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Silver Nitrate-Catalyzed Isocyanide Insertion/Lactamization Sequence to Imidazolones and Quinazolin-4-ones: Development and Application in Natural Product Synthesis

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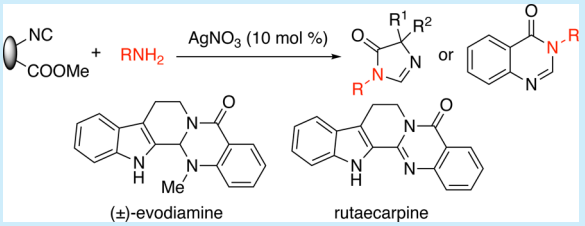
Supporting Information

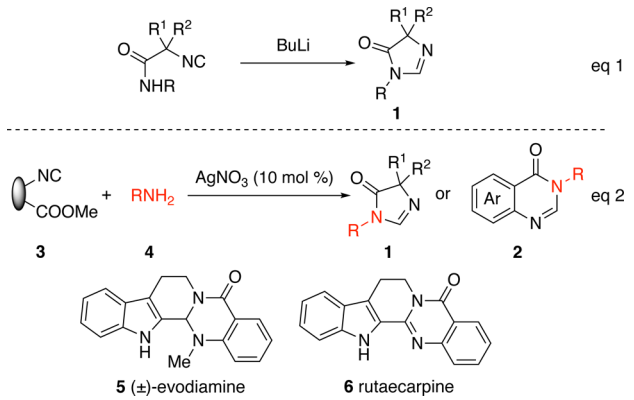
ABSTRACT: Silver nitrate-catalyzed reaction of methyl α,α-disubstituted α-isocyanoacetates with primary amines afforded 3,5,5-trisubstituted imidazolones in good to excellent yields. A silver salt-catalyzed insertion of the isocyano group into the N−H bond of the amine followed by in situ lactamization accounted for the reaction outcome. The same transformation between methyl 2-isocyanobenzoate and amines afforded quinazolin-4-ones in excellent yields. The utility of this chemistry was illustrated by the development of concise syntheses of (±)-evodiamine and rutaecarpine.



Imidazolones **1** are structural motifs found in bioactive natural products[1] and are key elements responsible for the luminescent properties of green fluorescent protein (GFP).[2] Compounds containing this nonaromatic heterocycle display potent inhibitory activities against fatty acid synthases[3] and are angiotensin II receptor antagonists.[4] Indeed, it is the key motif found in the marketed drug irbesartan for the treatment of hypertension.[5] Different synthetic routes have been developed, focusing mainly on the functionalization of simple imidazolones,[6] the cyclization of α-amidoamides,[7] of amino acid-derived formamidines,[8] transformation of azlactones,[9] and base-promoted cyclization of α-isocyanoacetamides (eq 1, Scheme 1)[10]

Metal-catalyzed isocyanide insertion reactions have attracted much recent attention, and a variety of heterocycles are now readily accessible by careful engineering of the substrate structure.[11−14] As part of our research program aimed at exploiting the diverse reactivities of the isocyano group,[15] we recently reported metal triflate-catalyzed domino processes initiated by the insertion of isocyanide into the N−H bond of amines.[16] We document herein the synthesis of 3,5,5-trisubstituted imidazolones **1** and quinazolin-4-ones **2** by silver nitrate-catalyzed reactions of primary amines with methyl α-isocyanoacetates and 2-isocyanobenzoates, respectively (eq 2, Scheme 1). The development of concise syntheses of (±)-evodiamine (**5**) and rutaecarpine (**6**) featuring this latter reaction as a key step will also be presented.

Scheme 1. Synthesis of 3,5,5-Trisubstituted Imidazolones



We began our research using methyl α,α-dibenzyl-α-isocyanoacetate (**3a**) and benzylamine (**4a**) as test substrates. Key observations are summarized in Table 1. Cupric salts were less efficient than cuprous salts in catalyzing this reaction (entries 1−5),[11a] whereas ytterbium triflate was completely ineffective (entry 6). Silver salts gave much better results, with $AgNO_3$ being superior to AgOTf (entries 7−9). In the presence of 10 mol % $AgNO_3$, the reaction of **3a** and **4a** in toluene (c 0.1 M) at 60 °C afforded **1a** in 90% isolated yield (entry 9). Reactions run at lower temperature (entry 10) and at lower catalyst loading (entry 11) afforded **1a** in diminished yields. While a similar yield of **1a** was obtained in ethyl acetate (entry 16), the reaction performed in other solvents afforded **1a** in reduced yields (entries 12−15).

With the optimum conditions in hand (toluene, 10 mol % $AgNO_3$, 60 °C), the scope of the reaction was next examined (Scheme 2). Various alkylamines, both linear and branched, including sterically demanding *tert*-butylamine, reacted with α-isocyanoacetate **3a** to afford the corresponding imidazolones in

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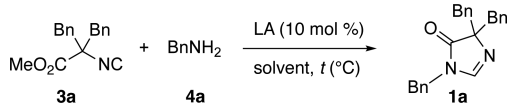
Table 1. Synthesis of 3,5,5-Trisubstituted Imidazolone 1a: Survey of Reaction Conditions[a]



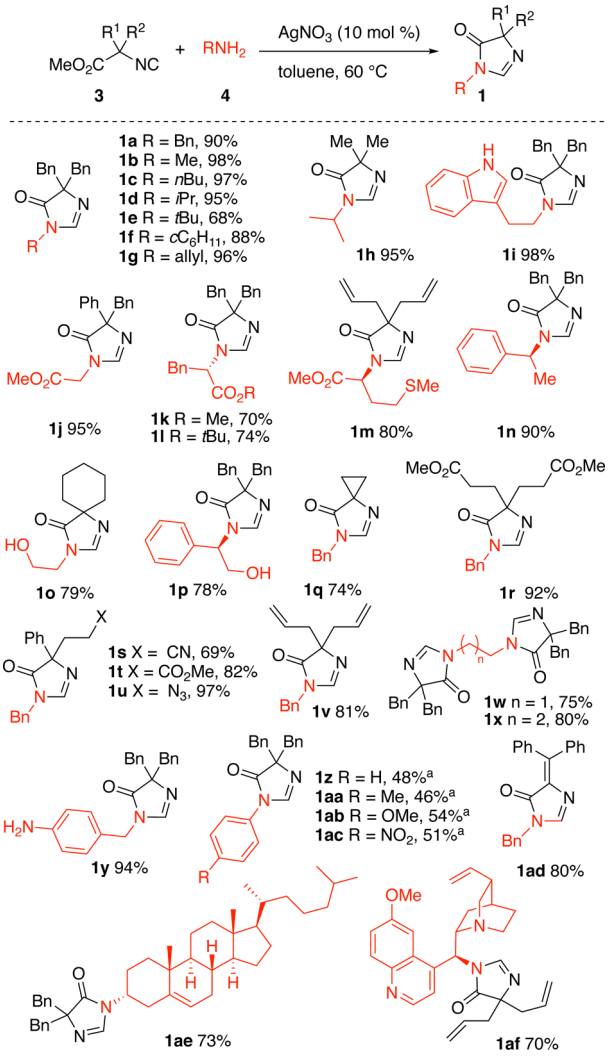
entry	Lewis acid	solvent	t (°C)	yield (%)[b]
1	CuO	toluene	80	no reaction
2	$Cu(OTf)_2$	toluene	80	10
3	$CuCl_2$	toluene	80	30
4	Cu_2O	toluene	60	48
5	CuCl	toluene	60	47
6	$Yb(OTf)_3$	toluene	80	no reaction
7	AgOTf	toluene	80	75
8	AgOTf	toluene	60	76
9	**$AgNO_3$**	**toluene**	**60**	**quant (90[c])**
10	$AgNO_3$	toluene	40	slow reaction
11[d]	$AgNO_3$	toluene	60	80
12	$AgNO_3$	dioxane	60	88
13	$AgNO_3$	DCM[e]	60	69
14	$AgNO_3$	THF	60	84
15	$AgNO_3$	DMF	60	75
16	$AgNO_3$	AcOEt	60	quant (90[c])

[a]Standard conditions: **3a** (0.1 mmol), **4a** (0.12 mmol), solvent (1.0 mL), metal salt (10 mol %). [b]Calculated on the basis of the ^{1}H NMR spectra using CH_2Br_2 as an internal standard. [c]Yield of isolated product in parentheses. [d]$AgNO_3$ (5 mol %). [e]The reaction was performed in a sealed tube.

excellent yields (**1a–f**, **1h**). Functionalized amines such as allylamine (**1g**), tryptamine (**1i**), enantioenriched α-amino esters (**1k–m**), a chiral amine (**1n**), and unprotected amino alcohols (**1o**, **1p**) participated well in this reaction. It is noteworthy that even thioether, known to have high affinity with silver, was compatible with our reaction conditions (**1m**). Different functional groups (COOMe, CN, N_3, olefin) on the α-isocyanoacetate were well-tolerated (**1r–v**). Spiroimidazolones (**1o**, **1q**) can also be prepared without event. Reaction of diamines with 2 equiv of **3a** afforded bisimidazolones (**1w**, **1x**) in good yields. On the other hand, the reaction of 4-aminobenzylamine with **3a** was highly chemoselective, affording **1y** (94% yield) in which the aniline nitrogen was untouched. However, when the reaction was performed at higher temperature (120 °C), anilines regardless their electronic nature participated in the reaction to afford the corresponding *N*-arylimidazolones, albeit in moderate yields (**1z–ac**). 5-Diphenylmethylene imidazolone (**1ad**), an analogue of the GFP chromophore, could also be prepared from methyl 2-isocyano-3,3-diphenylacrylate. Finally, the protocol could also be applied to complex natural products. Thus, 3α-amino-5-cholestene[17] and 9-aminoquinidine were converted to their imidazolone derivatives (**1ae**, **1af**) in yields of 73% and 70%, respectively. Derivatives of 3-amino-5-cholestene are important cellular probes with potential medical applications.[18] We believe that such a late-stage functionalization protocol could be a useful synthetic tool in medicinal chemistry. As expected, α-nonsubstituted and α-monosubstituted α-isocyanoacetates failed to participate in this reaction because of the competitive formation of oxazoles.[19]

An enantioenriched methyl α,α-disubstituted α-isocyanoacetate (*R*)-**3b**, prepared according to a literature procedure,[20] participated in the reaction to afford product (*R*)-**1u** without

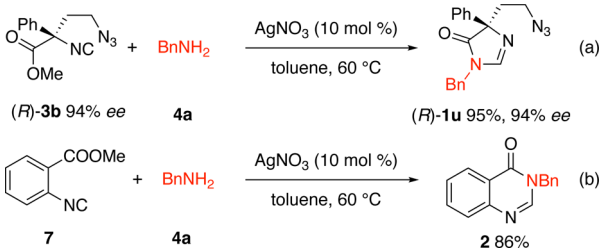
Scheme 2. Silver-Catalyzed Synthesis of Imidazolones 1[a]



[a]20 mol % $AgNO_3$, toluene, 120 °C.

erosion of enantiopurity (Scheme 3a). Notably, the reaction was also applicable to the synthesis of quinazolin-4(3*H*)-one, a

Scheme 3. Synthesis of C-5 Chiral Imidazolone (*R*)-1u and Quinazolin-4-one 2



privileged scaffold in medicinal chemistry (Scheme 3b).[21] Thus, reaction of methyl 2-isocyanobenzoate (**7**) with **4a** under the standard conditions afforded quinazolin-4-one **2** in 86% isolated yield.

A possible reaction pathway is shown in Scheme 4. Coordination of the isocyanide and amine to silver would afford complex **B**. Migratory insertion from **B** would afford **C** and HX, which would undergo salt metathesis to produce

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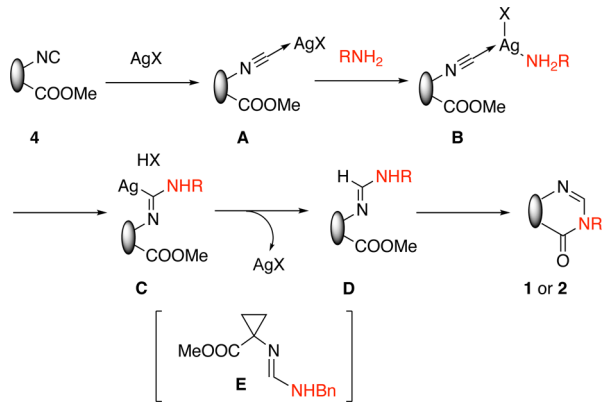
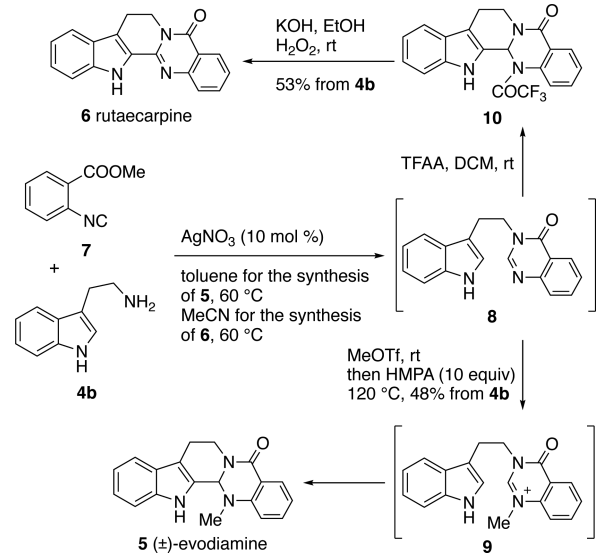
Scheme 4. Possible Reaction Pathway



amidine **D** with concurrent regeneration of the silver salt. Lactamization of **D** would then furnish the observed product. We note that no reaction took place in the absence of silver nitrate and that the formation of amidine **E** was clearly observed when the reaction was performed at 40 °C under otherwise standard conditions.

Evodiamine (**5**) and rutaecarpine (**6**) are quinazolinecarboline alkaloids isolated from the dried fruit of *Evodia rutaecarpa*, a plant used in traditional Chinese medicine against headache, dysentery, cholera, etc. Because of the medicinal importance of these alkaloids, various synthetic routes have been developed.[22] As an illustration of our methodology, the syntheses of evodiamine and rutaecarpine were undertaken (Scheme 5).

Scheme 5. Total Syntheses of (±)-Evodiamine and Rutaecarpine



Silver nitrate-catalyzed condensation of tryptamine (**4b**) with **7** afforded quinazolinone **8**, which without purification was methylated with methyl triflate to afford *N*-methylated intermediate **9**. Adding HMPA to the reaction mixture and heating the solution to 120 °C furnished (±)-evodiamine (**5**) in 48% overall yield. On the other hand, treatment of **8** with TFAA afforded **10**, which upon treatment with hydrogen peroxide under basic conditions provided rutaecarpine (**6**) in 53% overall yield.

In summary, we have developed a new protocol for the synthesis of imidazolones and quinazolin-4-ones by silver nitrate-catalyzed reactions of primary amines with methyl α,α-disubstituted-α-isocyanoacetates and 2-isocyanobenzoates, respectively. The utility of this method was illustrated by the development of concise syntheses of (±)-evodiamine (**5**) and rutaecarpine (**6**).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02334.

Experimental procedures, product characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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