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Organocatalyzed Synthesis of Isoxazolidin-5-ones: The Meldrum's Acid Approach

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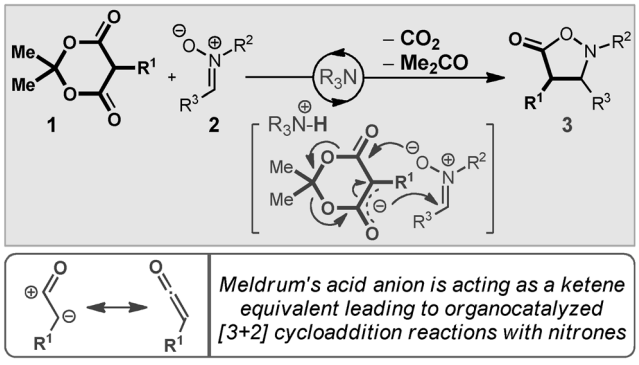
Abstract: Meldrum's acid has turned out to be a useful ketene equivalent when faced to nitrone dipoles to form various isoxazolidin-5-one derivatives under very mild Brønsted base organocatalytic conditions. The first asymmetric version of this original domino anionic formal [3+2]cycloaddition–decarboxylation reaction was demonstrated by means of quinine-based organocatalysts.

Keywords: cycloaddition; isoxazolidinones; ketene equivalents; Meldrum's acid; organic catalysis; organocatalysis

Isoxazolidin-5-one derivatives **3** belong to those architectures which are not only considered as useful heterocyclic platforms for the design of bioactive compounds (Scheme 1),[1] but are also versatile intermediates in organic synthesis. In just a few chemical transformations, for instance, this building block provides an expeditious access to nucleoside mimics,[2] or β-amino acids,[3] currently relevant compounds in medicinal chemistry. However, beside stoichiometric synthetic approaches to isoxazolidin-5-one structures **3**,[3] the one step catalytic and/or enantioselective construction of this heterocyclic framework has elicited few research programs thus far.[4] Sibi and co-workers reported a unique asymmetric version based on the addition of *N*-benzylhydroxylamine to activated acrylamides in the presence of chiral magnesium Lewis acid complexes.[5] Zhang and Ying developed an N-heterocyclic carbene organocatalyzed reaction of nitrosobenzene to enals giving rise to the formation of unstable *N*-phenylisoxazolidin-5-ones **3** (R^2 = Ph).[6] One enantioselective example was described with 44.5% *ee*. On the other hand, Córdova and colleagues achieved an elegant enantioselective aza-Michael reaction of *N*-carbamate-hydroxylamine, promoted by a catalytic amount of iminium salt intermediates, followed by an oxidation process of the obtained 5-hydroxyisoxazolidines.[7] This sequence provides a powerful but indirect two-steps approach to some isoxazolidin-5-one derivatives **3**. Alternatively, the nucleophilic addition of ketene acetals, either as enolate or silyl derivatives, to nitrones furnished a straightforward approach to isoxazolidin-5-ones after an intramolecular lactonization event.[8] The catalytic activity of thioureas or TMSOTf was proven in some cases.[9] Nonetheless, the use of strong bases or the implications of moisture sensitive nucleophiles were required.

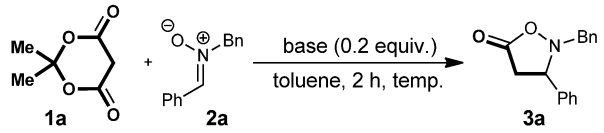


Scheme 1. Organocatalytic formal [3+2]cycloaddition.

In that context, we would like to report on a practical, yet innovative, organocatalytic synthetic approach to isoxazolidin-5-ones **3** from nitrone dipoles **2** based on an anionic formal [3+2]cycloaddition reaction (Scheme 1).[4,10] Notably, we highlight hereby the remarkable facile addition reaction of Meldrum's acid dipolarophile behaving as a user-friendly ketene equivalent formed upon a smooth catalytic deprotonation event.[11,12] We believe this original strategy affords new opportunity beside the known [3+2]cycloaddition processes involving ketene equivalents.[3d,13,14]

At the origin of this project, we were intrigued by the formation of isoxazolidinone **3a** simply by mixing

Table 1. Optimization of Brønsted base catalysts.[a]



Entry	Base	Temp. [°C]	Conversion [%][b]
1	–	40	10[c,d]
2	DABCO	40	62
3	DMAP	40	57
4	Et_3N	40	58
5	DBU	40	42
6	TBD	40	42
7	TMP	40	41
8	**(*i*-Pr)$_2$EtN**	**40**	**68 (64)**,[c] **(86)**[c,e]
9	(*i*-Pr)$_2$EtN	60	79
10	(*i*-Pr)$_2$EtN	20	14

[a] *Reaction conditions*: Meldrum's acid **1a** (1.1 equiv.), *N*-benzylnitrone **2a** (1 equiv.), base (0.2 equiv.), toluene (0.1 M), 2 h.
[b] Determined from the ^{1}H NMR spectrum of the crude product with respect to the remaining nitrone.
[c] Isolated yield after purification by column chromatography.
[d] After 18 h of reaction.
[e] At 0.5 M.

N-benzylnitrone **2a** and Meldrum's acid **1a** at 40 °C for 18 h, albeit in low yield (Table 1, entry 1). Pleasingly, this likely domino process was markedly accelerated in the presence of DABCO, DMAP or Et_3N. These bases displayed similar catalytic reactivity giving nearly 60% of conversion after 2 h (entries 2–4). Stronger bases such as DBU or triazabicyclo-[4.4.0]dec-5-ene (TBD) led to slower reaction rates (entries 5 and 6). Obviously, all these amines also possess a nucleophilic character, and it is conceivable that they react as such with Meldrum's acid derivative **3a**, through the formation of an acylketene species.[14,15] Nevertheless, when reactants **1a** and **2a** were subjected to sterically hindered and non-nucleophilic tetramethylpiperidine (TMP) a 41% of conversion was measured too (entry 7). Eventually, it was found that Hünig's base furnished the best result affording 64% isolated yield with 68% of conversion (entry 8). This transformation was improved by working at 0.5 M to afford 86% yield (entry 8). However, precipitation events during the reaction led to somewhat capricious outcomes along different attempts. Moreover, the reaction rate could be accelerated at 60 °C (entries 9 and 10).

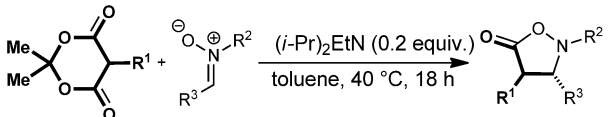
A rapid journey along the reaction conditions revealed an incompatibility of this process with dipolar aprotic solvents (Table 2, entries 1 and 2) and a poor transformation into isoxazolidinone **3a** in ethanol (entry 3). Slightly better reaction rates were measured

Table 2. Optimization of solvents with Hünig's base.[a]

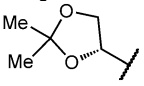
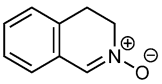
Entry	Solvent	Conversion [%][b]
1	DMF	0
2	DMSO	0
3	EtOH	22
4	ethyl acetate	36
5	dichloroethane	19
6	methylcyclohexane	35
7	toluene	68

[a] *Reaction conditions*: Meldrum's acid **1a** (1.1 equiv.), *N*-benzylnitrone **2a** (1 equiv.), (*i*-Pr)$_2$EtN (0.2 equiv.), solvent (0.1 M), 2 h.
[b] Determined from the ^{1}H NMR spectrum of the crude product with respect to the remaining nitrone.

Table 3. Scope and limitations.[a]



1a, R^1 = H
1b, R^1 = Bn
2a–m
3a–n (+/–)

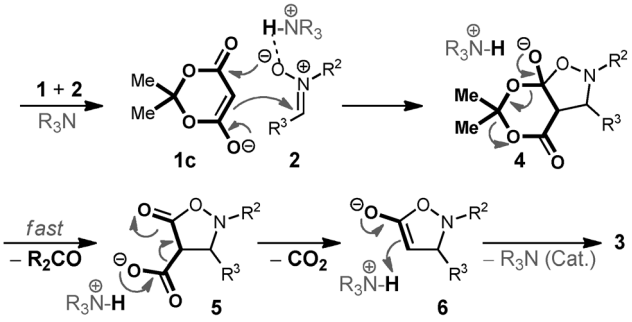
Nitrone/Product	R^1	R^2	R^3	Yield [%][b]
2a/3a	H	Bn	Ph	76
2b/3b	H	Ph	Ph	81[c]
2c/3c	H	Boc[d]	CH_2CH_2Ph	12 (63)[e]
2a/3d	Bn	Bn	Ph	55[f]
2d/3e	H	Bn	4-ClC_6H_4	76
2e/3f	H	Me	4-$MeOC_6H_4$	73
2f/3g	H	Bn	CH_2CH_2Ph	85
2g/3h	H	Bn	Cy	91
2h/3k	H	Bn	CH_2NHBoc	52 (61)[e]
2k/3l	H	Bn	CO_2Et	41
2l/3m	H	Bn		73[g]
2m/3n	H	–		58[h]

[a] *Representative reaction conditions*: Meldrum's acid **1a** (1.5 equiv.), *N*-benzylnitrone **2a** (0.5 mmol, 1 equiv.), (*i*-Pr)$_2$EtN (0.2 equiv.), toluene (0.1 M), 18 h, 40 °C.
[b] Isolated yield after purification by column chromatography.
[c] Yield determined on the basis of the crude product by means of an internal standard.
[d] Nitrone **2c** generated *in situ* with 1.2 equivalents of (*i*-Pr)$_2$EtN from the corresponding phenylsulfonylalkyl-*N*-hydroxycarbamates **2c′**.
[e] Obtained at room temperature for 18 h.
[f] >98:2 *anti*/*syn* ratio from the ^{1}H NMR spectrum of the crude product after 48 h at 40 °C.
[g] >73:27 *anti*/*syn* ratio from the ^{1}H NMR spectrum of the crude product.
[h] 91% of conversion at 60 °C for 42 h (75% of conversion at 40 °C for 18 h).

with less polar media (entries 4–6), although none of them surpassed toluene with regard to the conversion in 2 h (entry 7).

Then, we probed the scope and limitation of this new methodology by means of various types of nitrones (Table 3). The reactions were carried out at 40 °C for 18 h, which secure a complete conversion in most cases. *N*-Benzyl **2a** and *N*-phenyl nitrones **2b** were completely transformed into the corresponding isoxazolidinones **3a** and **3b** in good 76% and 81% isolated yields, respectively. Product **3b** could not be purified due to its known instability on silica gel but an easy rearrangement into valuable β-amino acid derivatives is achievable under acidic conditions as demonstrated by Zhang and Ying.[6] We subsequently evaluated the rather reactive *N*-Boc nitrone **2c**,[16] easily generated *in situ* by means of 1.2 equivalents of Hünig's base from the corresponding phenylsulfonylalkyl-*N*-hydroxycarbamates **2c′** [1.0 equivalent of $(i\text{-Pr})_2$EtN to trap the liberated sulfinic acid]. Gratifyingly, the catalytically formed Meldrum's acid **1a** anion afforded 63% yield of the corresponding *N*-Boc heterocycle **3c** at room temperature. The known instability of nitrone **2c** might explain why only 12% of product **3c** was formed at 40 °C.[16a] C-Benzyl-Meldrum's acid **1b** furnished the disubtituted compound **3d**, albeit a longer reaction time was required and some decomposition was observed. Pleasingly, the reaction proved to be highly stereoselective as the sole *anti*-diastereoisomer could be detected in the ^{1}H NMR spectrum of the crude product.[5b] This [3+2] cycloaddition type of process was also successful to construct isoxazolidinones derived from electron-poor and electron-rich aromatic aldehydes **3e** and **3f**, together with aliphatic linear or branched ones **3g** and **3h** in good yields. We also evaluated the reaction with nitrones bearing more sensitive functional groups without further optimization. The NHBoc (**3k**)[17] and ester (**3l**) functionalities were tolerated albeit giving moderate yield in the last case, due to the possible hydrolytic sensitivity of the electrophilic nitrone **2k** as testified by its complete transformation. Interestingly, the formal [3+2] cycloaddition sequence took place with acetal-protected D-glyceraldehyde with 73% yield and a 73:27 *anti*/*syn* ratio. This outcome parallels the one previously obtained by Merino and co-worker, who obtained up to 95:5 *anti*/*syn* ratio for the addition of ester enolates but in the presence of a Lewis acid.[8b,18] Eventually, this strategy was applied to the tetrahydroisoquinoline derived nitrone **2m** which yielded heterocycle **3n** with 58% yield at 60 °C, demonstrating the slightly lower reactivity of this cyclic dipole under those conditions.

In order to get an insight into this unique reactivity pattern of Meldrum's acid, we performed a couple of test reactions. First of all, a facile Mannich addition reaction was questioned by means of a more nucleophilic malonate anion, as already mentioned in the literature.[19] Interestingly, a mixture of diethyl malonate with *N*-benzylnitrone **2a** in the presence of either $(i\text{-Pr})_2$EtN or TBD bases (stirred at 40 °C in toluene for two hours) led to the recovery of reactants. Then, we tried to probe the possible fragmentation of Meldrum's acid into highly reactive acylketene species by means of EtOH as trapping nucleophile.[20] Nevertheless, after 22 h at 40 °C in an NMR tube ($CDCl_3$), the ^{1}H NMR spectra did not reveal any decomposition of Meldrum's acid **1a** in the presence of $(i\text{-Pr})_2$EtN and EtOH (1 equivalent for each). In that context, we proposed the following stepwise process (Scheme 2).

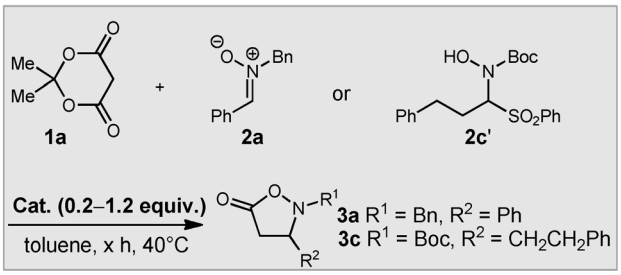


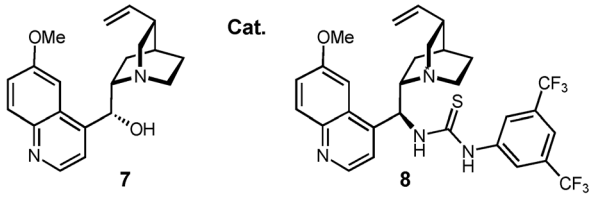
Scheme 2. Mechanistic proposal.

First of all, a formal anionic [3+2] cycloaddition would take place through a Mannich reaction followed by a cyclization event giving rise to **4** (or in a concerted manner).[3a] The obtained tetrahedral intermediate **4** rapidly undergoes a fragmentation to give carboxylate **5** by releasing a molecule of acetone; preventing thereby any equilibrated processes. This domino Mannich–cyclocondensation reaction would explain the difference in reactivity with ethyl malonate which is much more nucleophilic than Meldrum's acid but less prone to undergo an electrophilic addition during the annulation reaction, critical to drive the whole process towards more stable products.[21,22] Moreover, in line with the elegant and recent Grassi's study,[23] involving the reaction between enolizable 1,3-diketone compounds with electron-poor nitrones, we assume an activation of the nitrone through hydrogen bonding with the tertiary ammonium salt.[9b,24] As a matter of fact, the low pK_a of Meldrum's acid ($pK_a = 4.93$ in water) maximizes both concentration and acidity of the ion-pair intermediate **1c** + $(i\text{-Pr})_2$EtNH$^+$.[25] Then, a decarboxylation occurs to form the enolate anion **6**, sufficiently basic to trap the ammonium proton atom and liberating thereby the tertiary amine base for a new catalytic cycle.

Next, we turned our attention to an enantioselective version by means of chiral bases (Table 4). A screening endeavor revealed quinine derivatives as promising organocatalysts (see the Supporting Information). *N*-Benzylnitrone **2a** was transformed into

Table 4. Enantioselective approach.[a]





Entry	Cat. [equiv.]	External base	Yield [%][a]	*ee* [%][b]
1	**7** [0.2][c]	–	79	**3a** 35 (*S*)
2	**8** [0.2][c]	–	56	**3a** 48 (*R*)
3	**7** [1.2][d]	–	99	**3c** 61
4	**8** [1.2][d]	–	99	**3c** 63
5	**7** [0.2][d,e]	K_2CO_3	72	**3c** 43

[a] Isolated yield after purification by column chromatography.
[b] Determined by chiral HPLC.
[c] *Reaction conditions*: Meldrum's acid **1a** (1.5 equiv.), *N*-benzylnitrone **2a** (1 equiv.), catalyst (0.2 equiv.), toluene (0.1 M), 40 °C, 18 h.
[d] *Reaction conditions*: Meldrum's acid **1a** (1.1 equiv.), phenylsulfonylalkyl-*N*-hydroxycarbamate **2c′** (1 equiv.), catalyst (0.2–1.2 equiv.), toluene (0.1 M), room temperature, 3 h.
[e] At 0 °C for 24 h.

isoxazolidinone **3a** with up to 48% *ee* making use of thiourea-derived catalyst **8** (entry 2). Unfortunately, this sterically more demanding catalyst **8** gave lower yields than the corresponding quinine **7** (entries 1 and 2), despite providing higher *ee*. On the other hand, it was found that *N*-Boc nitrone precursor **2c′** was more reactive and provided the corresponding *N*-Boc-isoxazolidinone **3c** with high yields and similar enantiomeric excesses (61–63% *ee*) with both quinine promoters **7** and **8**, used in excess.[16] Thus far, any attempts to promote an organocatalytic process (entry 5), by means of 20 mol% of chiral amine and a stoichiometric mineral base to trap the liberated sulfenic acid, revealed a strong background reaction decreasing the *ee* to 43% albeit maintaining good yields (see the Supporting Information).

In conclusion, we have developed a straightforward and original domino Mannich–cyclocondensation–decarboxylation reaction towards the construction of isoxazolidin-5-one derivatives from a variety of nitrones and Meldrum's acid. This practical formal anionic [3+2] cycloaddition takes place under very mild basic organocatalytic reaction conditions, thanks to the high acidity of Meldrum's acid whose conjugated base behaves as a useful ketene equivalent. The first asymmetric version was demonstrated with quinine derived bases. We are currently carrying out a mechanistic investigation in order to broaden the scope and achieve an effective enantioselective version of this original process.

Experimental Section

Representative Procedure for Isoxazolidin-5-one Synthesis

To a mixture of *N*-benzylnitrone **2a** (0.5 mmol) and Meldrum's acid **1a** (0.75 mmol, 1.5 equiv.) were added toluene (5 mL) and $(i\text{-Pr})_2$NEt (17.4 μL, 0.1 mmol, 20 mol%). The resulting solution was stirred at 40 °C for 18 h, then cooled to room temperature and concentrated under vacuum. The crude product was purified by a column chromatography to give the desired 2-benzyl-3-phenylisoxazolidin-5-one **3a**.

Acknowledgements

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[25] A moderate transformation of nitrone **2a** into isoxazolidinone **3a** was observed with K_2CO_3 as a base, even in the presence of an ammonium phase-transfer catalyst, showing the importance of the deprotonated Meldrum's acid ion-pair structure in action, namely R_4N^+ *vs.* $R_3N{-}H^+$.

