaction time by thin-layer chromatography (TLC) (Table 1, entry 2), while at rt, we observed a series of unknown decomposition products (entry 1). $^1$H NMR spectroscopic analysis of the reaction mixture, obtained under the conditions of entry 2, in CD$_3$CN was inconclusive because the formation of a precipitate affected the spectra. After the evaporation of the solvent, $^1$H NMR analysis in CDCl$_3$ gave somewhat better indications, highlighting the disappearance of 2, the presence of signals compatible with the protonated Michael adduct of I-3a, and the lack of the cyclopropyl moiety (Table 1, entry 2). However, every attempt to purify the crude by chromatography led to decomposition together with the isolation of the starting materials, probably due to retro-Michael reaction occurring on silica gel. Therefore, we investigated the possibility to obtain stable products by the addition of...
electrophiles \( E - X \) at the end of the Michael reaction at \(-20^\circ C\), as previously reported with dimethyl malonate.\textsuperscript{18} Our choice focused on di-tert-butyl di-carbonate aiming to a N-selective interception of the I-3a intermediate. Under the conditions of entry 3, the sequential reaction allowed the isolation after chromatography of stable N-Boc-protected 4a, bearing an uncommon chloromethinephenylsulfonyl side chain in good yield and excellent dr >94:6. The use of weaker bases, \( K_2CO_3 \) and \( Et_3N \), was not effective in promoting the Michael reaction since unreacted starting materials were detected by TLC and \(^{1}H\) NMR analysis of the crude materials (entries 4 and 5).

Synthetic access to stable, highly functionalized isoxazol-5-ones is a very important aim since this class of compounds shows a wide range of biological activities and interesting optical properties (Figure 1).\textsuperscript{6–12} Therefore, the scope of the sequential reaction was thoroughly analyzed combining different readily available\textsuperscript{14,15} ((chloromethyl)sulfonyl)benzenes and 3-methyl-4-arylideneisoxazol-5-ones\textsuperscript{18} bearing electron-withdrawing and electron-donating groups on the aromatic rings of both the nucleophiles and electrophiles (Table 2). Apart from di-tert-butyl dicarbonate, two other reagents E–X, acetic anhydride and isodomethane, were used in order to investigate if they could lead to products with different substituents on the nitrogen of the heterocyclic ring (Table 2). Based on the data reported in Table 2, the method proved to be effective with all the combinations of substrates, affording in good yields a wide range of new N-protected, stable products 4 in the enamine form, demonstrating the efficiency of the electrophilic trapping strategy also in the presence of alkylating or acylating reagents.

Excellent diastereomeric ratios, up to >99/1 dr were detected in most of the cases. We have not investigated the mechanism to explain this rather general outcome and the few exceptions, which seem to be independent of the substituents and the type of electrophilic trapping reagents. It is likely that the high diastereoselectivity is the result of kinetic control and in a few cases, epimerization occurs to a certain extent. Since we were not able to prepare single crystals of the compounds obtained, the relative configuration was deduced by correlating the experimental and calculated \(^{1}H\) NMR spectra of the products of the further transformation of 4 (see the next section).

Investigation of the Reactivity of N-protected Isoxazole-5-ones under Reductive Cleavage of the O–N Bond. The obtained products 4 can be particularly useful in further transformations involving the cleavage of the N–O bond which can allow the access to unprecedented compounds. During the last years, there has been an increased interest of academia and industry in molybdenum compounds in organic synthesis.\textsuperscript{15} In particular, molybdenum hexacarbonyl \( Mo(CO)_6 \) has been used in various reactions, namely, C–C bond formation, cyclization, reductions, oxidations, and heterocyclic ring formation\textsuperscript{15,19–25} as well as in the ring cleavage of isoxazole and isooxazoline compounds.\textsuperscript{15,16}

In particular, reductive cleavage of the O–N bond of isoxazoles and isooxazolines in the presence of the \( Mo(CO)_6/H_2O \) system has been used in the synthesis of new heterocycles by further in situ rearrangement of the open intermediates.\textsuperscript{15,16}

### Table 1. Preliminary Investigation of the Michael Reaction of ((Chloromethyl)sulfonyl)benzene 1 with 3-Methyl-4-benzylideneisoxazol-5-ones 2

| entry | E       | T (°C) | time (h) | yield (%) |
|-------|---------|--------|----------|-----------|
| 1     | r.t.    |        |          |           |
| 2     | r.t.    | -20  | 2        |           |
| 3     | Boc₂O  | -20  | 4        |           |
| 4     | r.t.    |       |          |           |
| 5     | r.t.    |       | 18       | no react. |

*Unknown degradation products were detected. *Starting materials and decomposition products were isolated after chromatography. *Time addition + protection. *Isolated yield. *\( K_2CO_3 \) was used. \( Et_3N \) was used.
However, the effect of this system has been scarcely investigated on isoxazol-5-ones derivatives. After O–N cleavage of 4, in principle, the supposed formation of enamine or carboxylate groups could lead to competitive intramolecular displacements of chloride to afford five-membered heterocyclic compounds.

In order to explore the reactivity of 4 under reductive cleavage of the O–N bond with the Mo(CO)₆/H₂O system, a series of differently protected compounds 4 were subjected to react with Mo(CO)₆/H₂O under the conditions of Table 3. N-Methyl-enamine derivative 4o gave decomposition products. N-Acetyl-enamine derivative 4j did not react. Surprisingly, the N-Boc-protected 4a led smoothly to the isolation of an unprecedented β-alkylated γ-functionalized ketone 5a, which cannot be easily obtained by other methods such as 1,4-conjugate additions of electron-deficient alkene or by direct β-functionalization of saturated ketones in the presence of Pd catalysts.

As confirmed by a series of control experiments (Scheme 2), the reaction presumably follows the order of Boc-deprotection,
cleavage of O–N bond, enamine/imine hydrolysis, and decarboxylation (Scheme 3). The role of water is important since the presence of only Mo(CO)₆ led to NH-enamine as detected in the 1H NMR spectrum of the crude because of Boc-deprotection (Scheme 2a, Exp-a), while a longer reaction time led to decomposition products (Scheme 2a, Exp-c). The unprotected Michael adduct 3a obtained as crude, according to Scheme 2b (see also Table 1), was subjected to reaction in the presence of Mo(CO)₆ with or without water. In both the experiments, decomposition products were observed, demonstrating the importance of N-Boc-protection to accomplish this cascade reaction. On the other hand, the treatment of 4a with the TFA/DCM mixture under Boc-deprotection conditions afforded, after aqueous work-up, 3a and to certain extent 1 and 2 as a consequence of retro-Michael reaction (3a/1 about 3/1, Scheme 2a, Exp-b). This indicates that Boc-deprotection and acidic conditions are not sufficient to trigger the cleavage of the O–N bond and the following cascade reaction, but Mo(CO)₆ plays a key role. Based on these considerations, a stepwise mechanism has been proposed, highlighting all the possible intermediates (Scheme 3). After Boc-deprotection, the hydrolysis of the enamine/imine intermediate and decarboxylation of I-6 or I-7 are presumably faster than possible isomerization of the double bond and cyclizations, preserving the coordination of the nitrogen in the isoxazole-5-one to Mo(CO)₆ may facilitate both the deprotection and the reductive cleavage of the O–N bond.¹⁶c

Then, under the optimized conditions as reported in Table 3, the scope of the reaction was briefly analyzed with other N-Boc-protected isoxazole-5-ones 4, bearing different substituents on both the aromatic rings (Table 4). In all the cases, we obtained methylketones 5 in high yields and with a very high dr, unchanged with respect to starting materials 4. The relative configuration was determined to be (R*,R*) by comparison of experimental and calculated 1H NMR spectra determined on 5a, 5b, and 5c. This was achieved generating conformers for each diastereomeric species using confab²⁷ run with an energy window of 5 kcal mol⁻¹. These conformers have been then reoptimized using Gaussian 16²⁸ at the B3LYP-gCP-D3/6-31G* scheme (see the Supporting Information for further details).²⁹,³⁰ For analogy, this relative configuration can be extended to all the other ketones 5 and subsequently to Michael adducts 4.

As discussed in the Introduction section, 1,4-conjugate addition of ((chloromethyl)sulfonyl)benzenes has been exploited in cyclopropanation reactions,³ while the isolation of the Michael adducts is quite rare.² Nevertheless, ketones 5 may be obtained without involving isoxazol-5-one chemistry by direct 1,4-conjugate addition of ((chloromethyl)sulfonyl)-benzenes 1 to the α,β-unsaturated ketones 8 (Scheme 4). Several reaction conditions were tested as reported by Makosza et al. in the conjugated addition of ((chloromethyl)sulfonyl)-benzene to nitrochalcone³ or in accordance to the conditions described in Table 1. In all the cases, we obtained complex mixtures of unknown products, further demonstrating the utility of the approach herein described.

### CONCLUSIONS

1,4-Conjugate additions of ((chloromethyl)sulfonyl)benzene to arylideneisoxazol-5-ones were investigated. In order to overcome the drawbacks related of the scarce stability of the obtained Michael adducts, an effective N-trapping by a sequential one-pot addition of electrophiles was developed. This strategy allowed the isolation of a wide range of new, stable isoxazole-5-ones in good yields and with high diastereomeric ratios. Then, the obtained products were subjected to the reductive cleavage of the O–N bond in the presence of the Mo(CO)₆/H₂O system. This further investigation led to development of an effective cascade reaction, leading to a new class of methylketones β-substituted

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**Table 3. Preliminary Investigation of the Mo(CO)₆-Mediated Reaction**

| entry | 4   | E   | yield (%)<sup>a</sup> |
|-------|-----|-----|-----------------------|
| 1     | 4o  | Me  | decomp.               |
| 2     | 4j  | Ac  | no react.              |
| 3     | 4a  | Boc | 87%                   |

<sup>a</sup> Isolated yield.
with an unprecedented chloromethinephenylsulfonyl end group.

**Experimental Section**

**General Methods.** Unless otherwise noted, all chemicals, reagents, and solvents for the performed reactions are commercially available and were used without further purification. In particular, ((chloromethyl)sulfonyl)benzene is commercially available; all the other ((chloromethyl)sulfonyl)-benzenes were prepared according to ref 1a, while aryldieneisoxazol-5-ones were prepared according to ref 18 and (E)-4-arylbut-3-en-2-ones according to ref 31. All the reactions were monitored by TLC on precoated silica gel plates (0.25 mm) and visualized by fluorescence quenching at 254 nm. Flash chromatography was carried out using silica gel 60 (70−230 mesh, Merck, Darmstadt, Germany). Yields are given for isolated products showing one spot on a TLC plate, and no impurities were detectable in the NMR spectrum. The NMR spectra were recorded on Bruker DRX 600, 400, and 300 MHz spectrometers (600 MHz, 1H, 125 MHz, 13C; 400 MHz, 1H, 100.6 MHz, 13C; 300 MHz, 1H, 75.5 MHz, 13C). The internal reference was set to the residual solvent signals (δH 7.26 ppm, δC 77.16 ppm for CDCl3). The 13C NMR spectra were recorded under broad-band proton decoupling. The following abbreviations are used to indicate the multiplicity in NMR spectra: s-singlet, d-doublet, t-triplet, q-quartet, dd-doublet of doublets, m-multiplet, and brs-broad signal. Coupling constants (J) are quoted in Hertz. High-resolution mass spectroscopy (HRMS) spectra were acquired using a Bruker SolariX XR Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 7T refrigerated actively shielded superconducting magnet. At LMU München, HRMS spectra were recorded on a Finnigan MAT 90, a Finnigan MAT 95, a Thermo Finnigan LTQ FT Ultra Fourier Transform ion cyclotron resonance, or a Q Exactive GC Orbitrap GC/MS. For ionization of the samples, either electron-impact ionization (EI) or electrospray ionization (ESI) was applied. Selected IR spectra (4i, 4m, 4o, and 5c) were recorded in KBr on a Bruker Vertex 70 spectrometer.

**General Procedure for the Synthesis of Compounds 4a−4q.** 4-Alkylideneisoxazol-5-ones 2 (0.107 mmol, 1.0 equiv) were added to a solution of ((chloromethyl)sulfonyl)-benzenes 1 (0.128 mmol, 1.2 equiv) and potassium tert-butoxide (0.107 mmol, 12 mg, 1.0 equiv) in anhydrous CH3CN (0.21 M, 0.50 mL) at −20 °C. The reaction mixture was monitored by TLC until complete disappearance of starting materials; after that, the reaction mixture was treated with the electrophilic trapping reagents (E−X = Boc2O or Ac2O or CH3I, 0.214 mmol, 2 equiv) and warmed to room temperature. The reaction mixture was allowed to stir until the disappearance of the starting materials on TLC (hexane/ethyl acetate = 80:20). The solution was evaporated, affording the crude product as a white solid, which was purified by column chromatography (hexane/ethyl acetate 80:20) to provide 4a−4q (63−86%). The reaction with substrate 2a was scaled to 0.535 mmol (100 mg), leading to the product in 68% yield (0.364 mmol, 174 mg).

**Scheme 4. Control Experiments for the Reaction of ((Chloromethyl)sulfonyl)benzenes with (E)-4-Arylbut-3-en-2-one**

**Table 4. Scope of the Mo(CO)6-Mediated Reaction**

| entry | Ar | Ar′ | t (h) | yield | dr |
|-------|----|-----|------|-------|----|
| 1     | 5a | C6H5 | 3    | 87 | >95:5 |
| 2     | 5b | 4-Cl-C6H4 | 4-CN-C6H4 | 6 | 88 | >95:5 |
| 3     | 5c | C6H5 | 4-CN-C6H4 | 3 | 85 | >99:1 |
| 4     | 5d | C6H5 | 4-NO2-C6H4 | 4 | 92 | >99:1 |
| 5     | 5e | 4-Cl-C6H4 | 4-NO2-C6H4 | 4 | 93 | >99:1 |

**Scheme 3. Proposed Steps in the Cascade Reductive Cleavage of the Isoxazol-5-ones**

**Table 4. Scope of the Mo(CO)6-Mediated Reaction**

| entry | Ar | Ar′ | t (h) | yield | dr |
|-------|----|-----|------|-------|----|
| 1     | 5a | C6H5 | 3    | 87 | >95:5 |
| 2     | 5b | 4-Cl-C6H4 | 4-CN-C6H4 | 6 | 88 | >95:5 |
| 3     | 5c | C6H5 | 4-CN-C6H4 | 3 | 85 | >99:1 |
| 4     | 5d | C6H5 | 4-NO2-C6H4 | 4 | 92 | >99:1 |
| 5     | 5e | 4-Cl-C6H4 | 4-NO2-C6H4 | 4 | 93 | >99:1 |

*a* Isolated yield.
tert-Butyl 4-(2-chloro-2-((4-cyanophenyl)sulfonyl)-1-phe-nyethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (4b).
White solid (83%, 45 mg). Single diastereomer. mp 205–207 °C (chloroform/hexane). 1H NMR (400 MHz, CDCl3): δ 8.09 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 6.4 Hz, 2H), 7.32 (q, J = 8.5, 7.5 Hz, 3H), 6.60 (d, J = 11.1 Hz, 1H), 4.35 (d, J = 11.1 Hz, 1H), 2.60 (s, 3H), 1.56 (s, 9H).

13C{1H} NMR (101 MHz, CDCl3): δ 166.5, 154.4, 145.3, 141.0, 138.3, 132.9, 130.3, 129.8, 128.5, 128.2, 118.4, 117.1, 104.5, 87.0, 72.2, 42.7, 28.1, 13.1. ESI-HRMS: found, m/z, 501.0920 calcld for C24H23ClN2O6S (M – Na)+, 501.0893.

tert-Butyl 4-(2-chloro-2-((4-nitrophenyl)sulfonyl)-1-phe-nyethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (4c).
White solid (84%, 47 mg). Single diastereomer. mp 186–188 °C (chloroform/hexane). 1H NMR (400 MHz, CDCl3): δ 8.42 (d, J = 8.9 Hz, 2H), 8.18 (d, J = 8.9 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H), 7.33 (q, J = 8.8, 7.8 Hz, 3H), 6.23 (d, J = 11.1 Hz, 1H), 4.34 (d, J = 11.1 Hz, 1H), 2.61 (s, 3H), 1.56 (s, 9H).

13C{1H} NMR (101 MHz, CDCl3): δ 166.6, 154.5, 151.3, 154.3, 142.2, 138.2, 131.1, 129.4, 128.5, 128.2, 124.4, 104.4, 87.0, 72.2, 42.6, 28.1, 13.1. ESI-HRMS: found, m/z, 540.1201 calcld for C23H22ClINaO6S (M + Na)+, 540.1207.

tert-Butyl 4-(2-chloro-1-(4-methoxyphenyl)-2-((4-phenylsulfonyl)ethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (4d).
White solid (63%, 34 mg). Single diastereomer. mp 235–237 °C (ethanol/benzene). 1H NMR (400 MHz, CDCl3): δ 7.95 (d, J = 7.1 Hz, 2H), 7.71–7.67 (m, 1H), 7.58 (d, J = 7.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.09 (d, J = 11.1 Hz, 1H), 4.28 (d, J = 11.1 Hz, 1H), 3.77 (s, 3H), 2.59 (s, 3H), 1.56 (s, 9H).

13C{1H} NMR (101 MHz, CDCl3): δ 166.6, 159.4, 154.0, 154.5, 136.7, 134.6, 130.9, 129.6, 129.4, 129.2, 114.5, 105.3, 86.7, 72.6, 55.4, 42.0, 28.1, 13.1. ESI-HRMS: found, m/z, 530.1010 calcld for C23H21ClINaO7S (M + Na)+, 530.1016.

tert-Butyl 4-(2-chloro-2-((4-nitrophenyl)sulfonyl)-1-(4-methoxymethyl)ethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (4e).
White solid (85%, 49 mg). Single diastereomer. mp 212–213 °C (chloroform/hexane). IR (KBr) ν: 1767; 1732; 1608; 1353; 1338; 1144; 734 cm–1.

1H NMR (400 MHz, CDCl3): δ 8.43 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.18 (d, J = 11.1 Hz, 1H), 4.35 (d, J = 11.1 Hz, 1H), 2.62 (s, 3H), 1.54 (s, 9H).

13C{1H} NMR (101 MHz, CDCl3): δ 166.5, 154.7, 154.3, 140.8, 136.7, 134.5, 133.0, 129.6, 129.5, 118.5, 117.1, 104.0, 87.2, 72.0, 42.1, 28.1, 13.1. ESI-HRMS: found, m/z, 553.0514 calcld for C23H22ClINaO7S–Na+ (M – Na)+, 535.0503.

tert-Butyl 4-(2-chloro-1-(4-chlorophenyl)-2-((4-nitrophenyl)sulfonyl)ethyl)-3-methyl-5-oxoisoxazole-2(5H)-carboxylate (4f).
White solid (83%, 50 mg). Single diastereomer. mp 221–223 °C (chloroform/hexane). IR (KBr) ν: 1767; 1732; 1608; 1353; 1338; 1144; 734 cm–1.

1H NMR (400 MHz, CDCl3): δ 8.43 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.18 (d, J = 11.1 Hz, 1H), 4.35 (d, J = 11.1 Hz, 1H), 2.62 (s, 3H), 1.54 (s, 9H).

13C{1H} NMR (101 MHz, CDCl3): δ 167.4, 154.7, 154.3, 140.8, 136.7, 134.5, 133.0, 129.6, 129.5, 104.0, 87.2, 72.0, 42.1, 28.1, 13.1. ESI-HRMS: found, m/z, 553.0413 calcld for C23H22ClINaO7S (M + Na)+, 553.0401.
4-[(2-(Acetyl-3-methyl-5-oxo-2,5-dihydroisoxazol-4-yl)-1-chloro-2-phenylethyl)sulfonyl]benzonitrile (4k). White solid (82%, 39 mg). Single diastereomer. mp 220–222 °C (ethyl acetate/hexane). \(^\text{1}H\) NMR (250 MHz, CDCl\(_3\)): \(\delta\) 8.09 (d, \(J = 8.3\) Hz, 2H), 7.88 (d, \(J = 8.3\) Hz, 2H), 7.46 (d, \(J = 5.9\) Hz, 2H), 7.40–7.30 (m, 3H), 6.14 (d, \(J = 11.1\) Hz, 1H), 4.36 (d, \(J = 11.2\) Hz, 1H), 2.68 (s, 3H), 2.41 (s, 3H). \(^{13}C\) NMR (63 MHz, CDCl\(_3\)): \(\delta\) 166.0, 165.1, 153.8, 140.8, 137.8, 132.9, 130.5, 129.4, 128.6, 128.2, 118.4, 117.1, 105.8, 77.7, 76.7, 72.0, 42.3, 22.8, 13.3. EI-HRMS: found, 444.0537 \(m/z\) calcld for \(C_{23}H_{17}ClIN_{2}O_{5}S\) (M + H\(^+\)).

2-Acetyl-4-(2-chloro-2-(4-nitrophenyl)sulfonyl)-1-phenylethyl)-3-methylisoxazol-5(2H)-one (4l). White solid (70%, 40 mg). Single diastereomer. mp 226–228 °C (chloroform/hexane). \(^\text{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.42 (d, \(J = 8.7\) Hz, 2H), 8.18 (d, \(J = 8.7\) Hz, 2H), 7.46 (d, \(J = 7.5\) Hz, 2H), 7.38–7.30 (m, 3H), 6.16 (d, \(J = 11.1\) Hz, 1H), 4.37 (d, \(J = 11.1\) Hz, 1H), 2.69 (s, 3H), 2.42 (s, 3H). \(^{13}C\) NMR (101 MHz, CDCl\(_3\)): \(\delta\) 166.0, 165.1, 153.8, 142.2, 132.7, 131.8, 131.2, 129.5, 128.6, 128.2, 124.4, 105.8, 72.1, 42.3, 22.9, 13.4. MALDI-HRMS: found, 487.0359 \(m/z\) calcld for \(C_{23}H_{19}ClIN_{2}O_{5}S\) (M + Na\(^+\)).

5-Chloro-4-phenyl-5-(phenylsulfonyl)pentan-2-one (5a). Colorless oil (87%, 20 mg). Single diastereomer. \(^\text{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.85 (d, \(J = 7.2\) Hz, 2H), 7.64 (t, \(J = 7.5\) Hz, 1H), 7.51 (t, \(J = 7.8\) Hz, 2H), 7.39–7.28 (m, 5H), 5.29 (d, \(J = 5.3\) Hz, 1H), 4.58–4.26 (m, 1H), 3.28 (dd, \(J = 18.2, 7.6\) Hz, 1H), 3.06 (dd, \(J = 18.2, 6.0\) Hz, 1H), 2.13 (s, 3H). \(^{13}C\) NMR (101 MHz, CDCl\(_3\)): \(\delta\) 169.7, 160.2, 141.5, 137.6, 134.2, 132.9, 130.2, 129.8, 129.3, 128.3, 111.3, 71.9, 71.2, 42.6, 37.5, 10.7. ESI-HRMS: found, 451.0270 \(m/z\) calcld for \(C_{21}H_{17}ClN_{2}O_{4}S\) (M + H\(^+\)).

Mol(CO)\(_4\)-Mediated Reductive Cascade Reactions. Molybdenum hexacarbonyl (0.067 mmol, 18 mg, 1.0 equiv) was added to a solution of 4 (0.067 mmol, 1.0 equiv) in an H\(_2\)O/McCN mixture (0.2 + 1.3 mL) at 85 °C in an oil bath. The reaction mixture was monitored by TLC until complete disappearance of starting materials. The reaction mixture was allowed to cool down to room temperature, diluted with CHCl\(_3\) and filtered over Celite. The solvent was evaporated, affording the crude product as a yellow solid, which was purified by column chromatography (hexane: ethyl acetate from 95:5 to 80:20) to provide products 5a–5e (84–93%). The reaction of 4h was scaled to 0.201 mmol (108 mg, 1 equiv), affording 5b in 80% yield (0.161 mmol, 64 mg).
5-Chloro-5-((4-nitrophenyl)sulfonyl)-4-phenylpentan-2-one (5d). Colorless oil (92%, 24 mg). Single diastereomer. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.28 (d, $J$ = 8.9 Hz, 2H), 7.95 (d, $J$ = 8.8 Hz, 2H), 7.53–7.18 (m, 5H), 5.44 (d, $J$ = 4.8 Hz, 1H), 4.49–4.25 (m, 1H), 3.24 (dd, $J$ = 18.4, 8.2 Hz, 1H), 3.01 (dd, $J$ = 18.4, 5.4 Hz, 1H), 2.15 (s, 3H). $^{13}$C{1H} NMR (75 MHz, CD$_2$Cl$_2$): $\delta$ 206.0, 151.5, 142.7, 137.5, 131.3, 130.2, 128.9, 128.7, 124.5, 77.7, 47.0, 40.9, 30.7. ESI-HRMS: found 413.9975.

5-Chloro-4-(4-chlorophenyl)-5-((4-nitrophenyl)sulfonyl)-pentan-2-one (5e). Colorless oil (93%, 26 mg). Single diastereomer. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.7 Hz, 2H), 8.03 (d, $J$ = 8.8 Hz, 2H), 7.53–7.18 (m, 5H), 5.44 (d, $J$ = 4.8 Hz, 1H), 4.49–4.25 (m, 1H), 3.24 (dd, $J$ = 18.4, 8.2 Hz, 1H), 3.01 (dd, $J$ = 18.4, 5.4 Hz, 1H), 2.15 (s, 3H). $^{13}$C{1H} NMR (75 MHz, CD$_2$Cl$_2$): $\delta$ 205.8, 151.7, 142.7, 136.1, 134.6, 131.7, 131.1, 129.0, 124.6, 77.3, 46.8, 40.2, 30.7. ESI-HRMS: found 413.9980 m/zcalcd for C$_{17}$H$_{14}$Cl$_2$NO$_5$S ($^1$M$^-$), 413.9975.

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Author Information

Corresponding Author
Antonio Massa − Dipartimento di Chimica e Biologia “A. Zambelli”, Università degli studi di Salerno, 84084 Fisciano, Salerno, Italy; orcid.org/0000-0003-4921-4766; Email: amassa@unisa.it

Authors
Antonio Macchia − Dipartimento di Chimica e Biologia “A. Zambelli”, Università degli studi di Salerno, 84084 Fisciano, Salerno, Italy
Francesco F. Summa − Dipartimento di Chimica e Biologia “A. Zambelli”, Università degli studi di Salerno, 84084 Fisciano, Salerno, Italy
Guglielmo Monaco − Dipartimento di Chimica e Biologia “A. Zambelli”, Università degli studi di Salerno, 84084 Fisciano, Salerno, Italy; orcid.org/0000-0001-5268-940X
Andreas Eitinger − Department Chemie, Ludwig-Maximilians-Universität München, 81377 München, Germany
Armin R. Oñal − Department Chemie, Ludwig-Maximilians-Universität München, 81377 München, Germany
Antonia Di Mola − Dipartimento di Chimica e Biologia “A. Zambelli”, Università degli studi di Salerno, 84084 Fisciano, Salerno, Italy

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c07081

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