Communications

Reissert-Based "Traceless" Solid-Phase Synthesis: Isoquinoline, and Isoxazoline-Containing Heterocycles

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Received October 10, 1996

The isoquinoline nucleus has been the basis for many compounds, showing a wide variety of biological applications,[1] particularly isoquinolines substituted at C1 with basic-containing substituents including N and O heterocycles.[2] One such moiety, the isoxazoline heterocycle, has been used extensively to modify a variety of other biologically active systems.[3] Thus, we sought to combine these two structural features on a single framework giving novel isoquinoline−isoxazoline heterocycles. An efficient method of incorporating substitution at C1 of isoquinolines is by use of Reissert compounds[4,5] which takes advantage of the increased acidity at C1 of the 2-acyl-1,2-dihydroisoquinaldonitriles. This type of chemistry has been used in the polymer area to produce monomers for both subsequent polymerization[6] and polymerization of Reissert compounds themselves.[7] These observations, plus the importance of methodological developments in solid-phase[8] and combinatorial strategies,[9] led us[10] to investigate a "traceless" solid-phase approach for construction of the isoquinoline−isoxazoline heterocyclic system.

Intrigued by the combinatorial potential of heterocycles containing both isoquinoline and isoxazoline subunits (i.e., generalized structure **III**), we set out to validate the solid-phase synthetic strategy outlined in Figure 1 by exploring four pivotal chemical questions relevant to preparing this class of compounds. Can solid-phase Reissert formation be effected in such a way that the resulting complex provides coincident substrate−resin linkage (isoquinoline → **1**)? Can the resulting solid-phase Reissert complex be C1-allylated (**I** → **II**)? Will nitrile oxide reagents undergo olefin- or enamide-selective 1,3-dipolar cylcoaddition (see **II**)? If the Reissert complex can be successfully exploited for linker, activation (C1), and protection (endocyclic enamide C═C), will hydrolysis deconvolute the complex delivering the targeted heterocycle (**II**) and thus constitute a "traceless"[11] solid-phase approach to isoquinoline−isoxazoline heterocycles of generalized structure **III**? Herein, we relate our investigation of these issues and report a six-compound array of isoquinoline−isoxazoline heterocycles[12] that have been held to the characterization standards of organic chemistry.

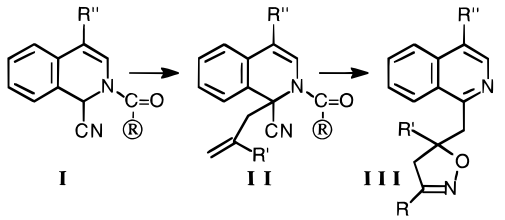

Figure 1. Solid-phase Reissert-based approach to isoquinoline−isoxazoline heterocycles (® = styrene/2% divinyl resin).

Amide[13] and sulfonamide-based[14] Reissert complexes have been prepared in solution. However, on the basis of our previous experience with polymer-bound benzoyl chloride,[15] we elected to pursue an amide-based Reissert strategy. Starting with unfunctionalized polystyrene−2% divinylbenzene copolymer (®C_6H_5), metalation, carbon dioxide quench, and workup[16] delivered a benzoic acid-functionalized resin (®$C_6H_4CO_2H$; 1.5 mequiv/g resin). Conversion to polymer-bound benzoyl chloride [®$C_6H_4C(=O)Cl$][17] was effected by treatment with $SOCl_2$ (DMF, reflux, 2−3 h). Reissert formation was accomplished by treating this CH_2Cl_2-swollen resin with 5 equiv of isoquinoline and TMSCN at room temperature for 48 h. FT-IR analysis showed loss of the acyl chloride stretch at 1760 cm^{-1} and formation of an amide stretch at 1680 cm^{-1} (very weak cyano absorption is found between 2337 and 2367 cm^{-1}).

With Reissert complex ®**1**[18] in hand, we turned to the question of C1-alkylation. While solution-phase Reissert alkylations traditionally use NaH activation,[19] we were concerned that this insoluble base would not be effective in deprotonation of ®**1**; we instead turned to the soluble base LDA. Thus, THF-swollen ®**1** was treated with LDA (5 equiv −78 °C, 30 min). Ethyl iodide (10 equiv) was added, and the reaction vessel was allowed to warm to room temperature. After 48 h, the resin was filtered and

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(18) A systematic numbering system is used to represent the targeted heterocycles. For example, isoquinoline−isoxazoline **1.7.A** is prepared by the following series: isoquinoline + ®$C_6H_4CO_2H$ (® = styrene/2% divinyl resin) → ®**1**, ®**1** + allyl bromide (**7**) → ®**1.7**, ®**1.7** + $CH_3CH_2C{\equiv}N^+O^-$ (**A**) → ®**1.7.A**, and ®**1.7.A** + aqueous KOH/THF → **1.7.A** where the first number indicates the isoquinoline subunit (**1**−**3**), the second number indicates the C1 alkyl unit (**4**−**8**), and the letter indicates the nitrile oxide unit (**A** or **B**).
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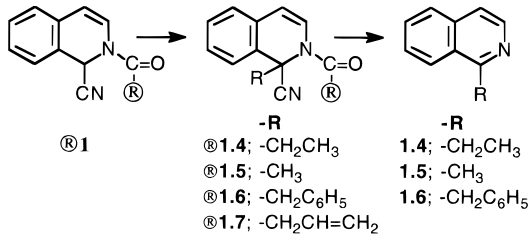
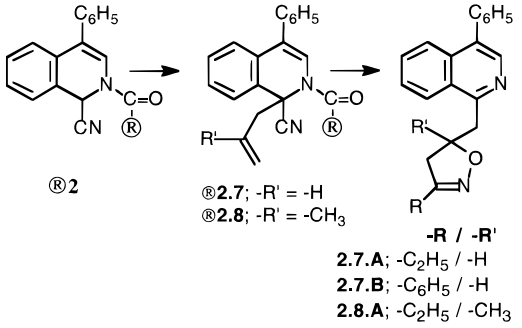
S0022-3263(96)01916-0 CCC: $12.00

Scheme 1. C1-Alkylation of the Solid-Phase Reissert Complex



Scheme 2. Preparation of C4-Substituted Isoquinoline−Isoxazoline Heterocycles

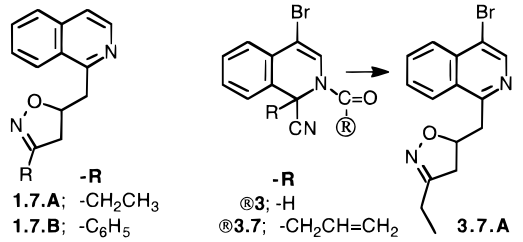


washed (THF, aq HCl/THF, water, and THF) to give ®**1.4**. This resin, having now been exposed to four synthetic transformations (carbonylation, acid chloride formation, Reissert condensation, and C1-alkylation), was swollen in THF and treated with aqueous KOH (1 M; 2:1 THF:H_2O) to effect Reissert hydrolysis. Subsequent filtration and ether wash followed by normal aqueous workup delivered 1-ethylisoquinoline (**1.4**; 59% overall yield from ®$C_6H_4CO_2H$). In similar fashion, C1-substituted isoquinolines **1.5** and **1.6** were prepared from methyl iodide (56% overall yield) and benzyl bromide (50% overall yield), respectively. Capillary GC analysis of each of these Reissert/C1-alkylation/hydrolysis reaction mixtures shows nearly complete C1-alkylation; in all cases only a very minor trace (<5%) of unalkylated isoquinoline could be detected.

Having established the viability of this Reissert-based traceless linker strategy to prepare C1-substituted isoquinolines, we turned to the question of olefin selectivity in the 1,3-dipolar cycloaddition step. Our previous experiences with both solution-phase[20] and solid-phase[15,21] nitrile oxide cycloaddition reactions[22] establish that steric and electronic factors influence olefin selectivity in 1,3-dipolar cycloadditions suggesting that C1-allylated Reissert compound **II** would perhaps undergo olefin selective cycloaddition.

As a first test of this exo-olefin versus endo-enamide competition in the Reissert series, we felt it prudent to bias the system toward exo-addition by placing a bulky substituent at the isoquinoline C4-position; thus, 4-phenylisoquinoline[24] was selected. Reissert formation (®**2**) and subsequent LDA-mediated C1-allylation delivered

Scheme 3. C4-Unsubstituted and C4-Bromo-Substituted Isoquinoline−Isoxazolines



resin ®**2.7**. We were pleased to find that the key step, *in situ* generation of $CH_3CH_2C{\equiv}N^+O^-$ [**A**; nitropropane (5 equiv) + PhNCO (10 equiv) + Et_3N (cat.)] with concomitant 1,3-dipolar cycloaddition proceeds with complete exo-selectivity based on analysis of the crude hydrolysis (aq KOH/THF) product; i.e., only isoquinoline-isoxazoline **2.7.A** was obtained (27% overall yield from ®$C_6H_4CO_2H$).[25] This result is impressive given the fact that 5 equiv of nitrile oxide **A** was employed! Moreover, alkylation of ®**2** with methallyl bromide delivers ®**2.8**, which, in spite of increased steric hindrance at the exo-olefin, also undergoes only exo-1,3-dipolar cycloaddition, giving **2.8.A** on hydrolysis (24% overall yield from ®$C_6H_4CO_2H$).[25b] Finally, the olefin selectivity found for $CH_3CH_2C{\equiv}N^+O^-$ reacting with ®**2.7** is also observed in the reaction of $C_6H_5C{\equiv}N^+O^-$ (**B**) with ®**2.7**; i.e., only exo-cycloadduct **2.7.B** is obtained (23% overall yield from ®$C_6H_4CO_2H$).[25b]

Encouraged by this exo-selectivity in ®2.7, we returned to resin ®**1** and allylated with allyl bromide to give resin ®**1.7** (see Scheme 1).[26] Now 1,3-dipolar cycloaddition confronted a much less hindered enamide C=C and very much brought to the forefront the question of whether exo-selectivity would still prevail. In the event, treating resin ®**1.7** with excess $CH_3CH_2C{\equiv}N^+O^-$ or excess $C_6H_5C{\equiv}N^+O^-$ delivered only the exo-cycloadducts **1.7.A** and **1.7.B** (25% and 26% overall yield from ®$C_6H_4CO_2H$)![25b] These results, especially with excess nitrile oxide, suggest that the enamide C=C is electronically deactivated in the solid-phase Reissert compound.

As one last example, 4-bromoisoquinoline was put through the Reissert/C1-allylation/1,3-dipolar cycloaddition/hydrolysis sequence and delivered isoquinoline−isoxazoline **3.7.A** (Scheme 3) in 26% overall yield from ®$C_6H_4CO_2H$.[25b] This result, while perhaps not unexpected given the exo-olefin selectivities of ®**1.7**, ®**2.7**, and ®**2.8**, is an important one in that it sets the stage for incorporating a Suzuki coupling step in this reaction sequence. This aspect is currently under investigation.

In summary, we have developed a traceless solid-phase strategy for the synthesis of novel isoquinoline−isoxazoline heterocycles. This chemistry appears well suited for application in combinatorial discovery programs.

Acknowledgment. We are grateful to the National Science Foundation (Grant CHE-9406891) and the DuPont Educational Aid Program for financial support of this research.

Supporting Information Available: Tabular ^{1}H NMR spectral data for **1.4**, **1.5**, **1.6**, **1.7.A**, **1.7.B**, **2.7.A**, **2.7.B**, **2.8.A**, and **3.7.A**; ^{1}H NMR spectra for **1.4**, **1.5**, **1.6**, **1.7.A**, **1.7.B**, **2.7.A**, **2.7.B**, **2.8.A**, and **3.7.A** (12 pages).

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(25) (a) The crude ^{1}H-NMR show no evidenced of a second isoxazoline-containing product. (b) The purity of the crude product was judged to be ≥90% by ^{1}H-NMR analysis.

(26) Hydrolysis of this Reissert compound is complicated by the fact that a fair degree of olefin isomerization occurs, leading to a 1:4 mixture of 1-(2-propenyl)isoquinoline and 1-(1-propenyl)isoquinoline.