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PII: S0040-4039(15)00009-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.01.006
Reference: TETL 45675

To appear in: *Tetrahedron Letters*

Received Date: 27 November 2014
Revised Date: 18 December 2014
Accepted Date: 2 January 2015

Please cite this article as: Shiroodi, R.K., Rivera Vera, C.I., Dudnik, A.S., Gevorgyan, V., Synthesis of furans and pyrroles via migratory and double migratory cycloisomerization reactions of homopropargylic aldehydes and imines, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.01.006

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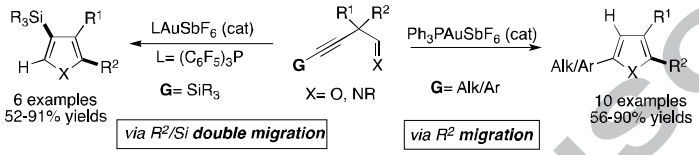

Tetrahedron Letters
journal homepage: www.elsevier.com

Synthesis of furans and pyrroles via migratory and double migratory cycloisomerization reactions of homopropargylic aldehydes and imines

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

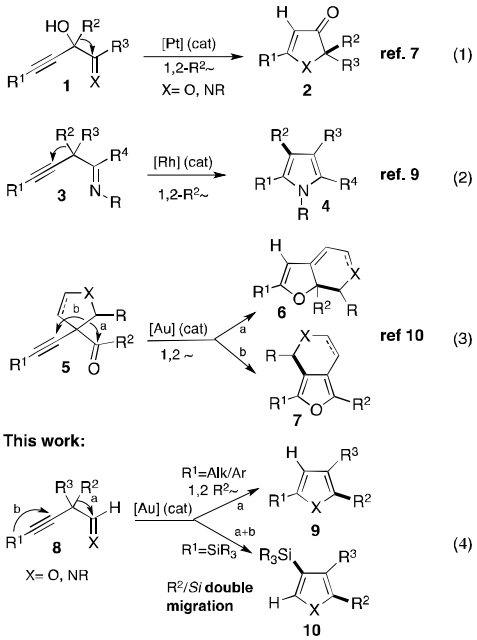
Keywords:
Cycloisomerization
Heterocycles
Double migration
Silicon migration
Gold catalyst

ABSTRACT

A novel gold-catalyzed divergent sysnthesis of furans and pyrroles employing readily available homopropargylic aldehydes and imines have been developed. The regiochemical outcome of this reaction is dependent on the substituent on the terminal alkyne of substrate. Thus, substrates possessing alkyl and aryl substituent at the alkyne moiety produce 2,3,5-substituted furans and pyrroles via a migratory cycloisomerizaton reaction. Whereas, their silicon analogues are capable to undergo a double migratory process leading to 2,3,4-substituted heterocycles.

Furans and pyrroles are highly important motifs exist in a broad range of biologically active natural products[1] and drugs.[2] They also have broad applications as synthetic intermediates[3] and are widely used in material science.[4] Accordingly, a vast number of efficient methodologies toward these important scaffolds have been developed.[1a,5] Among these methods, the transition metal-catalyzed migratory cycloisomerization reaction is one of the powerful approaches, which offers mild and selective assembly of furans and pyrroles with a diverse substitution pattern.[6] Readily available homopropargylic ketones and imines have been employed in migratory cascade reactions [5a,6a] giving access to a variety of heterocycles (Scheme 1). For instance, Kirsch reported[7] a platinum-catalyzed cascade reaction of **1** toward 3(2H)-furanones and 3-pyrrolones **2** proceeding via a pinacol-type 1,2-alkyl migration[8] (eq. 1). Moreover, Tang and Shi reported synthesis of densely-substituted pyrroles **4** from the rhodium-catalyzed reaction of propargylic imines **3**, where one of the substituents of the heterocyclic core is formed via a 1,2-alkyl migration from the adjacent carbon (eq. 2).[9] Recently, Zhang disclosed a divergent reactivity of ketones **5** in the presence of gold catalysts, where a selective 1,2-alkyl migration to the neighboring carbon affords dihydrofurans **6** or furans **7** (eq. 3).[10] Herein, we report a mild and regiodivergent reaction of homopropargylic aldehydes and imines **8** in the presence of gold catalysts towards heterocycles **9** and **10**. Thus, a gold-catalyzed *migratory cycloisomerization* of **8** (R^1= Alk/Ar) produces 2,3,5-substituted heterocycles **9**. Whereas, employment of silylated **8** (R^1=SiR_3) affords 2,3,4-substituted furans and pyrroles **10**

Scheme 1. Cycloisomerization of homopropargylic systems involving a 1,2-migration



proceeding via a *double migratory cycloisomerization* reaction (eq. 4).

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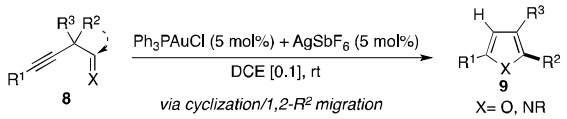
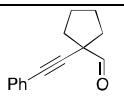
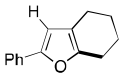
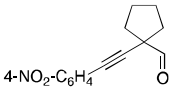
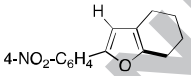
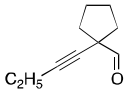
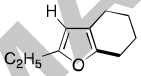
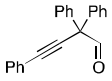
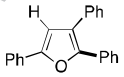
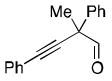
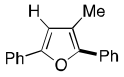
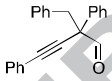
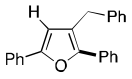
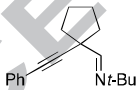
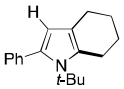
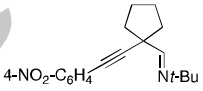
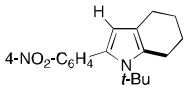
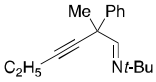
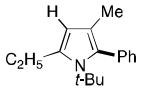
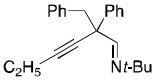
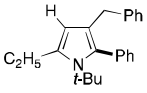
In continuation of our interest in development of cycloisomerization reactions toward synthesis of densely substituted heterocycles,[11] we aimed at employing aldehyde **8** possessing a cyclopentyl group (Scheme 1, X=O, R^1=Ph, R^2=R^3= $(CH_2)_4$) in the transition metal-catalyzed migratory cascade reaction. It was hypothesized that cyclization of the latter in the presence of a metal catalyst would be accompanied with a five-to-six-membered ring expansion[12] and therefore producing the bicyclic fused furan **9** (Scheme 1, X=O, R^1=Ph, R^2=R^3= $(CH_2)_4$). Our optimization study indicated that the use of the cationic gold catalyst,[13] such as triphenylphosphine gold with hexafluoroantimonate counter ion, was the best choice. Thus, we explored the scope of this migratory cycloisomerization. Hence, aldehydes **8a-c** possessing phenyl, electron poor aryl, as well as alkyl substituents at the terminal alkyne position underwent a five-to-six-membered ring expansion during the cycloisomerization process to afford furans **9a-c** in good to excellent yields (entry 1-3). Importantly, this reaction is not limited to cyclic substrates only. Thus, by employing 2,2-diphenyl homopropargyl aldehyde **8d**, a phenyl group migration occurs smoothly to afford the triarylated furan **9d**

Table 1. Scope of the migratory cycloisomerization reaction



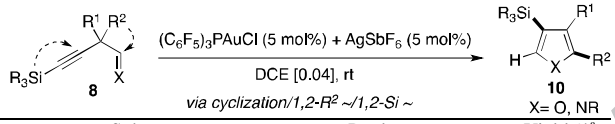
Entry	Substrate		Product		Yield %[a,b]
1		**8a**		**9a**	90
2		**8b**		**9b**	80
3		**8c**		**9c**	71
4		**8d**		**9d**	90
5		**8e**		**9e**	56
6		**8f**		**9f**	58
7		**8g**		**9g**	74
8		**8h**		**9h**	72
9		**8i**		**9i**	70
10		**8j**		**9j**	71

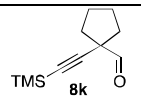
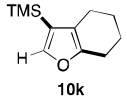
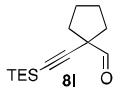
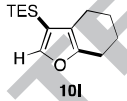
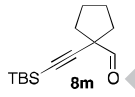
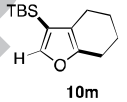
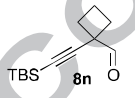
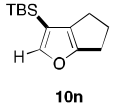
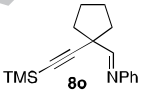
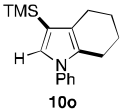
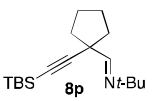
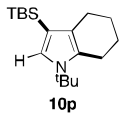
[a] Isolated Yield.
[b] Reactions were performed in 0.5 mmol scale

in an excellent yield (entry 4). Expectedly,[12] a phenyl migration took place over the methyl- and benzyl group migration in cycloisomerization of **8e** and **8f** to furnish **9e** and **9f** in moderate yields (entries 5 and 6). Moreover, tetrasubstituted pyrrols can also be synthesized using 2,2-substituted homopropargylic imines under these reaction conditions. Therefore, the five-to-six-membered ring expansion of imines **8g** and **8h** proceeded smoothly during cyclization to provide pyrroles **9g** and **9h** in good yields (entry 7 and 8). Expectedly, a phenyl group migration occurred preferably over the methyl- and benzyl group migrations to produce pyrroles **9i** and **9j** selectively in good yields (entry 9 and 10).

Next, we hypothesized that employing homopropargylic aldehyde **8** possessing a silicon terminus (Scheme 1, X=O, R^1=$SiMe_3$, R^2=R^3= $(CH_2)_4$) would enable a 1,2-migration of silicon group during the cyclization process.[14] This 1,2-alkyl-/*Si*-double migratory cascade[15] would allow synthesis of 2,3,4-trisubstituted fused furan **10**. Indeed, it was found that cationic $(C_6F_5)_3PAuSbF_6$ catalyst[16] efficiently catalyzes this reaction (Table 2).[17] Thus, homopropargylic aldehyde **8k-m** underwent a facile ring expansion/trimethyl-, triethyl-, and *t*-butyldimethylsilyl migration-cycloisomerization cascade to efficiently produce furans **10k-m**, respectively. Aldehyde **8n** possessing a strained four-membered ring produced bicyclic furan **10n** in a reasonable yield (entry 4). Notably, employment of *t*-Bu- and Ph-protected imines **8o** and **8p** in this double migratory process afforded silylated fused pyrroles **10o** and **10p**.

Table 2. Scope of double migratory reaction

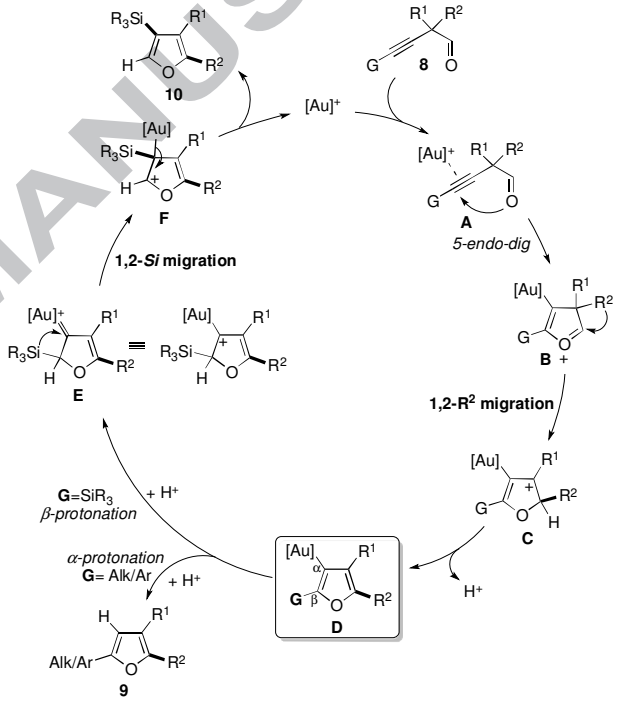


Entry	Substrate	Product	Yield %[a]
1			86
2			91
3			89
4			61
5			52[b]
6			74[b]

[a] Isolated yield.
[b] NMR yield.

We propose the following plausible mechanism for these cascade reactions (Scheme 2). First, the π-philic gold catalyst activates substrate **8**, which upon the following nucleophilic attack of carbonyl at the activated alkyne moiety of **A** in a *5-endo-dig* fashion produces cyclic oxonium intermediate **B**. A 1,2-R^2 migration in the latter takes place to generate an allylic cation **C**, which upon proton loss furnishes the key furyl gold intermediate **D**. In the case of G=Alk or Ar, a protiodematallation (α-protonation) of **D** takes place to produce 2,3,5-trisubstituted furan **9**. Whereas, the β-protonation of the furyl gold species **D** occurs[14] when G=SiR_3 to furnish **E**, in which the positive charge at the carbene carbon is stabilized by the silicon atom.[18] A 1,2-silicon- over hydrogen 1,2-migration in the latter takes place[14] to form F, which upon aromatization affords 2,3,4-trisusbstituted furan **10**.

Scheme 2. Proposed Mechanism for the migratory and double migratory cascade reactions



In summary, two complementary gold-catalyzed cycloisomerization reaction protocols of homopropargylic aldehydes and imines toward differently substituted furans and pyrrols have been developed. The regiochemical outcome depends on the substituent at the terminal alkyne moiety of the substrates. Thus, employment of homopropargylic aldehydes and imines possessing alkyl and aryl substituent at the alkyne moiety produces 2,3,5-substituted heterocycles via a migratory cycloisomerizaton reaction. Whereas, substrates possessing a silicon atom at the terminal position of alkyne undergo a double migratory cascade to afford 2,3,4-substituted furans and pyrrols.[19]

Acknowledgments

We thank National Institutes of Health (GM-64444) for financial support of this work.

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19. (a) *General Procedure for the migratory cycloisomerization reaction of **8** to furans and pyrroles **9***: An oven dried 1 mL V-shape vial equipped with magnetic stir bar was loaded with commercially available chloro(triphenylphosphine) gold (5 mol%, 12.5 mg) and silver hexafluoroantimonate (5 mol%, 8.5 mg) in the glove box. 1,2-dichloroethane (500 μL) was then added and reaction mixture was stirred for 5 min at room temperature. Homopropargylic aldehydes or imines **8** (1.0 equiv, 0.5 mmol) as a solution in 1,2-dichloroethane (500 μL) was added through cannula and the reaction mixture stirred at room temperature until judged completed by GC/MS. The reaction mixture was then passed through Celite®, solvents were removed under reduced pressure, and the residue was purified by flash chromatography using silica gel (Hex/EtOAc= 40/1) to give furans or pyrroles **9**. Representative example: **9e:** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.75 (d, *J* = 7.4 Hz, 4 H), 7.47 (t, *J* = 7.8 Hz, 2 H), 7.42 (t, *J* = 7.8 Hz, 2 H), 7.35-7.24 (m, 2H), 6.64 (s, 1 H), 2.36 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 151.7, 148.2, 131.8, 130.8, 128.7, 128.6, 127.2, 126.7, 125.3, 123.7, 118.7, 110.8, 12.2.

*(b) General Procedure for the double migratory cycloisomerization reaction of **8** to furans and pyrroles **10**:* An oven dried 20 mL round buttom flask equipped with magnetic stir bar was loaded with commercially available chloro[tris(2,3,4,5,6-pentafluorophenyl)-phosphine] gold (5 mol%, , 19.1 mg) and silver hexafluoroantimonate (5 mol%, 8.5 mg) in the glove box. 1,2-dichloroethane (11 mL) was then added and reaction mixture was stirred for 5 min at room temperature. Homopropargylic aldehyde or imine **8** (1.0 equiv, 0.5 mmol) as a solution in 1,2-dichloroethane (1.5 mL) was added through cannula and the reaction mixture stirred at room temperature until judged completed by GC/MS. The reaction mixture was then passed through Celite®, solvents were removed under reduced pressure, and the residue was purified by flash chromatography using silica gel (pure hexanes) to give furans or pyrroles **10**. Representative example: **10k:** ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.15 (s, 1 H), 2.64 - 2.55 (m, 2 H), 2.48 (tt, J = 1.8, 6.1 Hz, 2 H), 1.88 - 1.80 (m, 2 H), 1.79 - 1.72 (m, 2 H), 0.23 (s, 9 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 151.2, 145.1, 120.3, 118.7, 23.3, 23.1, 23.0, 22.9, -0.7.