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Mild Aminoacylation of Indoles and Pyrroles through a Three-Component Reaction with Ynol Ethers and Sulfonyl Azides

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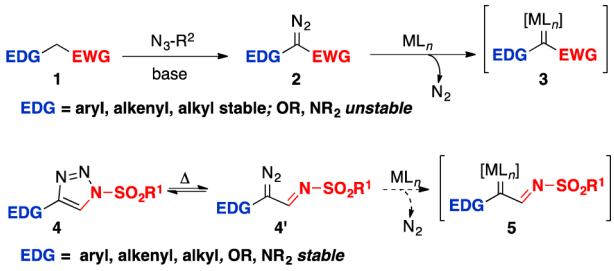
Supporting Information

ABSTRACT: An effective method for aminoacylation of indoles and pyrroles has been achieved. The transformation involves a multicomponent one-pot cascade reaction between indoles or pyrroles, ynol ethers, and sulfonyl azides, creating four different bonds regioselectively through *N*-sulfonyltriazole intermediates. The *oxo*-tryptamines and *oxo*-pyrroloethanamines are generated in moderate to high yields under mild reaction conditions.

The metal-catalyzed decomposition of diazo compounds to generate transient metal carbenes has broad application in organic synthesis.[1] In recent years, donor/acceptor-substituted metallocarbenes **3** have been extensively studied because their reactivity is attenuated compared to the more traditional transient metallocarbenes lacking a donor group (Scheme 1).[2]

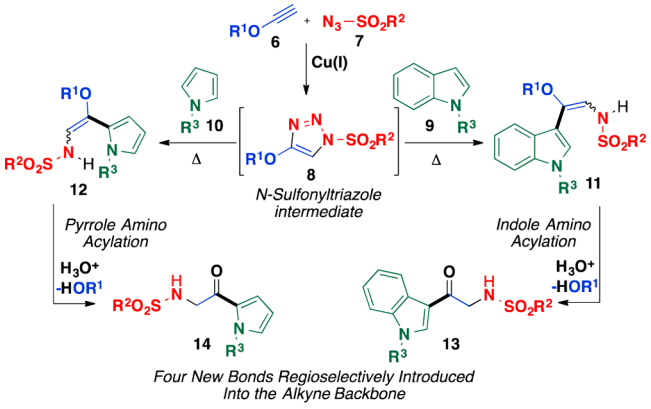
Scheme 1. Donor/Acceptor Metallocarbenes



In order for this chemistry to reach its full potential, however, a broader range of donor groups need to be developed. Particularly attractive systems would be those in which the donor group is amino[3] or alkoxy,[4] but these types of carbenes cannot be accessed from preformed diazo compounds **2** because of their inherent instability. Therefore, we have become interested in the use of *N*-sulfonyltriazoles **4**, which Fokin, Gevorgyan, and Murakami have shown could be used as alternative precursors to rhodium carbenes **5** in the presence of an appropriate dirhodium tetracarboxylate catalyst.[5] Since these initial studies, a majority of the work with *N*-sulfonyltriazoles has centered on the use of 4-aryl or 4-alkyl *N*-sulfonyltriazoles as carbene precursors.[6,7] We have been intrigued by the possibility of developing new chemistry for *N*-sulfonyltriazoles by incorporation of other types of donor groups into the *N*-sulfonyltriazole scaffold.

In our early exploratory studies to expand the range of *N*-sulfonyl triazole derivatives, we showed that 4-alkenyl triazoles underwent a formal [4 + 3] cycloaddition with dienes[7f] and an electrocyclization reaction to provide fused pyrroles and substituted indoles.[7g] The stability of the *N*-sulfonyltriazole was found to be greatly influenced by the nature of the C(4) substituent.[3] 4-Phthalimido *N*-sulfonyltriazoles are more labile than their 4-aryl and 4-alkyl triazole counterparts. They decompose thermally at 55 °C in the absence of a catalyst to generate a transient donor/acceptor carbene,[8] leading to a ready access to cyclopropaneamino acids.[3] These studies prompted us to explore the chemistry of 4-alkoxy *N*-sulfonyltriazoles **8**,[9] which has led to the discovery of a novel cascade sequence between ynol ethers **6**, sulfonyl azides **7**, and electron-rich heterocycles such as indoles **9** and pyrroles **10** (Scheme 2). The resulting enol ethers **11** and **12** were readily converted to the amino ketones **13** and **14**, resulting in a facile method for α-aminoacylation of electron-rich heterocycles.[10,11]

Scheme 2. Acylation Variant for Indoles and Pyrroles



We began our investigations with the synthesis of various 4-alkoxy-1-sulfonyl triazoles **8** from the corresponding sulfonyl azides **7** and commercially available or easily prepared ynol ethers **6**.[12,13] These electron-rich triazoles were submitted to a metal-free thermal denitrogenative reaction with indole **9a** at 0.2 mmol scale under microwave irradiation in which rapid evolution of gas occurred and the reaction proceeded to completion within 15 min. The intermediate enol ether product **11** was subsequently hydrolyzed *in situ* to provide the α-amino ketone product (see Table 1). A range of alkoxy and phenolic substituents were compatible with the reaction as well as many

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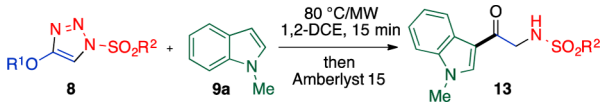
Table 1. Scope of the Oxygen Surrogate[a]



8 9a 13

entry	triazole 8	R^1	$-SO_2R^2$	product 13	% yield[b]
1	8a	Et	Ms	13a	53
2	8b	Et	Ts	13b	83
3	8c	Cy	Ms	13a	81
4	8d	Ph	Ms	13a	91(87)[b]
5	8e	Ph	TMS	13c	84
6	8f	Ph	Ts	13b	90
7	8g	2-Naph	Ms	13a	87

[a]Triazole **8** (0.20 mmol, 1.0 equiv) and indole **9a** (0.30 mmol, 1.5 equiv) were combined in solvent (2.0 mL) and heated at 80 °C for 15 min; then Amberlyst 15 was added and heated at 50 °C for 2–4 h. Isolated yields. [b]Reaction was conducted under conventional heating at 70 °C for 12 h on a 5.0 mmol scale.

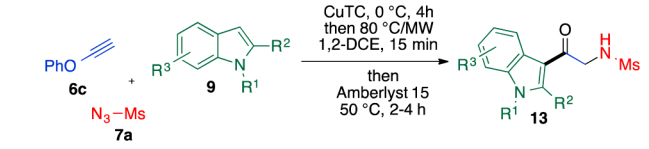
different sulfonyl groups including the easily deprotected SES group (**13c**, entry 5). The reaction can also be conducted at larger scale (5.0 mmol) using conventional heating conditions at 70 °C with similar performance (entry 4).

The next series of experiments were directed toward determining whether a one-pot, three-step procedure was feasible starting with the ynol ether, indole, and sulfonyl azide. A mixture of ynol ether **6c**, indole **9**, and mesyl azide **7a** was stirred at 0 °C for 4 h in the presence of CuTC (copper(I) thiophene-2-carboxylate; 3 mol %) and then warmed to 80 °C for 15 min under microwave irradiation, which was followed by the addition of Amberlyst 15 to provide the hydrolyzed product **13**. As shown in Table 2, a broad range of indole derivatives reacted to provide the corresponding aminoacylated products in good to excellent yields. An evaluation of the substituents on the indolic nitrogen revealed that *N*-H, *N*-alkyl, and *N*-benzyl are compatible with this transformation (**13a,13d–e**, entries 1–3); however, electron-withdrawing groups on the indolic nitrogen are not tolerated (e.g., 1-Ts, 1-Boc). An array of electron-rich and -deficient indoles substituted at C(5) or C(7) of the indolic core also provided the corresponding amino-acylated products in excellent yields (**13f–i**, entries 4–7). The reaction was found to be applicable to a range of C(2)-alkyl and aryl indoles as well (**13j–n**, entries 8–12).

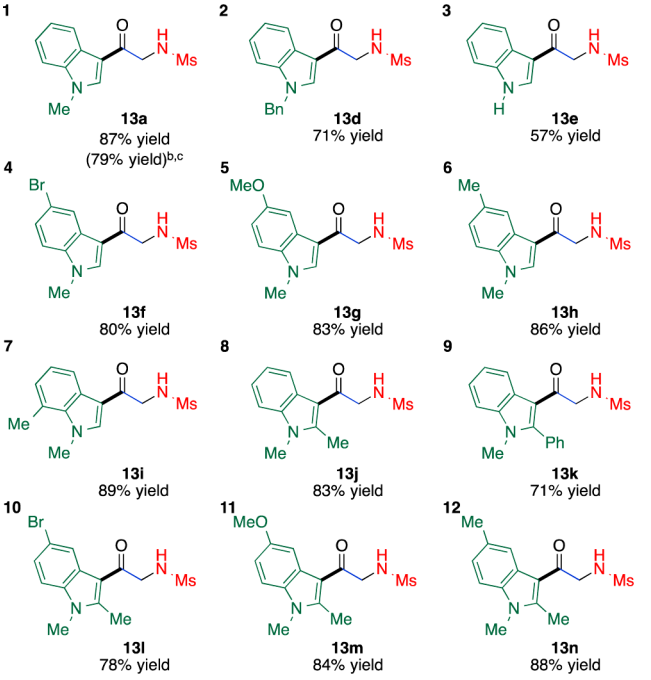
Further investigation into substituted indoles with C(3)-substituents revealed that these were also reactive substrates; however, instead of the expected C(2)-acylated product, the dearomatized [3 + 2] annulation product **16a** was observed (Scheme 3). This reaction was found to be less sensitive to steric effects as both bulkier sulfonyl groups (e.g., 1-Ts, **16b** and **18b**) and substituents at C(2) were tolerated.[7e] Attempted hydrolysis of the enol ether **16a** and **16b** failed to provide the desired pyrroloindolone products.[14]

The amino acylation reaction was also applicable to electron-rich pyrroles giving either the C(2) or C(3) amino acylated products as shown in Table 3. Starting from 4-phenoxy-1-sulfonyl triazoles **8d,f**, a range of pyrrole derivatives **5** reacted under metal-free thermal conditions to provide the corresponding amino acylated products **14** in moderate to excellent yields. Similar to the results with indole derivatives, *N*-H, alkyl, and aryl are well tolerated, but pyrroles with electron-withdrawing groups failed to provide the desired products. The use of the bulkier sulfonyl group is also well tolerated (**14b**, entry 2) as

Table 2. Scope of Indole Component[a]

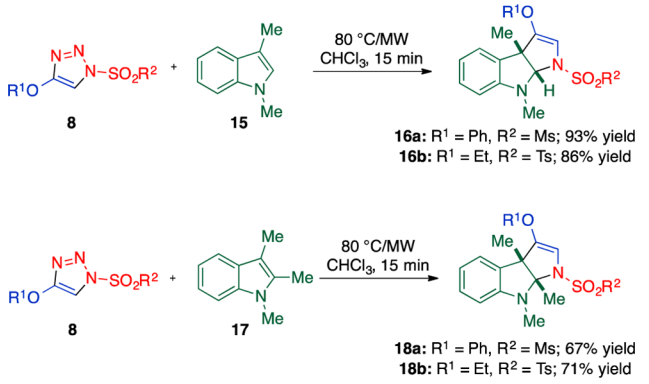


6c 7a 9 13



[a]Ynol ether **6c** (0.24 mmol, 1.2 equiv), MsN_3 (0.20 mmol, 1.0 equiv), CuTC (0.006 mmol, 0.03 equiv), and indole **9** (0.40 mmol, 2.0 equiv) were combined in solvent (2.0 mL), stirred at 0 °C for 4 h, and then heated at 80 °C for 15 min. Amberlyst 15 was added and heated at 50 °C for 2–4 h. Isolated yields. [b]Reaction was conducted under conventional heating at 70 °C for 4 h on a 12.0 mmol scale. [c]TsOH hydrate (30 mol %) used for hydrolysis.

Scheme 3. Reaction with C(3)-Substituted Indoles



well as various substitutions of the pyrrole (entries 3–5). Interestingly, both the starting pyrrole derivatives in entries 3 and 4 can be derived from *N*-sulfonyl triazoles,[7g,o] further showcasing the applicability of the *N*-sulfonyl triazole chemistry. Lastly, the C(3) aminoacylated product **14f** is obtained when both the C(2) and C(5) positions of the pyrrole derivative are substituted (entry 6).

A proposed mechanism for the one-pot formation of the amino acylated product **13a** from alkyne **6c** and indole **9a** is depicted in Scheme 4. Initially, a copper(I)-catalyzed cyclo-

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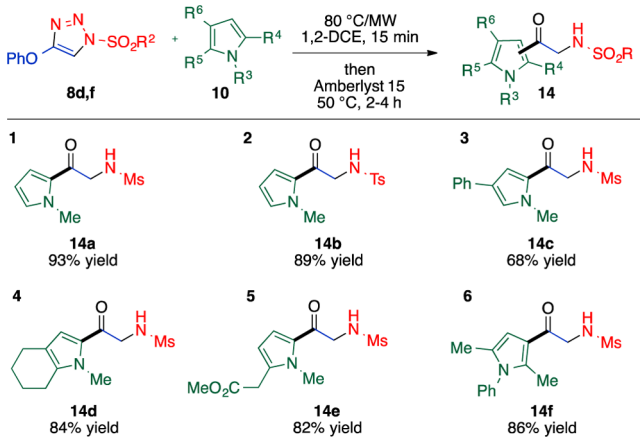
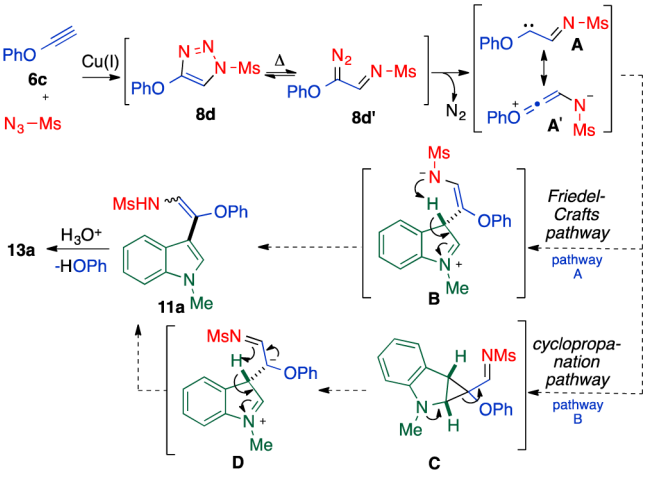
Table 3. Scope of Pyrrole Component[a]



[a]Triazole **8** (0.20 mmol, 1.0 equiv) and pyrrole **10** (0.30 mmol, 1.5 equiv) were combined in solvent (2.0 mL) and heated at 80 °C for 15 min; then Amberlyst 15 was added and heated at 50 °C for 2−4 h. Isolated yields.

Scheme 4. Proposed Mechanistic Pathways



addition reaction of the alkoxy alkyne **6c** with mesyl azide occurs, resulting in the formation of 4-alkoxy-1-mesyl triazole **8d**.[11b] Subsequent microwave irradiation causes the triazole to isomerize to the α-diazo imine **8d′** which then undergoes a thermal nitrogen extrusion furnishing the resonance-stabilized carbene intermediate **A**.[4,9,15] At this point, there are two possible reaction pathways. In pathway A, the intermediate **A** is engaged by the electron-rich indole derivative at C(3) in a Friedel−Crafts-type substitution to furnish the zwitterionic intermediate **B**, followed by a subsequent rearomatization of the indole moiety to form enol ether **11a**. However, with the observation of the formal [3 + 2] product **16a**, we propose that intermediate **A** undergoes a thermal cyclopropanation reaction with the electron-rich indole (intermediate **C**, pathway B).[3,7e,16] An immediate ring opening of the strained cyclopropylindoline intermediate leads to intermediate **D**, which tautomerizes to the enol ether **11a** with subsequent rearomatization of the indole moiety. Hydrolysis of the enol ether leads to the amino acylated product **13a**. We have proposed a similar initial cyclopropanation step with C(3)-substituted indoles in our previous studies on [3 + 2] annulation with 4-aryl *N*-sulfonyltriazoles.[7e] It is presumed that a similar mechanism operates with electron-rich pyrroles.

In summary, we have developed an efficient method for aminoacylation of indoles and pyrroles through 4-alkoxy *N*-sulfonyltriazole intermediates from readily available starting materials. The *oxo*-tryptamine and *oxo*-pyrroloethanamine products are synthesized in a multicomponent one-pot cascade reaction. As previously observed with amino-substituted triazoles, the alkoxy-substituted triazoles undergo nitrogen extrusion under relatively mild conditions without requiring the use of a dirhodium catalyst. These studies further demonstrate that metal-free donor/acceptor carbenes are capable of selective high-yielding transformations.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic detail and spectral 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.

■ ACKNOWLEDGMENTS

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