Communication

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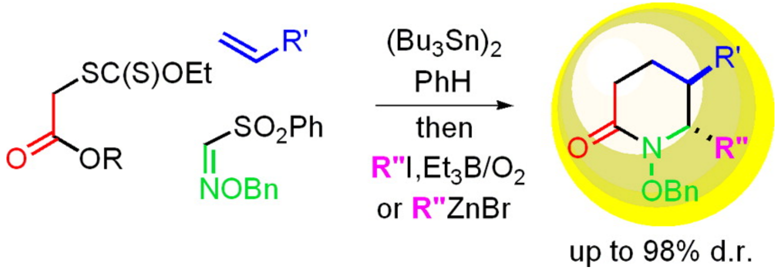

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Multicomponent Radical Processes: Synthesis of Substituted Piperidinones

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Multicomponent reactions (MCR)[1] allow the rapid building up of functionalized molecules in a single operation, with high bond-forming efficiency[2] and minimal functional group manipulations. Although historically these reactions first implied components assembled in an ionic fashion, several MCR have been reported that involve radical processes. Three-[3] and four-[4]component radical reactions have thus been described that demonstrate the high synthetic potential associated with these radical cascades. Combination of radical and ionic processes has also been reported that furnish in a one-pot operation, highly functionalized substrates.[5] In this communication, we report a new and straightforward method for accessing ubiquitous piperidine skeleton **I** in a one-pot operation using such dual mechanisms. The piperidine unit has received considerable attention due to its abundance in naturally occurring and designed targets of biological relevance.[6,7] Our strategy relies on three- and four-component reactions (3-CR and 4-CR) in which **I** is assembled through a formal [2 + 2 + 2]-process,[8] involving a tandem radical intermolecular additions−lactamization sequence, starting from readily available building blocks (Figure 1). The first step would involve the intermolecular reaction between a carbonyl-substituted radical **A** and an olefin **B**, generating a new nucleophilic carboradical which would then be trapped by an appropriate oxime $\mathbf{C_1}$. At this stage, two C−C bonds would be generated upon two intermolecular radical events, the sequence being terminated by the formation of the C−N bond via an irreversible ionic ring closure.[9] It was also envisaged that a careful choice of the unsaturated nitrogen-component, i.e., $\mathbf{C_2}$ would bring the cascade to an even higher degree of complexity through the introduction of a fourth component **D**. In this sequential 4-CR, a control of the C2−C3 relative configuration of the piperidinone through 1,2-stereoinduction may also be envisaged.

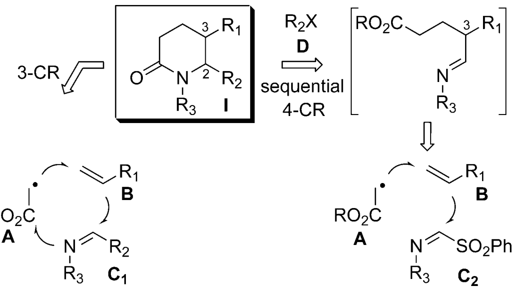
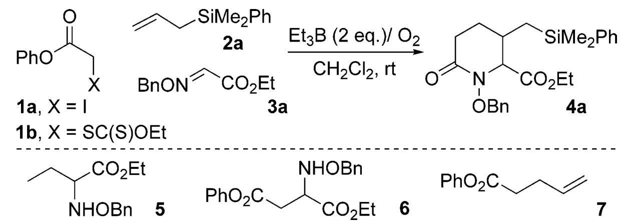


Figure 1. Three- and four-component formal [2 + 2 + 2]-synthesis of piperidinones.

The first part of our study was devoted to the identification of the best reaction conditions and partner's ratios (Table 1). Among the several initiators tested, Et_3B/O_2 in CH_2Cl_2 was found to be the most convenient to promote the radical chain transfer and mediate the lactamization.[10] Ambiphilic radicals **A** are known to react efficiently with activated olefins[11] but also with electron-poor oximes.[12,13] Initial competitive experiments clearly showed that the radical arising either from **1a** or **1b**[14] added faster onto allylsilane **2a** than onto oxime **3a**, only traces of **6** being detected. The second intermolecular process is also involved in competitive additions. We thus found that secondary nucleophilic radicals—formed during the first event—added to **3a** inherently faster than ethyl radicals generated from Et_3B. Eventually, decreasing the proportion of ethyl radicals by repeated minute injections of air led to reduced amounts of undesired **5**. Additional experimentations (Table 1) were then carried out to define the most suitable precursor's ratio. In the presence of an excess of olefin **2a**, xanthate **1b** led to the desired piperidinone **4a** but only in modest yields (entries 1−2). Significantly better yields of **4a** were observed using α-iodoester **1a** (entry 4); however, a small amount of olefin **7** was produced. Formation of **7** only occurs in the presence of an excess of **1a** and likely results from an iodine atom transfer reaction followed by a subsequent β-elimination of $PhMe_2SiI$. This was eventually suppressed by using only 1.5 equiv of **1a** (entry 5). Under these conditions, **4a** was obtained in a notable 74% yield, given the number of crossover products that can be formed.

Table 1. Three-Component Radical Cascade: Preliminary Studies



entry	ester (equiv)	olefin (equiv)	oxime (equiv)	yield[a,b] **4a** (%)	side-products[a] (yield %)
1	**1b** (1)	**2a** (2)	**3a** (2)	35	–
2	**1b** (1)	**2a** (2)	**3a** (1)	43	**5** (18), **6** (12%)
3	**1a** (1)	**2a** (2)	**3a** (2)	47	**5** (25%)
4	**1a** (2)	**2a** (2)	**3a** (1)	71	**6** (12), **7** (17%)
5	**1a** (1.5)	**2a** (2)	**3a** (1)	74	**5** (11)

[a] Isolated yields. [b] dr 1:1.

With the above conditions in hand, the 3-CR was then extended to a series of olefins and oximes (Table 2). Reactive oximes such as **3a** and **3b**[15] provided the desired piperidinones in good yields. As expected, the reaction is more efficient with electron-richer olefins such as **2a**−**c** (entries 1−4) as compared to **2d** (entry 5). Disubstituted olefins such as **2e** led to piperidinones having a quaternary center albeit in modest yield (entry 6).

A sequential 4-CR was then envisioned, based on the utilization of sulfonyl oximes such as **3c**[13] (Scheme 1). It was anticipated that radical addition onto these oximes should be followed by a fast β-fragmentation of the $PhSO_2$ group, resulting in the generation of a new, unactivated oxime that could then be engaged in further reactions with a fourth component. Reaction conditions above were slightly modified for this purpose, i.e. xanthate **1b** was found to provide better yields than **1a**, and $(Bu_3Sn)_2$ instead of Et_3B was

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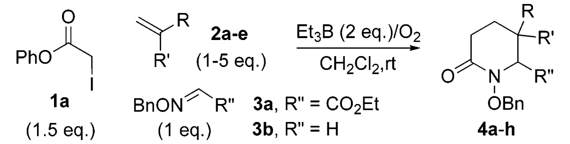
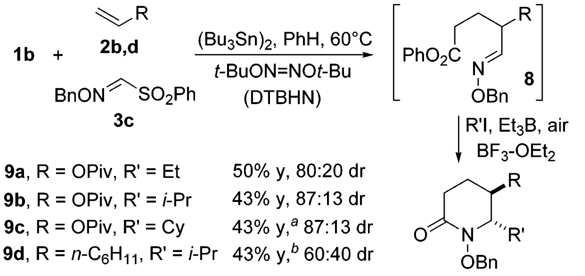
Table 2. Three-Component Radical Cascade



entry	olefin (equiv)	oxime	R	R′	product	yield[a] (%)
1	**2b** (1)	**3a**	OPiv	H	**4b**	64[b]
2	**2b** (5)	**3a**	OPiv	H	**4b**	88[b]
3	**2b** (5)	**3a**	OPiv	H	**4b**	92[b,c]
4	**2c** (2)	**3a**	OAc	H	**4c**	81[b]
5	**2d** (2)	**3a**	n-C_6H_{11}	H	**4d**	32[d]
6	**2e** (2)	**3a**	OAc	Me	**4e**	31[b]
7	**2a** (2)	**3b**	CH_2SiMe_2Ph	H	**4f**	80
8	**2b** (2)	**3b**	OPiv	H	**4g**	55
9	**2b** (20)	**3b**	OPiv	H	**4g**	72
10	**2d** (2)	**3b**	n-C_6H_{11}	H	**4h**	45

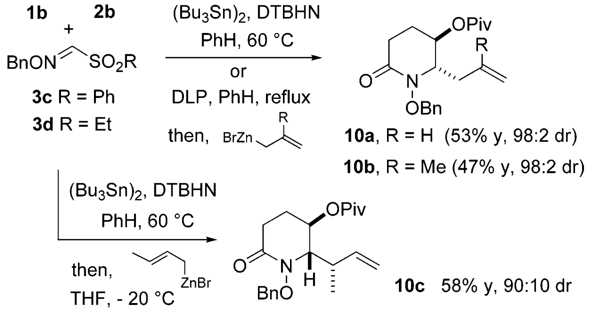
[a] Isolated yields. [b] dr 1:1. [c] Reaction run at −78 °C. [d] dr 3:1.

Scheme 1. Four-Component [2 + 2 + 2]-Radical Cascade



[a] 52% based on recovered **8**. [b] 68% based on recovered **8**.

Scheme 2. Four-Component [2 + 2 + 2]-Radical−Organometallic Cascade



used to sustain the radical chain. Under these conditions, oxime intermediate **8** was obtained[16] and treated in situ with an alkyl iodide and a Lewis acid (BF_3-OEt_2).[17] The expected piperidinones **9a**−**d** were isolated in reasonable overall yield and moderate to good diastereocontrol in favor of the *trans*-diastereomer (Scheme 1).[18,19] Secondary radicals were found to be efficient partners, furnishing higher degrees of stereocontrol.

Organometallic reagents (Scheme 2) were also envisaged as fourth components. Whereas alkyl-lithium and Grignard reagents reacted unselectively with ester and oxime functions, we found that allylzinc reagents added chemoselectively onto the oxime moiety[20] to afford the desired disubstituted piperidinones **10a**−**c** in reasonable overall yield and high level of diastereocontrol.[21] Up to three stereogenic centers (**10c**) could thus be generated in a single-pot operation. It is finally noteworthy to add that the radical cascade can also be conducted under tin-free conditions, using oxime **3d**[13b,14] and DLP as an initiator. Under these conditions, **10a** was obtained in 48% overall yield (7.5:1 dr).

In summary, we have described a cascade reaction with high bond-forming efficiency—up to three C−C bonds and one C−N bond—leading to useful highly substituted piperidinones with up to three stereogenic centers generated in one pot from readily available reagents. The combination of radical cascades and organometallic processes in a single pot displays a high synthetic potential that should attract a substantial interest in the future.

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Supporting Information Available: Experimental and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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