LETTERS

Chemoselective Double Annulation of Two Different Isocyanides: Rapid Access to Trifluoromethylated Indole-Fused Heterocycles

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(5) Supporting Information

ABSTRACT: An unprecedented chemoselective double annulation of α -trifluoromethylated isocyanides with *o*-acylaryl isocyanides has been developed. This new reaction provides a rapid, efficient, and complete atom-economic strategy for the synthesis of trifluoromethylated oxadiazino[3,2-*a*]indoles in a single operation from readily available starting materials. Isocyanide insertion into C==O double bonds is disclosed for the first time as indicated by the results of ¹⁸O-labeling



experiment. A mechanism for this domino reaction is proposed involving chemoselective heterodimerization of two different isocyanides, followed by indole-2,3-epoxide formation and rearrangement.

ue to their unique structures and reactivities, isocyanides are versatile building blocks in chemical synthesis.¹ Beside the well-known multicomponent Ugi^{1a,2} and Passerini³ reaction, isocyanide-based $[3 + n]^4$ and $[1 + m]^5$ annulations became the most powerful tools for the preparation of heterocycles in recent years. Generally, activated methylene isocyanides act as threeatom components and react with polar multiple bonds,^{4a,b} 1,3dipole,^{4c} or 1,6-dipole^{4d} to participate in the [3 + n] reaction, and isocyanides can also act as a one-atom component to participate in the [1 + m] reactions.⁵ Among these transformations, the chemoselective annulation of two different isocvanides has seldom been explored, $^{6-10}$ probably because of the readiness of homodimerization⁶ or polymerization^{1a} of isocyanides. In 2005, Yamamoto's group first reported the cross-cycloaddition of activated methylene isocyanides with aryl isocyanides for the synthesis of imidazoles (Scheme 1, eq 1).⁷ Recently, Hong's⁸ and Bi's⁹ groups successfully extended the scope of this reaction for the preparation of 1,4-diaryl- and 1,4,5-trisubstituted imidazoles, respectively. We recently found that a [4 + 2] rather than [3 + 2]annulation took place to access fused pyridones when α substituted isocyanoacetamides were employed instead of other activated methylene isocyanides (Scheme 1, eq 2).^{10a} Moreover, a tandem heterocoupling and [3 + 2] cycloaddition of 2isocyanochalcones and isocyanides was also developed by our research groups recently (Scheme 1, eq 3).^{10b} Despite these research efforts, exploiting new annulation of different isocyanides associated with isocyanide new reactivity profiles remains highly desirable.

On the other hand, isocyanide insertion reactions have attracted extensive attention for the construction of nitrogencontaining heterocycles in the past few decades.¹¹ Accordingly,





isocyanide insertion into heteroatom-H,^{11a,12} C-H,^{11a,13} C-heteroatom,^{11a,14} C-metal,^{11a-c,15} and C-C bonds¹⁶ have been investigated. Recently, isocyanide insertion reactions with radicals have emerged as an efficient and useful protocol for the synthesis of heterocycles.^{11d,17} Although isocyanide insertion into

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single bonds, $^{11-14,16}$ including C–O bonds of epoxides¹⁸ and ketals or acetals, 19 was reported, to our knowledge, the insertion into the C=O double bond has not yet been established.

To develop a practical and efficient protocol to access valuable trifluoromethylated heterocycles, we recently designed α trifluoromethylated methyl isocyanides as new synthons.²⁰ Preliminary results revealed that a wide range of CF₃-containing oxazolines, imidazolines, and pyrrolines were conveniently constructed by formal [3+2] cycloaddition of α -trifluoromethylated methyl isocyanides with polar multiple bonds.²⁰ In continuation of our studies on isocyanide-based annulation reactions,²¹ we report herein a unique and unprecedented chemoselective double annulation of α -trifluoromethylated methyl isocyanides with o-acylaryl isocyanides for the efficient synthesis of trifluoromethylated oxadiazino [3,2-a] indoles with complete atom-economy (Scheme 1, eq 4). In this domino reaction, new reactivity profiles are disclosed, including isocvanide formal insertion into the C=O bond and chemoselective heterodimerization of two different isocyanides. Moreover, indoles²² and oxadiazines²³ are widespread skeletons in numerous biologically active natural products and pharmaceuticals. It was also reported that fused oxadiazines were ideal drug motifs for treating Alzheimer's disease.²⁴ This double annulation provides an efficient protocol for the rapid assembly of new oxadiazine-fused indole scaffolds.

Initially, the reaction of *o*-acylphenyl isocyanide **1a** and 1methyl-4-(2,2,2-trifluoro-1-isocyanoethyl)benzene **2a** was employed to optimize the reaction conditions. It was found that, catalyzed by Ag_2CO_3 (30 mol %) in acetonitrile at 100 °C for 6 h, the trifluoromethylated oxadiazino[3,2-*a*]indole **3aa**²⁵ was obtained in 57% yield (Table 1, entry 1). When the amount of

Table 1. Optimization of Reaction Conditions ^a					
	€ N	`Ph + C /	p-Tol CF ₃ Ag ₂ C solver	O ₃ (x mol %) tt, temp, 6 h	Ph
	1a		2a	:	3aa
	entry	x	solvent	temp (°C)	3aa (%) ^b
	1	30	CH ₃ CN	100	57
	2	50	CH ₃ CN	100	74
	3	60	CH ₃ CN	100	70
	4	50	1,4-dioxane	100	53
	5	50	THF	100	39
	6	50	CH ₃ OH	100	
	7	50	CF ₃ Ph	100	41
	8	50	DME	100	27
	9	50	CH ₃ CN	110	80
	10	50	CH ₃ CN	120	70
	11	50	CH ₃ CN	110	87 (91) ^c

^{*a*}Reaction conditions: 1a (0.1 mmol), 2a (0.15 mmol), Ag_2CO_3 (30 mol %), in solvent (2 mL) for 6 h. ^{*b*}Determined by ¹H NMR spectroscopy using 1,2-dibromoethane as an internal standard; isolated yields are given in parentheses. ^{*c*}2a (2.0 equiv).

Ag₂CO₃ was increased to 50 mol % in the reaction, the yield of **3aa** was improved to 74% (Table 1, entry 2). Further increasing the amount of Ag₂CO₃ to 60 mol % led to a comparable yield of **3aa** (Table 1, entry 3). A survey of solvents such as 1,4-dioxane, THF, methanol, benzotrifluoride, and dimethoxyethane identified acetonitrile as the most suitable medium (Table 1, entry 2 vs entries 4–6). When the reaction was performed at 110 °C, **3aa**

was produced in 80% yield (Table 1, entry 9), whereas at 120 °C, 70% yield of **3aa** was obtained (Table 1, entry 10). The isolated yield of **3aa** was improved to 91% when 2.0 equiv of **2a** was added to the reaction mixture (Table 1, entry 11).

With the optimal conditions in hand (Table 1, entry 11), the substrate scope toward this double annulation was investigated. The reaction of viable *o*-acylphenyl isocyanides 1 with isocyanide 2a was examined (Scheme 2). First, wide variation of the \mathbb{R}^1 group

Scheme 2. Scope of Isocyanides $1^{a,b}$



^{*a*}Reaction conditions: 1 (0.2 mmol), 2a (0.4 mmol), Ag_2CO_3 (50 mol %), CH_3CN (2 mL) for 6 h. ^{*b*}Isolated yields. ^{*c*}Yield of 1.0 mmol scale.

on isocyanides **1** including electron-neutral (e.g., Ph), -poor (e.g., 4-ClC₆H₄), and -rich (e.g., 4-MeC₆H₄) aryl and alkyl groups (e.g., Me, Et, *n*-Pr, and *i*-Pr) allowed the formation of diverse trifluoromethylated oxadiazino[3,2-*a*]indoles (**3aa-ga**) in 48–91% yields. Furthermore, this annulation tolerated isocyanides **1** bearing both electron-withdrawing (e.g., F, Cl, and Br) and electron-donating (e.g., Me) R² groups on either 4 or 5 positions and afforded the corresponding trifluoromethylated oxadiazino[3,2-*a*]indoles (**3ha-oa**) in good to high yields. Notably, the chloro and bromo groups are compatible with these reaction conditions and can be used as handles for further diversification.

Subsequently, the scope of this double annulation was evaluated with respect to some selected trifluoromethylated isocyanides **2** (Scheme 3). Trifluoromethylated isocyanides **2** bearing various R groups including electron-neutral phenyl, -poor aryl (e.g., 4-FC₆H₄, 4-ClC₆H₄, and 4-BrC₆H₄), and -rich aryl (e.g., 4-MeOC₆H₄, 3-MeC₆H₄) groups afforded the oxadiazino[3,2-*a*]indoles (**3ab**-**ag**) in high yields. Furthermore, heteroaryl-substituted isocyanide **2h** produced the oxadiazino[3,2-*a*]indole **3ah** in moderate yield. When benzyl-substituted trifluoromethyl isocyanide **2i** was employed in this double annulation, the corresponding oxadiazino[3,2-*a*]indole **3ai** was not detected. In the case of α -phenylethyl isocyanide **2j**, replacing the

Scheme 3. Scope of Trifluoromethylated Isocyanides $2^{a,b}$



^aReaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), Ag₂CO₃ (50 mol %), CH₃CN (2 mL) for 6 h. ^bIsolated yields. ^cND = not detected.

trifluoromethyl with a methyl group, the corresponding oxadiazino[3,2-a] indole **3aj** was not detected either. This result indicated that the trifluoromethyl group is essential for this transformation.

To shed light on the mechanism of this double annulation, several control experiments were performed. When 2.0 equiv of TEMPO or 2,6-di-*tert*-butyl-4-methylphenol was added to the standard reaction, **3aa** was obtained in 61 and 62% yields, respectively (Scheme 4, eqs 1 and 2). These results indicated that

Scheme 4. Control Experiments



this double annulation probably does not proceed via a radical pathway. Moreover, to determine the source of the oxygen atom in product 3, we carried out an isotope-labeling experiment. When ¹⁸O-labeled isocyanide $1a^{-18}O$ was used as substrate under the standard conditions, ¹⁸O-labeled product $3aa^{-18}O$ was obtained in 81% yield, as evidenced by mass spectrometry (Scheme 4, eq 3). This result clearly illustrated that the oxygen atom in oxadiazino[3,2-*a*]indoles 3 comes from the carbonyl group of isocyanides 1, and that adventitious H₂O or O₂ are not involved in the double annulation process.

On the basis of above experimental results and literature precedent, ${}^{6,7,9,10,25,26}_{,,2,a}$ a possible reaction pathway leading to oxadiazino[3,2-*a*]indoles 3 is depicted in Scheme 5 (exemplified by the generation of 3aa). The coordination of Ag₂CO₃ to

Scheme 5. Proposed Mechanism



trifluoromethylated isocyanide **2a**, followed by the abstraction of a proton, forms a silver complex I.^{6,7,10} Meanwhile, Ag₂CO₃ coordinates to isocyanide **1a** to form complex II. Nucleophilic attack of the intermediate I on complex II produces the imidoyl silver intermediate III.^{9,10} Bicyclization of III generates the zwitterionic intermediate IV, followed by intramolecular cylization to form the indole epoxide intermediate V,²⁶ which is protonated to regenerate the catalyst Ag₂CO₃ along with the production of intermediate VI. Finally, ring opening of the epoxide²⁶ and imidazoline forms the zwitterionic intermediate VII, which generates the oxadiazino[3,2-*a*]indoles **3aa** by ring closing.²⁷

In summary, an unprecedented silver-promoted chemoselective double annulation of α -trifluoromethylated isocyanides with *o*-acylaryl isocyanides has been developed. This new reaction provides a rapid, efficient, and complete atom-economic strategy for the synthesis of biologically potential trifluoromethylated oxadiazino[3,2-*a*]indoles in a single operation from readily available starting materials. In this domino transformation, new reactivity profiles such as isocyanide insertion into C==O bonds, chemoselective heterodimerization of two different isocyanides, and an indole-2,3-epoxide formation and rearrangement were exhibited. Investigation of the reaction mechanism and the synthetic potential of this double annulation is ongoing.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02582.

Experimental procedures and characterization data for all compounds (PDF) X-ray data of **3aa** (CIF)

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Notes

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(25) CCDC 1566762 (**3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

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