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Cyclization Cascades via *N*-Amidyl Radicals toward Highly Functionalized Heterocyclic Scaffolds

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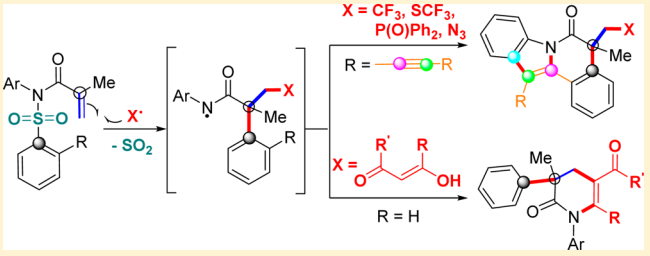
Supporting Information

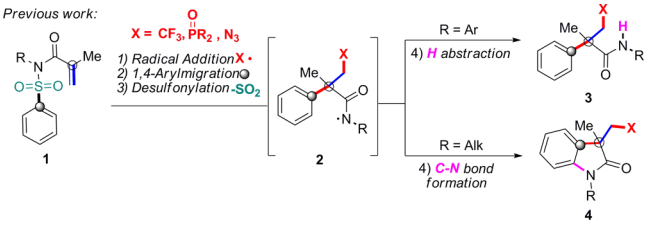
ABSTRACT: The addition of a variety of radicals to the double bond of *N*-(arylsulfonyl)acrylamides can trigger cyclization/aryl migration/desulfonylation cascades via amidyl radical intermediates **2**. Herein, we demonstrate the synthetic utility of these intermediates in subsequent C−C and C−X bond-forming events to rapidly build up molecular complexity. First, we describe a regioselective one-pot synthesis of CF_3-, SCF_3-, $Ph_2(O)P$-, and N_3-containing indolo[2,1-*a*]isoquinolin-6(5*H*)-ones from *N*-[(2-ethynyl)arylsulfonyl]acrylamides through a multi-step radical reaction cascade. The process involves the one-pot formation of four new bonds (one C−X, two C−C, and one C−N), a formal 1,4-aryl migration, and desulfonylation of the starting material. Second, we present a one-pot synthesis of 3,3-disubstituted-2-dihydropyridinones from *N*-(arylsulfonyl)acrylamides and 1,3-dicarbonyl compounds. In this case, a silver-catalyzed radical cascade process involving the sequential formation of two new C−C bonds and one C−N bond, a formal 1,4-aryl migration, and desulfonylation of the starting material explains the regioselective formation of densely functionalized heterocycles in a straightforward manner. Control experiments have unraveled the key intermediates as well as the sequence of individual steps involved in these transformations.



The quest for novel chemical blueprints represents an endeavor of utmost importance in both academia and industry. Although drug development campaigns continue to offer useful clinical candidates for a broad array of pathologies, it is widely accepted that only a small fraction of chemical space has been explored thus far, and new areas will need to be examined in order to tackle "undruggable" targets.[1] As such, novel synthetic methods to assemble unprecedented, highly complex molecular scaffolds are strongly demanded and continue to attract the attention of the synthetic community. Alkenes and alkynes are privileged building blocks, as they allow the simultaneous introduction of different functional groups via addition across the π-C=C[2] or -C≡C[3] bond system. Reactions of substrates endowed with both unsaturated moieties, namely 1,*n*-enynes, have enabled the assembly of elaborate compounds in a highly efficient fashion.[4] On the other hand, radical reaction cascades represent a valuable tool to access densely functionalized structures, as multiple C−C/C−X bond-forming reactions can be orchestrated in a highly selective and functional-group-compatible manner.[5] Beautiful applications of radical reaction cascades can be found in the total syntheses of complex natural products such as scholarisine A[6] or garcibracteatone,[7] to cite some recent examples.

Recently, our group reported the addition of a variety of radicals to the double bond of *N*-(arylsulfonyl)acrylamide substrates **1**.[8] In these transformations, radical addition/aryl migration/desulfonylation cascades were postulated involving the participation of an amidyl radical intermediate, **2**. Depending on the nature of the substituents at the nitrogen atom, different reaction outcomes were observed. Hydrogen abstraction could take place to give α-aryl-β-functionalized amides **3** (*N*-aryl). Alternatively, oxindoles **4** could be regioselectively obtained by reaction with the aromatic ring in the case of the *N*-alkyl-substituted starting materials, as shown in Scheme 1.

Scheme 1. Previously Developed Radical Reaction Cascades



We hypothesized that the amidyl radical intermediates **2** generated *in situ* in these transformations could be engaged in additional bond-forming events in the presence of adequate partners, thus expanding the synthetic utility of these processes. Amidyl radicals, generated either by fragmentation of N−X bonds or by chemical or electrochemical oxidation of amides, have been previously engaged in radical cyclizations mostly involving alkene counterparts.[9] We thus set out to design complex cascade reactions based on these intermediates that

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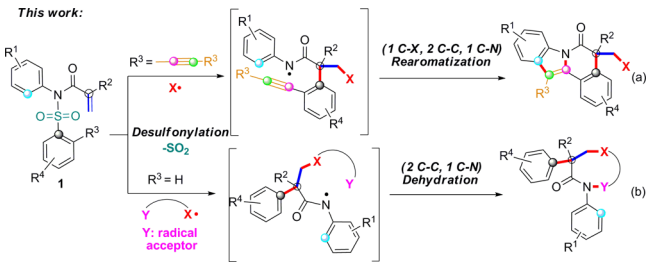
would give access to new structural motifs in a highly controlled manner.

First, we decided to incorporate an alkyne moiety at the *ortho* position relative to the arylsulfonyl group in substrates **1**. Our goal was to engage the amidyl radical intermediate **2** in an additional N−C bond-forming event with the triple bond. The reaction success would be determined by the chemoselectivity (alkene vs alkyne) in the addition of the *in situ*-generated radicals X·, which could be controlled by the electronic nature of the substituents installed on each of these unsaturated moieties (Scheme 2a).

Scheme 2. Envisaged New Reactivity of *N*-Amidyl Radicals



Second, we speculated that the addition of difunctional C-centered radicals such as 1,3-dicarbonyl compounds, capable of simultaneously acting as both radical donors and acceptors, to the acrylamide moiety could yield additional C−C and C−N bond-forming reactions with the amidyl radical **2** to produce densely functionalized heterocycles (Scheme 2b).

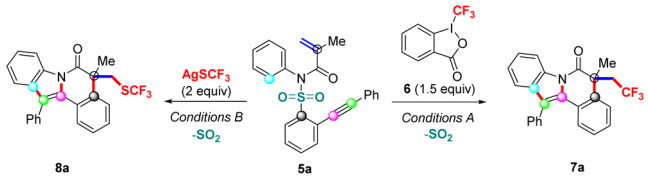
Herein we present the realization of these concepts via two different radical reaction cascades which enabled the one-pot synthesis of two scaffolds, namely, indolo[2,1-*a*]isoquinolin-6(5*H*)-ones and 3,3-disubstituted-dihydropyridinones, with unprecedented substitution patterns in a completely regioselective manner. In addition, to unravel the nature of the productive reaction intermediates involved in these transformations, control experiments and mechanistic probes were designed, and the results of these investigations will also be presented.

RESULTS AND DISCUSSION

Reactivity of *N*-(Aryl)[(2-ethynyl)arylsulfonyl]-acrylamides. *Optimization of the Reaction Conditions.* On the outset, *N*-(aryl)[(2-ethynyl)arylsulfonyl]acrylamide **5a** was selected as benchmark substrate to explore the addition of diverse *in situ*-generated radicals. As the development of methods to incorporate C−F bonds in relevant building blocks has recently attracted a lot of attention based on the improved pharmacological properties observed for F-containing molecules compared to their non-fluorinated analogues, we decided to start our investigation targeting the incorporation of CF_3[10] and SCF_3[11] moieties. As such, the reaction of substrate **5a** with Togni's reagent **6**[12] in the presence of different copper salts in acetonitrile as solvent was investigated first.[13]

Using 20 mol% of both $Cu(MeCN)_4PF_6$ and 2,2′-bipyridine ligand, we were pleased to observe the clean formation of indolo[2,1-*a*]isoquinoline **7a** together with some unreacted starting material (Table 1, entry 1). Cu_2O did not yield full conversion of **5a** either (Table 1, entry 2). However, an increased load of both catalyst and ligand delivered trifluoromethylated isoquinolinone **7a** in 64% yield with full consumption of the starting material (Table 1, entry 3).

Table 1. Optimization of the Reaction Conditions



entry	reaction conditions[a]	additives	product, conversion (yield, %)[b]
1	A	$Cu(MeCN)_4PF_6$ (20%), 2,2′-Bipy (20%)	**7a**, <100
2	A	Cu_2O (25%), 2,2′-Bipy (50%)	**7a**, <100[c]
3	A	Cu_2O (40%), 2,2′-Bipy (40%)	**7a** (64)
4	**A**	**Cu_2O (25%), 2,2′-Bipy (50%)**	**7a (70)**
5	B	$K_2S_2O_8$ (3 equiv), HMPA (50%) in CH_2Cl_2	**5a**
6	B	$K_2S_2O_8$ (3 equiv), HMPA (50%) in DMF	**8a**, <100
7	B	$K_2S_2O_8$ (3 equiv), HMPA (50%) in CH_3CN	**8a** (59)[d]
8	B	as entry 7, $K_2S_2O_8$ (1.5 equiv)	**8a** (64)
9	B	as entry 7, HMPA (25%)	**8a** (66)
10	**B**	**$K_2S_2O_8$ (1.5 equiv), HMPA (25%) in CH_3CN**	**8a (66)**[e]

[a]Reaction conditions A: **5a** (1 equiv), **6** (1.5 equiv), MeCN (0.05 M), 80 °C, 20 h. Reaction conditions B: **5a** (1 equiv), $AgSCF_3$ (2 equiv), solvent (0.05 M), 75 °C, 20 h. [b]Isolated yield after column chromatography in silica gel with 100% conversion of the starting material. [c]Reaction performed in DMF. [d]Reaction carried out at 0.1 M. [e]$AgSCF_3$ (1.5 equiv)

Finally, fine-tuning the ratio between catalyst and ligand allowed us to isolate **7a** in 70% yield as shown in Table 1, entry 4. With the optimized conditions in hand for the trifluoromethylation reaction, we set out to explore the addition of trifluoromethylthio radicals using $AgSCF_3$.[14] In the presence of $K_2S_2O_8$ (3 equiv) and 50 mol% of HMPA in refluxing CH_2Cl_2 only starting material could be detected (Table 1, entry 5). In contrast, the reaction in both DMF and acetonitrile showed the clean formation of **8a**, although only with full conversion of the starting material in the latter case (Table 1, entries 6 and 7). The reaction proved to be amenable to a decrease of both $K_2S_2O_8$ and HMPA, as shown in entries 8 and 9. Finally, 1.5 equiv of $AgSCF_3$ and $K_2S_2O_8$ and 25 mol% of HMPA sufficed to produce the desired trifluoromethylthiolated isoquinolinone **8a** in an optimal 66% yield (Table 1, entry 10).

Indolo[2,1-*a*]isoquinolines constitute a privileged scaffold present in a wide variety of natural compounds and pharmaceuticals.[15] Molecules containing this valuable motif have been reported to exert tumor inhibition, anti-inflammatory, anti-bacterial, and anti-fungal activities among many others, but efficient methods to access densely functionalized forms of this scaffold are scarce.[16] Thus, given the efficiency of our radical cascade to produce highly functionalized derivatives of this type of compounds, we decided to explore the scope of this reaction.

Reaction Scope. With the optimized reaction conditions for both trifluoromethylation and trifluoromethylthiolation processes in hand, first we set out to explore the substrate scope. Acrylamides bearing an electron-donating group (methyl and methoxy) at the *para* position of the aromatic ring directly bound to the N-atom produced the corresponding trifluoromethyl- and trifluoromethylthio-substituted indolo[2,1-*a*]-

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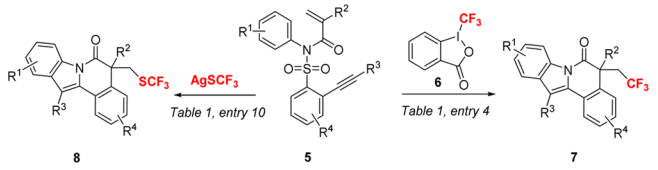
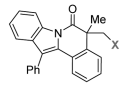
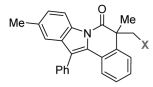
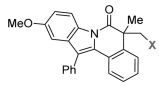
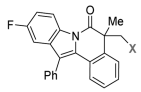
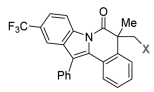
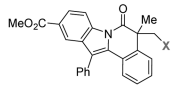
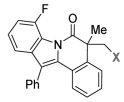
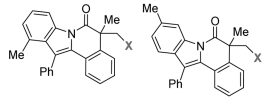
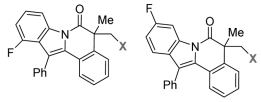
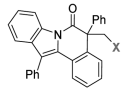
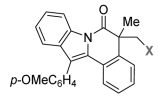
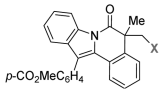
Table 2. Reaction Scope[a,b]



Entry	React. Cond.	Substrate[a]	Product[b]	Product (yield,%)[c]
1	A	**5a**, R^2 = Me, R^3 = Ph		**7a**, X = CF_3 (70)
2	B			**8a**, X = SCF_3 (66)
3	A	**5b**, R^1 = *p*-Me, R^2 = Me, R^3 = Ph		**7b**, X = CF_3 (60)
4	B			**8b**, X = SCF_3 (63)
5	A	**5c**, R^1 = *p*-OMe, R^2 = Me, R^3 = Ph		**7c**, X = CF_3 (46)
6	B			**8c**, X = SCF_3 (61)
7	A	**5d**, R^1 = *p*- F, R^2 = Me, R^3 = Ph		**7d**, X = CF_3 (69)
8	B			**8d**, X = SCF_3 (73)
9	A	**5e**, R^1 = *p*-CF_3, R^2 = Me, R^3 = Ph		**7e**, X = CF_3 (54)
10	C			**7e**, X = CF_3 (51)
11	B			**8e**, X = SCF_3 (65)
12	A	**5f**, R^1 = *p*-CO_2Me, R^2 = Me, R^3 = Ph		**7f**, X = CF_3 (67)
13	B			**8f**, X = SCF_3 (68)
14	A	**5g**, R^1 = *o*-F, R^2 = Me, R^3 = Ph		**7g**, X = CF_3 (53)
15	C			**7g**, X = CF_3 (56)
16	B			**8g**, X = SCF_3 (56)
17	A	**5h**, R^1 = *m*-Me, R^2 = Me, R^3 = Ph		**7h**, X = CF_3 (54)[d]
18	B			**8h**, X = SCF_3 (61)[d]
19	A	**5i**, R^1 = *m*-F, R^2 = Me, R^3 = Ph		**7i**, X = CF_3 (54)[e]
20	B			**8i**, X = SCF_3 (61)[e]
21	A	**5j**, R^2 = R^3 = Ph		**7j**, X = CF_3 (69)[f]
22	B			**8j**, X = SCF_3 (65)
23	A	**5k**, R^2 = Me, R^3 = *p*-OMePh		**7k**, X = CF_3 (61)
24	B			**8k**, X = SCF_3 (60)
25	A			**7l**, X = CF_3 (70)
26	B	**5l**, R^2 = Me, R^3 = *p*-CO_2MePh		**8l**, X = SCF_3 (60)

[a]Unless otherwise stated, R^x = H. [b]Conditions A: Table 1, entry 4. Conditions B: Table 1, entry 10. Conditions C: Togni's reagent **6** (2 equiv), nBu_4NI (50 mol%), MeCN, 0.05 M, 80 °C, 20 h (ref 8b). [c]Isolated yield after column chromatography. [d]Mixture of regioisomers: 2.6:1. [e]Mixture of regioisomers: 2.8:1 [f]Reaction performed at 60 °C.

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isoquinolin-6(5*H*)-ones **7b,c** and **8b,c** in good yields, respectively (Table 2, entries 3−6).

The presence of electron-withdrawing substituents (fluorine, trifluoromethyl, methylcarboxylate) at this position seemed to improve the efficiency of the reaction, as the corresponding products **7d−f** and **8d−f** could be isolated in slightly higher yields (Table 2, entries 7−13). Interestingly, the metal-free trifluoromethylation reaction of compound **5e** delivered **7e** in comparable yield to that of the copper catalyzed one (Table 2, entry 10).[8b] An *ortho*-F substituent was also well tolerated, so copper and metal-free conditions delivered compound **7g** as single regioisomer in 53 and 56% yield, respectively (Table 2, entries 14 and 15). Trifluoromethylthiolated product **8g** could also be obtained in 56% yield (Table 2, entry 16). Substrates bearing substituents at the *meta* position relative to the N-atom were also prepared. Thus, *m*-methyl- and *m*-fluoro-substituted substrates **5h,i** delivered the trifluoromethyl and trifluoromethylthiolated products as a ca. 2.5:1 mixture of regioisomers as the new C−C bond formation can occur at both *ortho* and *para* positions relative to the methyl or fluorine group, respectively (Table 2, entries 17−20).

Variations in the substitution pattern of the acryl moiety were also sought. Substrate **5j** bearing a phenyl group at C1 of the Michael acceptor unit was efficiently transformed into the corresponding indolo-isoquinolinone derivatives **7j** and **8j** (Table 2, entries 21 and 22). The influence of the substituent at the alkyne moiety was also investigated. Aromatic rings bearing both electron-donating (methoxy) and electron-withdrawing groups (methylcarboxylate) in the *para* position were well tolerated giving the corresponding trifluoro- and trifluoromethylthiolated tetracycles **7k,l** and **8k,l** in good yields respectively (Table 2, entries 23−26). Finally, modifications in the arylsulfonyl moiety (substrates **5m−o**) were also studied proving to be amenable to the above-mentioned conditions as shown in entries 27−32.

The structure of the product **7a** could be confirmed by X-ray diffraction analysis (Figure 1).[17]

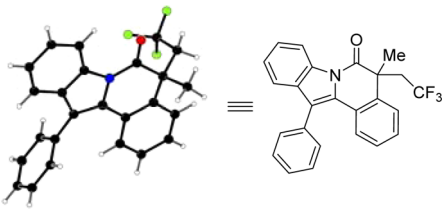
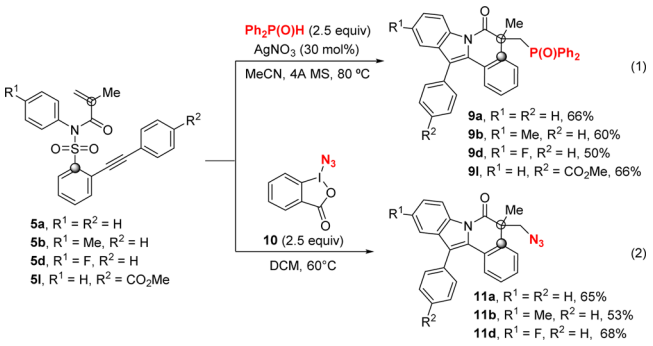


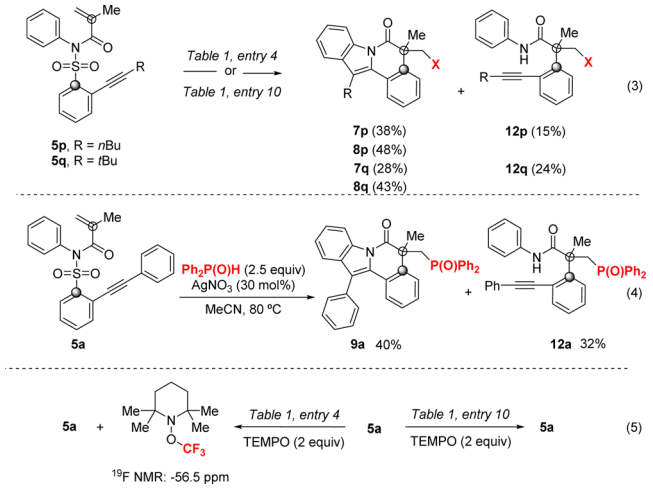
Figure 1. X-ray diffraction analysis of product **7a**.

To expand the synthetic utility of this methodology, the introduction of additional heteroatom-centered radicals was investigated. To our delight, the reaction of substrates **5a**, **5b**, **5d**, and **5l** with 30 mol% of $AgNO_3$ and 2.5 equiv of $Ph_2P(O)H$ in acetonitrile at 80 °C in the presence of 4 Å molecular sieves (reaction conditions previously optimized for the *in situ* generation of a phosphonyl radical under silver catalysis)[8c] afforded the clean formation of products **9a**, **9b**, **9d**, and **9l** in synthetically useful yields as shown in eq 1. The reaction of these substrates with 1-azido-1,2-benziodoxol-3-(1*H*)-one **10**[18] furnished the corresponding N_3-containing products **11a**, **11b**, and **11d** in 65, 53, and 68% yield, respectively (eq 2).

Control Experiments. The results summarized in Table 2 seemed to indicate that the ability of amidyl radical intermediates to interact with the alkyne moiety was rather



influenced by the substitution pattern in the aromatic ring directly connected to the N-atom and not so strongly by the electronic nature of the aromatic substituents in the acetylene moiety (compare entries 5,6 with entries 7,8 and entries 23,24 with entries 25,26 in Table 2). We thus decided to evaluate the effect of alkyl substituents at the terminal position of the triple bond. Interestingly, in the presence of Togni's reagent **6** under the standard reaction conditions (Table 1, entry 4), substrates **5p,q** delivered the corresponding trifluoromethylated indolo-[2,1-*a*]isoquinolines **7p,q** in 38 and 28% yield, respectively (eq 3). In these reactions, *α*-aryl-*β*-trifluoromethyl amides **12p** and



12q could also be obtained in 15 and 24% yield, respectively. In contrast, under the standard trifluoromethylthiolation conditions (Table 1, entry 10), **8p** and **8q** were the only products observed but the efficiency of the process was diminished compared to the arylethynyl-substituted substrates presented in Table 2. Interestingly, a detailed analysis of the reaction mixture stemming from substrate **5a** under the phosphonylation conditions reported in eq 1 but in the absence of molecular sieves was also revealing: in addition to the expected product **9a**, the corresponding *α*-aryl-*β*-phosphonylated amide **12a** could be isolated in 32% yield (eq 4). Amide products **12a**, **12p**, and **12q** seem to confirm the involvement of amidyl radical intermediates in the transformations yielding the tetracyclic isoquinoline products **7** and **8**.

Finally, the reactions of substrate **5a** under the standard conditions reported in Table 1 (entries 4 and 10) were carried out in the presence of 2 equiv of TEMPO (eq 5). In both cases, no conversion to the expected products **7a** or **8a** was observed, and only the starting materials were recovered. In addition, in the first of these reactions, the TEMPO−CF_3 adduct could be detected by both GC-MS (225.16) and ^{19}F NMR (−56 ppm).

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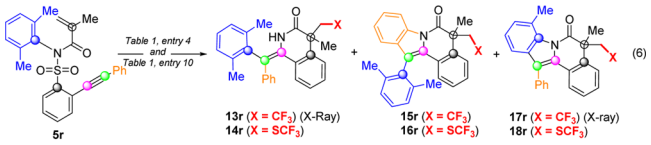
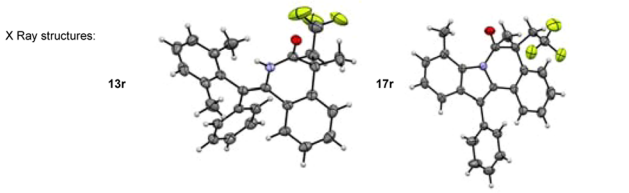
TEMPO−SCF_3 adduct proved to be more labile and could not be detected under the reaction conditions.[14] These experiments seem to substantiate the hypothesis of radical intermediates along the reaction pathway.

To gain additional insight into the reaction mechanism, an *o,o*-dimethyl-substituted aniline substrate, **5r**, was prepared and submitted to the standard trifluoromethylation and trifluoromethylthiolation conditions (eq 6). Although in low yields,[13]



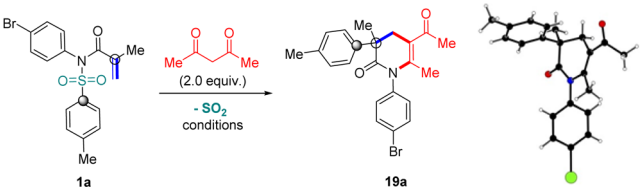


three different scaffolds—**13,14r**, **15,16r**, and **17,18r**—could be isolated from the reaction mixtures. X-ray diffraction analyses of two of these compounds, **13r** and **17r**,[19] and extensive spectroscopic analysis of **15r** and **16r** allowed the unambiguous confirmation of their structure. The formation of compounds **13r** and **14r** can be explained by an unusual 1,3-aryl migration of the *o,o*-dimethylbenzene ring from the N-atom to the terminal C-atom of the alkyne.[20] In contrast, compounds **15−18r** reflect intriguing additional cyclization events of the N-atom either onto the arene moiety originally attached to the alkyne (**15r,16r**) or onto the *o,o*-dimethyl-substituted benzene ring (**17r,18r**) with concomitant loss of one of the methyl substituents in the latter case.[21]

Addition of 1,3-Dicarbonyl Compounds to *N*-(Aryl)-(arylsulfonyl)acrylamides. Once the addition of different radicals onto *N*-(aryl)[(2-ethynyl)arylsulfonyl]acrylamides **5** had been explored confirming the reactivity of *in situ*-generated amidyl radical intermediates toward alkynes, we turned our attention toward the addition of difunctional C-centered radicals onto the parent *N*-(aryl)(arylsulfonyl)acrylamide substrates **1**. We speculated that the use of 1,3-dicarbonyl compounds, capable of simultaneously acting as both radical donors and acceptors, could trigger additional C−C and C−N bond-forming reactions with the postulated amidyl radical intermediates enabling the synthesis of alternative densely functionalized heterocycles (Scheme 2b). 1,3-Dicarbonyl compounds have been previously successfully utilized in cascade reactions leading to complex molecular scaffolds.[22] Metal-free[23] as well as transition-metal-mediated[24] oxidative couplings of the methylene Csp^3−H bond in 1,3-dicarbonyl compounds with other partners, have been reported in the past few years. At the outset of many of these transformations, radical intermediates were proposed.[5c−e,g]

Optimization of the Reaction Conditions.[13] *N*-(4-Bromophenyl)-*N*-tosylmethacrylamide (**1a**) and pentane-2,4-dione were used as benchmark substrates to search for the optimal reaction conditions. Complex mixtures were obtained in the reaction of these two starting materials with *tert*-butyl hydroperoxide (TBHP, 2 equiv) in the presence of catalytic amounts of protic or Lewis acids (Table 3, entry 1).

Table 3. Optimization of the Reaction Conditions



entry	reaction conditions	yield of **19a**[a] (%)
1	TBHP (2 equiv), TsOH or $FeCl_2$ or $Cu(OTf)_2$ (10 mol %), DCM, 60 °C	complex mixture
2	$K_2S_2O_8$ (2.0 equiv), $AgNO_3$ (10 mol %), MeCN/H_2O = 1/1, 50 °C	60
3	$K_2S_2O_8$ (1.5 equiv), $AgNO_3$ (10 mol %), MeCN/H_2O = 1/1, 50 °C	42
4	$K_2S_2O_8$ (2.0 equiv), $AgNO_3$ (10 mol %), MeCN or H_2O, 50 °C	–[b]
5	**$K_2S_2O_8$ (2.0 equiv), $AgNO_3$ (10 mol %), MeCN/H_2O = 4/1, 50 °C**	**73 (70)**
6	$(NH_4)_2S_2O_8$ (2.0 equiv), $AgNO_3$ (10 mol %), MeCN/H_2O = 4/1, 50 °C	66

[a] ^{1}H NMR yield. In brackets, isolated yield after column chromatography in silica gel. [b] No conversion was observed in pure MeCN or pure H_2O.

In contrast, treatment of **1a** in the presence of $AgNO_3$ (10 mol%) and $K_2S_2O_8$ (2 equiv) in a mixture MeCN−H_2O (1:1) at 50 °C for 16 h, afforded 3-methyl-3p-tolyl dihydropyridinone **19a** in 60% yield (Table 3, entry 2). The structure of **19a** could be confirmed by X-ray diffraction analysis.[25] Further control experiments showed that an excess of $K_2S_2O_8$ (2 equiv) was necessary for a productive reaction outcome (Table 3, entry 3). Single solvent systems (water or MeCN) were also tested; however, no conversion of the starting material was observed likely due to the lack of solubility of the substrate and the oxidant in water and MeCN, respectively (Table 3, entry 4). A 4:1 MeCN−H_2O mixture proved to be the best solvent system furnishing the desired product **19a** in 70% yield (Table 3, entry 5). Different oxidants including $(NH_4)_2S_2O_8$ were tested but they proved to be unable to increase the yield of the product (Table 3, entries 6).[13]

Reaction Scope. With the optimized conditions in hand (Table 3, entry 5), the substrate scope of this transformation was explored (Tables 4 and 5). First, the substitution pattern on the aromatic ring directly linked to the N-atom in **1** (R^1, head of Table 4) was evaluated. *N-p*-Bromophenyl- and *p*-methoxyphenyl-substituted arylsulfonamide substrates were efficiently transformed into the corresponding products **19a** and **19b** in 70 and 68% yield, respectively. *Ortho*-substitution was well-tolerated and substrates bearing di- and trimethoxy-substituted aromatic rings afforded the corresponding products (**19c−e**) in good yields. Electron-donating substituents (methoxy or *tert*-butyl) or the presence of hydrogen at the *para* position of the arylsulfonyl group yielded the expected products (**19f−h**), with comparable levels of efficiency as single regioisomers. When both aromatic rings were substituted with methoxy groups the product **19i** was isolated in 63% optimal yield. *o*-Bromophenylsulfonyl-substituted substrate **1j**, afforded the corresponding product **19j** in 58% yield.

When the reaction was carried out with substrate **1k** (*o*-methyl-substituted), the product **19k** could be isolated in 24% yield. Additionally, amide **20k** was also recovered in 26% yield from the reaction mixture. An efficient transformation was also

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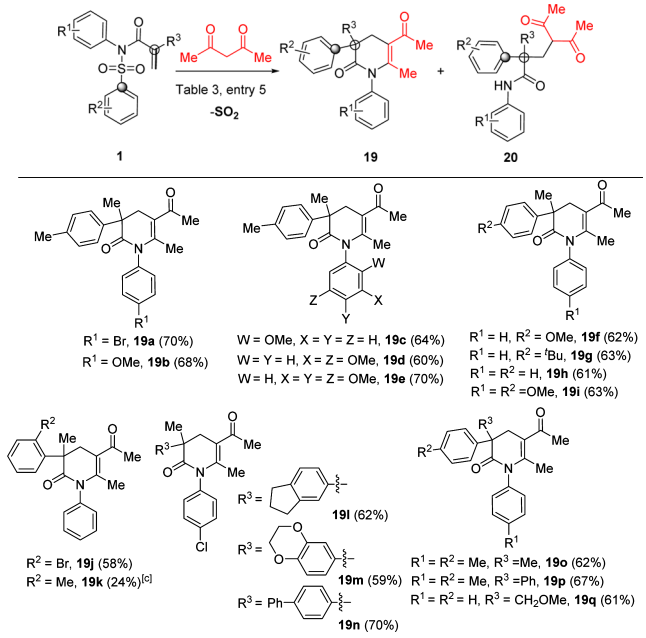
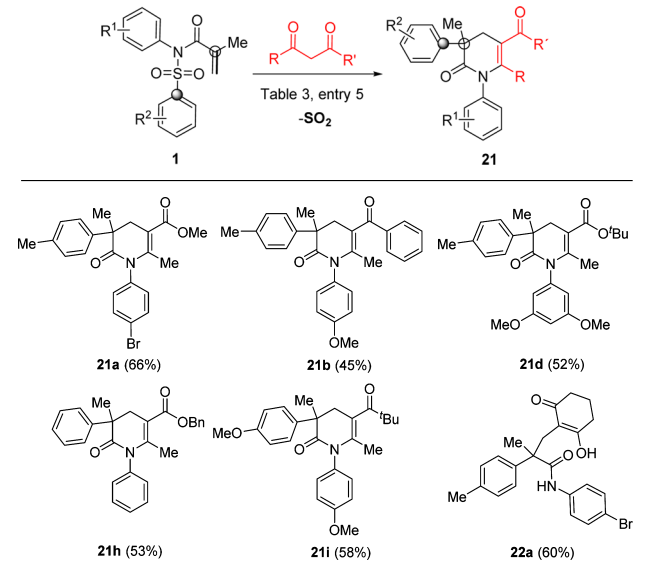
Table 4. Reaction Scope toward the Synthesis of Dihydropyridinones 19 from Substituted *N*-(Arylsulfonyl)acrylamides 1[a,b]



[a]Reaction conditions: Same as Table 3, entry 5. [b]The value in brackets shows the isolated yield after column chromatography in silica gel. [c]The corresponding amide, **20k** was isolated in 26% yield.

Table 5. Reaction Scope with Different 1,3-Dicarbonyl Compounds[a,b]

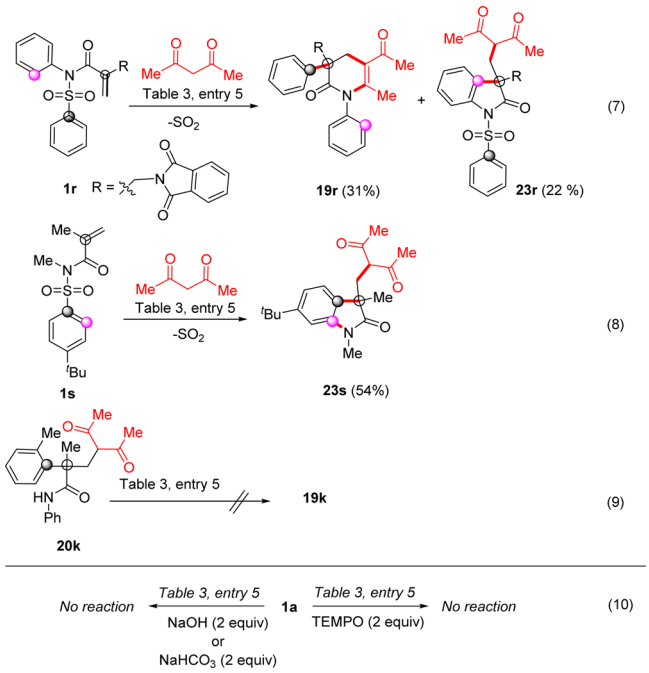


[a]Reaction conditions: Same as Table 3, entry 5. [b]The value in brackets shows the isolated yield after column chromatography in silica gel.

achieved with more elaborated indane-, 1,4-benzodioxolane-, or *p*-phenylbenzene-sulfonyl-substituted substrates (**19l–n**). Finally, acrylamides bearing methyl, phenyl, and methoxymethyl substituents at the internal position of the alkene moiety afforded the products **19o–q** in synthetically useful yields. Unfortunately, the reaction of substrates bearing trisubstituted alkenes did not afford the desired dihydropyridinones under the standard reaction conditions.

Next, different 1,3-dicarbonyl compounds were tested (Table 5). *β*-Ketoesters delivered exclusively products **21a**, **21d**, and **21h** stemming from the chemoselective attack of the N-atom on the keto-carbonyl group. In addition, in the case of non-symmetrically substituted 1,3-diketone substrates, only one regioisomer resulting from the attack at the less hindered C=O group was detected in the reaction media (**21b** and **21i**). When a cyclic 1,3-diketone was used, **22a** was exclusively observed and could be isolated in 60% yield. In this case, likely due to steric reasons, the formation of an N–H bond is favored compared to the reaction with the carbonyl group affording *α*-aryl-*β*-functionalized amide **22a**.

Control Experiments. Interestingly, the reaction of a 2-*N*-phthalimide-substituted substrate **1r** afforded the expected compound **19r**, together with oxindole **23r** in 31 and 22% yield, respectively (eq 7). Compound **23r** is generated as a



result of a new $Csp^2–Csp^3$ bond at the *ortho* position relative to the N-atom, a reactivity commonly found in the carbodifunctionalization of *N*-aryl-substituted acrylamide substrates.[26] The nature of the substituent on the N-atom proved to be crucial to obtain the desired reactivity. Thus, an *N*-alkyl-substituted arylsulfonyl substrate **1s** delivered indole **23s** in 54% yield in a complete regioselective manner. In this case, due to the presence of a more electron-donating alkyl moiety on the N-atom, the formation of a new $N–Csp^2$ bond is favored over the reaction of the N-atom with the carbonyl group (eq 8).

When amide **20k** was submitted to the standard reaction conditions no conversion into dihydropyridinone **19k** was observed thus suggesting that amides are not intermediates in the formation of the observed products (eq 9). Additional control experiments were conducted to investigate the mechanism governing these transformations. The reaction was suppressed upon addition of TEMPO to the reaction mixture, thus suggesting the intervention of radical intermediates along the reaction pathway. Moreover, no desired product was observed when stoichiometric amount of base like NaOH or $NaHCO_3$ were used. These results suggested that the reaction is favored in slightly acidic medium (eq 10).

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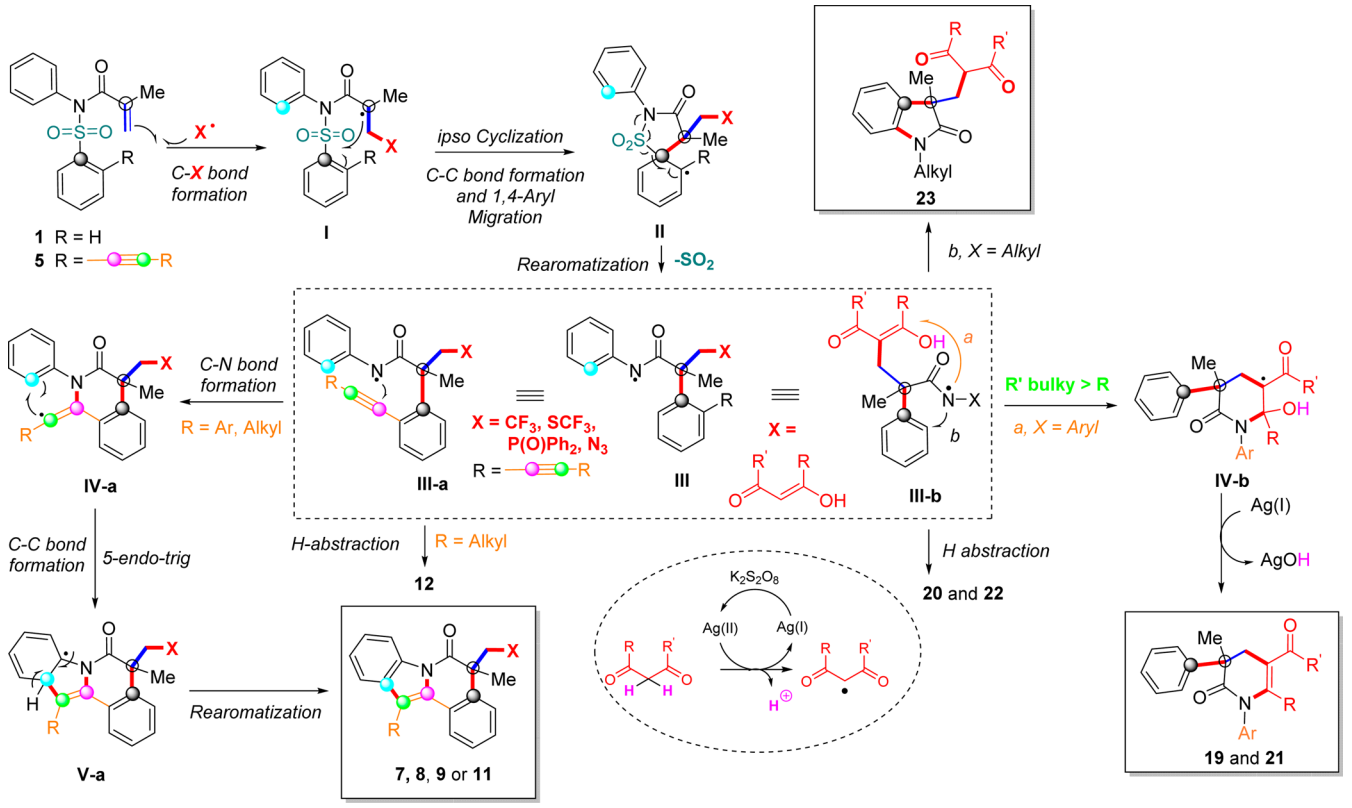
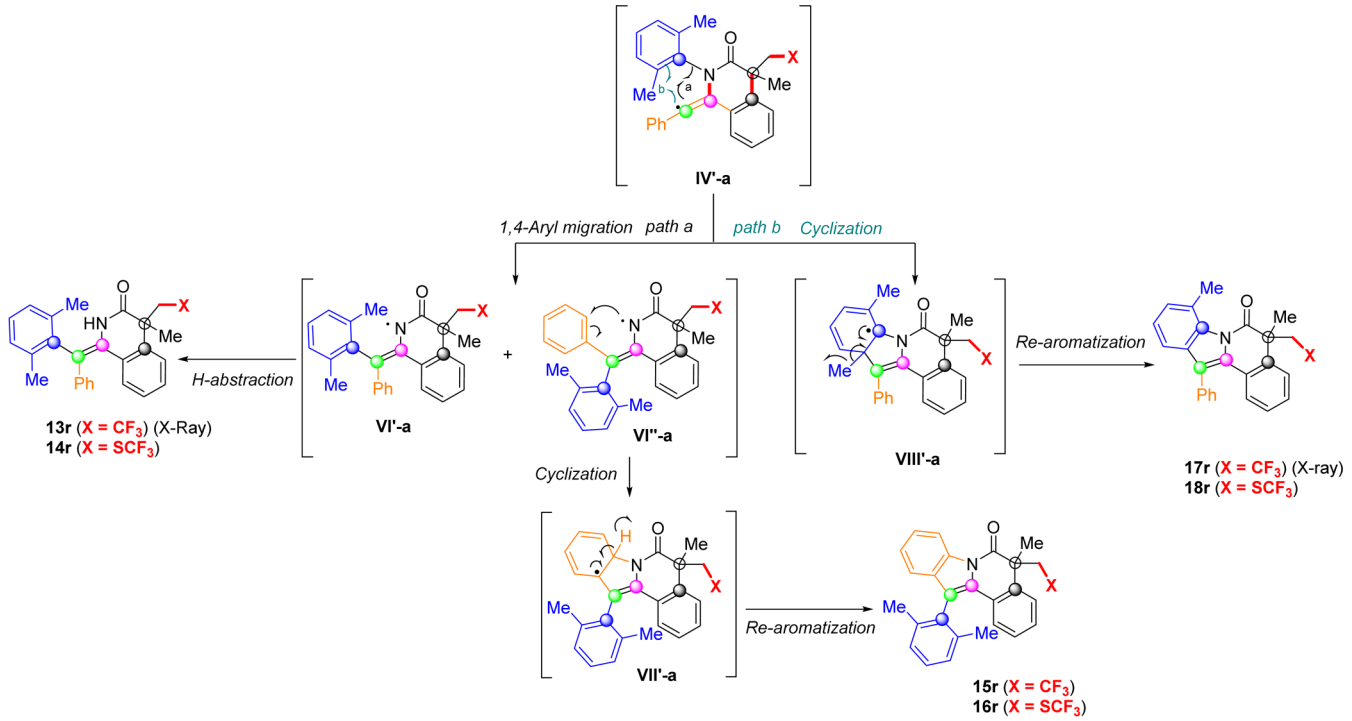
Scheme 3. Mechanistic Proposal



Scheme 4. Mechanistic Proposal To Explain the Formation of Products 13r−18r



Mechanistic Proposal. A mechanistic proposal for the transformations described above is presented in Scheme 3. At the outset of these processes, an *in situ*-generated radical X· (X· = ·CF_3, ·SCF_3, ·$P(O)Ph_2$, ·N_3, ·$CH(COR)_2$) reacts chemoselectively with the acrylic moiety of *N*-acrylamide substrates **1** and **5**, forming a new Csp^3−X bond and an α-carbonyl radical intermediate **I**. Next, an *ipso*-cyclization onto the Csp^2−SO_2 atom takes place, generating a spirocyclic intermediate **II** in a new C−C bond-forming event. Upon re-aromatization, SO_2 is expelled, and amidyl radical intermediate **III** is generated *in situ*, involving the concomitant 1,4-migration of the aryl sulfonyl group[27,28] in a Smiles-type rearrangement reaction.[29] *N*-Amidyl

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radicals are considered to be electrophilic, adopting a π-configuration in its ground state (i.e., single electron located in a p orbital perpendicular to the plane of the molecule).[30] Although addition of amidyl radicals to triple bonds is rare, experimental and computational evidence points toward a kinetically feasible reaction.[31]

The presence of a vicinal alkyne moiety in substrates **5** results in a cyclization of amidyl radical **III-a** to form a new N−Csp^2 bond and a vinyl radical intermediate **IV-a**. This intermediate undergoes an additional cyclization to assemble the tetracyclic product via Csp^2−Csp^2 bond formation. Upon re-aromatization of intermediate **V-a**, the observed indolo[2,1-*a*]isoquinolin-6(5*H*)-one products **7** (X = CF_3), **8** (X = SCF_3), **9** (X = $P(O)Ph_2$), and **11** (X = N_3) were formed (Scheme 3, left).

When 1,3-dicarbonyl compounds were added to *N*-acrylamide substrates **1**, initial proton abstraction is proposed to give a C-centered radical likely involving a Ag(I)−Ag(II) catalytic cycle in the presence of $K_2S_2O_8$ as stoichiometric oxidant. This stabilized C-centered radical undergoes addition onto the acrylate moiety of **1** to afford an α-keto radical **I**. The amidyl radical intermediate **III-b** (*N*-aryl) is proposed to react with the less bulky carbonyl group present in the molecule, which under the reaction conditions might be present in its enol form (see compound **22a** in Table 5 and control experiments in eq 10). As a result, intermediate **IV-b** is produced, which undergoes elimination of the OH group to give the desired pyridinones **19** and **21** as shown in the right-hand side of Scheme 3. Alternatively, intermediate **III-b** can evolve via H abstraction (explaining the formation of **20k** and **22a**) or cyclize onto the vicinal aromatic group (for *N*-alkyl) explaining the formation of oxindole **23s** respectively.

As already reported,[8] different reaction outcomes can arise depending on the substituents on the N-atom of the amidyl radical (*N*-alkyl vs *N*-aryl). Previous studies on the kinetics of cyclization of amidyl radicals with alkenes by Newcomb and Moeller[32] reveal an up to 3−4 orders of magnitude lower reactivity for anilidyl radicals (*N*-aryl) vs the standard amidyl (*N*-alkyl) radical, which might explain why in certain cases, for anilidyl radicals H abstraction to give the corresponding amides competes with the cyclization thus yielding compounds **12**, **20**, and **22**.[33] In the case of the more reactive *N*-alkyl amidyl radicals, a 5-*endo-trig* cyclization seems to be favored delivering, exclusively, oxindole **23s**.

Interestingly, the presence of the two methyl groups in *ortho*-position of the aniline seems to favor alternative reaction pathways as shown in eq 6 with the formation of products **13**−**18r**. As shown in Scheme 4, the α-aryl vinyl radical intermediate **IV′-a**, likely existing in linear form,[34] can trigger a 1,4-aryl migration via pathway a,[20,27,28] producing two geometrical isomers of anilidyl radical intermediates **VI′-a** and **VI″-a**. H-abstraction from the reaction media in the former will deliver compounds **13r** and **14r** as single stereoisomers. Alternatively, *E*-isomer **VI″-a** can engage in an additional cyclization with the phenyl group originally attached to the alkyne unit, delivering, upon re-aromatization, compounds **15r** and **16r**. Vinyl radical intermediate **IV′-a** can also evolve via pathway b in which cyclization takes place at the methyl-substituted C-atom of the aniline moiety to produce intermediate **VIII′-a**, which upon re-aromatization and a rare methyl extrusion[35] provides compounds **17r** and **18r**. Although isolated in low yields, these set of molecules seem to confirm the proposed radical pathways operating in these transformations and the exquisite control on the selectivity of the individual steps operating in the reactions described in Tables 2, 4, and 5, despite the numerous alternative manifolds.

CONCLUSIONS

In summary, two one-pot syntheses of highly functionalized heterocycles are presented here. Tetracyclic trifluoromethyl-, trifluoromethylthio-, phosphonyl-, and azidyl-substituted indolo[2,1-*a*]isoquinolin-6(5*H*)-ones can be obtained from *N*-[(2-ethynyl)arylsulfonyl]acrylamides. The chemoselective addition of an *in situ*-generated radical to the activated double bond is able to trigger a multi-step radical reaction cascade, yielding the observed products in an efficient complexity-building process. The reaction enables a remarkable number of highly selective bond-forming/breaking events; namely, four new bonds (Csp^3−X, Csp^3−Csp^2 with concomitant 1,4-aryl migration and desulfonylation, N−Csp^2, and finally a new Csp^2−Csp^2) are formed in a single synthetic operation.

A silver-catalyzed radical reaction cascade enabling the efficient, one-pot, regioselective synthesis of unprecedented 3,3-disubstituted-2-dihydropyridinones from *N*-(arylsulfonyl)-acrylamides is also described here. The formation of the observed products can be explained by sequential formation of two new C−C bonds and an additional C−N bond triggered by the initial addition of a C-centered 1,3-dicarbonyl radical onto the acrylamide moiety of the starting materials. Additionally, the reaction involves a formal 1,4-aryl migration and a desulfonylation process, producing the heterocyclic products in synthetically useful yields.

Nitrogen-centered radicals, including amidyl, iminyl, aminium, and aminyl radicals, have recently emerged as a powerful synthetic platform for the formation of new C−N bonds.[9,36] In this work we showcase one of the first examples in which addition of multiple radicals to alkenes produce amidyl radical intermediates via Smiles rearrangement, evolving additional radical cyclizations to construct new C−N and C−C bonds.[37] We also demonstrate that the reactivity of these key intermediates can be fine-tuned by electronic as well as steric factors through a careful choice of the substituents directly attached to the N-atom (alkyl vs aryl). Investigation of new reactivity modes for these intermediates and application toward the synthesis of bioactive molecules is currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, additional experiments, characterization of all the new compounds, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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