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$AuCl_3$ catalyzed [3 + 2 + 1] cycloaddition: first use of aldehyde as a carbon monoxide-like one carbon synthon for triple C–C coupling†

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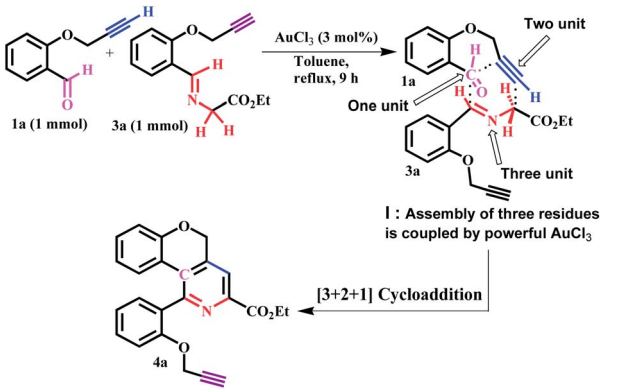
A new [3 + 2 + 1] cycloaddition strategy is demonstrated using an aldehyde, an aldimine of a glycine ester and a terminal triple bond with $AuCl_3$ catalyst. Aldehyde is exploited as the first alternative to the crucial partner CO for triple C–C coupled annulation for the synthesis of novel fused-tricyclic heterocycles.

The cycloaddition reaction is an attractive synthetic tool in organic chemistry which is most frequently used for the direct construction of valuable ring structures.[1] Since the pioneering discovery of CO insertion reactions from carbene chromium carbonyls,[2] the formal [3 + 2 + 1] cycloaddition approach has found innovative applications in the direct synthesis of difficult-to-access functionalized cyclohexanone and other valuable compounds.[3] Carbon monoxide is the crucial one carbon partner in the cycloaddition assembly for dual C–C coupling. Only a few examples are reported to date which may be due to the unavailability of alternative one carbon synthons. Less hazardous and readily available aldehydes (RCH=O) can be utilized as a one carbon synthon for the [3 + 2 + 1] strategy which has the advantage of a triple C–C coupling involving both C=O and C–H. This approach does not need the specially designed reaction set up required for CO which is undetectable to human senses and a "silent killer".[4] We used the aldehyde group of *O*-propargyl salicylaldehyde (**1a**, Scheme 1), its terminal alkyne residue and ethyl glycinate aldimine (**3a**) to undergo a [3 + 2 + 1] cycloaddition through the formation of a complex assembly (**I**, Scheme 1). The natural polycyclic and fused-chromone pyridines are used as traditional medicines and displayed anticancer, antimalarial, antiulcer, antiinflammatory, anti-hepatitis, protein kinase and acetylcholine esterase inhibition activities.[5] In spite of the practical importance of the heterocyclic scaffolds, only a limited number of synthetic methods were developed such as the cycloaddition of nitriles and imines.[6] Therefore, development of a conceptually different catalytic synthetic approach is desirable to afford a new class of 5*H*-benzopyrano[4,3-*c*]pyridines (**4**).

In our initial experiments we were looking for a powerful metal catalyst for the triple C–C coupled intermolecular cycloaddition between the three, two and one units (**I**) of **1a** and **3a**.

To our embarrassment, the [3 + 2 + 1] intermolecular cycloaddition was unsuccessful during our survey with prospective rare-earth[7] ($CeCl_3$, $Yb(OTf)_3$, $La(OTf)_3$ *etc.*) and transition metal[8] catalysts (CuI, $FeCl_3$, $PdCl_2$, $RuCl_3$, $RhCl_3$, $[Ir(COD)Cl]_2$, AgOTf, $PtBr_2$ *etc.*) under refluxing conditions in toluene. Gold compounds are soft Lewis acids and have recently emerged as a powerful catalyst for alkyne, allene and C–H activated functionalization.[9] We found $AuCl_3$ (3 mol%) to be an efficient catalyst to afford the desired compound 5-hydro-1-(2-prop-2-ynyloxyphenyl)-3-ethoxycarbonylbenzopyrano [4,3-*c*]pyridine (**4a**) in a 61% yield after refluxing in toluene for 9 h. The moderate yield was attributed to the formation of a



Scheme 1 [3 + 2 + 1] cycloaddition with one carbon aldehyde synthon.

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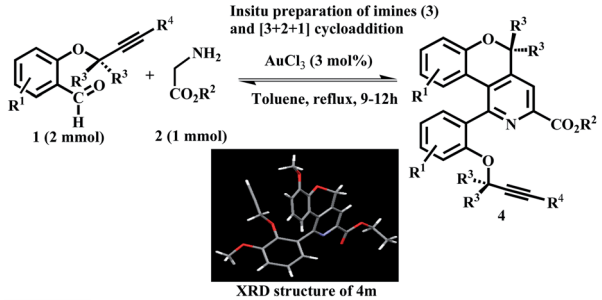
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra, and CIF file. CCDC 938786. For ESI and crystallographic data in CIF see DOI: 10.1039/c3ra47093h



XRD structure of 4m

Entry	Aldehyde (1)	Imine (3)	Time (h)	4, Yield (%)	Product (6)
1	1a		9	4a, 55	
2			12	4b, 56	
3			12	4c, 54	
	R^4= Et (3a); Me (3b); CMe_3 (3c)				
4	1b		10	4d, 50	
5			12	4e, 52	
6			12	4f, 54	
	R^4= Et (3d); Me (3e); CMe_3 (3f)				
7	1c		12	4g, 56	
8			12	4h, 58	
9			9	4i, 52	
	R^4= Et (3g); Me (3h); CMe_3 (3i)				
10	1d		10	4j, 51	
11			10	4k, 50	
12			12	4l, 50	
	R^4= Et (3j); Me (3k); CMe_3 (3l)				
13	1e	3m	10	4m, 55	
14	1f	3n	12	4n, 56	
15	1g	3o	10	4o, 58	
16	1h	3p	18	4p, –	No reaction
17	1i	3q	24	4q, –	No reaction
18	1j	3r	20	4r, –	
19	1a	3s	18	4s, –	

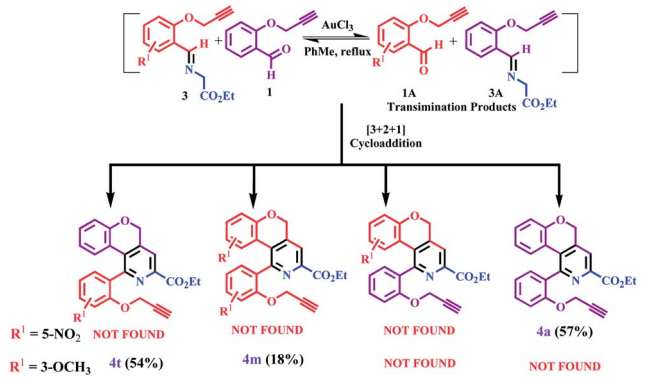
Scheme 2 Synthesized 5*H*-benzopyrano[4,3-*c*]pyridines (**4**).

small amount of the corresponding intramolecular [3 + 2] cycloaddition product 4-hydro-2-ethoxycarbonyl-1*H*-benzopyrano[4,3-*b*]pyrrole (**5a**) from **3a**.

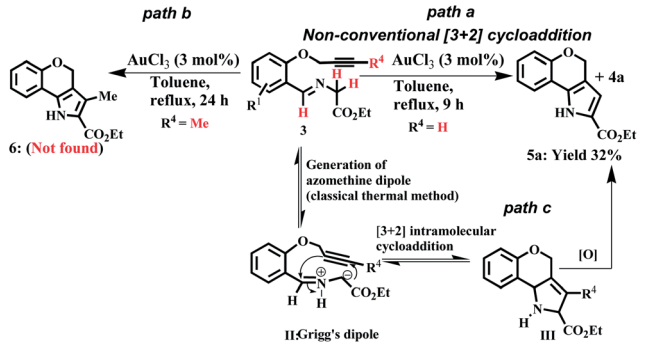
With this initial success we further optimized the [3 + 2 + 1] cycloaddition reaction to prepare the imine **3a** *in situ* and the reaction proceeded smoothly by treatment of 2 mmol of aldehyde (**1a**) and 1 mmol of glycine ester (**2a**) to afford **4a** with a slightly lower yield (55%, entry 1, Scheme 2). The scope of the reaction was explored with unsubstituted and activated phenyl rings which proceeded well with different glycine esters (**4b–o**, entries 1–14). The structure of this new class of fused-heterocyclic compounds was established by single crystal XRD. The structure of **4m** (Scheme 2) and the spectroscopic data (FT-IR, NMR and ESI-MS) of all the new compounds are in the ESI.† The involvement of the C–H of the aldehyde in the cycloaddition was further confirmed by carrying out a reaction using the corresponding ketimine (**3p**) and ketone (**1h**) as the reactants (entry 16) which did not proceed at all. Herein, the terminal triple bond is a crucial partner in the assembly (**I**, Scheme 1) because the reactions were completely blocked on replacement of the propargyloxy group by allyloxy (**1i**, **3q**, entry 17) and also the methylpropargyloxy group (R^2 = Me, **1j**, **3r**, entry 18). Moreover, the free triple bond in the imine (**3**) has a role during construction of the desired 5*H*-benzopyrano[4,3-*c*]pyridine skeleton because the corresponding benzyloxy substituted imine (**3s**) could not synthesize compound **6s** on treatment of **1a** in an unsymmetrical coupling reaction (entry 19). The possibility of the $AuCl_3$-catalyzed [3 + 2 + 1] cycloaddition reaction through formation of an allene-type intermediate[10] was also nullified by executing the reaction with a dimethyl propargyl precursor (**3o**, entry 15) which afforded the desired tricyclic heterocycle **4o**.

To realize the electronic requirements of the [3 + 2 + 1] reaction in the transition state, crossover experiments were executed between two different imines [**3t** (R^1 = 3-OMe) and **3m** (R^1 = 5-NO_2), Scheme 3] and unsubstituted *O*-propargyl salicylaldehyde (**1a**). Interestingly, we observed the occurrence of transimination under the catalytic conditions to form corresponding aldehydes **1A** (**1a,k**) from imines **3** (**3t,m**), imine **3A** from the aldehyde **1a** and *in situ* generated ethyl glycinate (**2a**) from **3**. The construction of the four possible 5*H*-benzopyrano[4,3-*c*]pyridines are depicted in Scheme 3. Surprisingly, out of the four possible products, the imine **3t** bearing the NO_2 group produced **4a** (entry 1, table in Scheme 2) as the sole product which was generated from the relatively electron rich transiminated imine **3a**. However, in the second experiment with aldimine (**3m**) bearing the activated aromatic nucleus afforded the desired compound **4t** as a major product along with **4m** in 3 : 1 yield ratio. The other two possible compounds were not found in the post reaction mixture. These crossover experiments indicated that the transition state of the new [3 + 2 + 1] cycloaddition reaction is assisted by electron donating and unfavoured by electron withdrawing substituents present in the aromatic ring of the imines (**3**) and aldehydes (**1**).

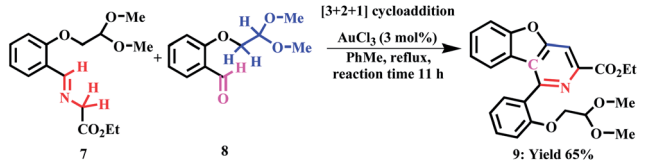
Interestingly, Grigg *et al.*[11a] and Tsuge *et al.*[11b] reported the classical [3 + 2] intramolecular 1,3-dipolar cycloaddition (DC) involving Grigg's dipole[11c] (*path c*, **II**, Scheme 4) generated *in situ* through 1,2-prototropic shift under heating conditions (1–2 days) using phenyl glycinate and non-terminal alkyne derivatives of **3a** to afford the corresponding cycloadduct of **III** along



Scheme 3 Cross coupling reaction with the transimination.



Scheme 4 Non-conventional [3 + 2] intramolecular cycloaddition.



Scheme 5 A new [3 + 2 + 1] cycloaddition to synthesize benzofurano [3,2-*c*]pyridine.

with dehydrogenated pyrrole (only 3%).[11] However, the glycine ester aldimine **3** bearing a non-terminal alkyne was never attempted for the 1,3-DC reaction. Our attempts for the conventional monocatalytic 1,3-dipolar cycloaddition (*path c*) of **3a** under heating conditions to **III** or the valuable **5a** [12] was unsuccessful. The 1,3-DC reaction with $AuCl_3$ was also completely arrested on replacement of ≡C–H by ≡C–Me (*path b*) to afford the desired heterocycle **6**. It indicates that the [3 + 2] cycloaddition (*path a*) is passing through a non-conventional pathway to construct **4a** along with **5a**. Thus, it is expected that the activation of ≡C–H by $AuCl_3$ is crucial for executing both the [3 + 2] and [3 + 2 + 1] cycloaddition reactions.

Next, we sought to expand the scope of the C–H activation by the powerful $AuCl_3$ catalyst in other precursors towards the direct construction of new *N*-heterocycles. We used aldehyde **7** and imine **8** (Scheme 5) bearing no triple bond. To our delight, it responded well to construct a new class of benzofurano[3,2-*c*] pyridines (**9**) involving a new [3 + 2 + 1] strategy. The synthesis of this compound is unknown in the literature.[13] Herein, the C_3–H bonds of the 3,3-dimethoxyethoxy group of the aldehyde (**7**) and CH_2 of imine (**8**) are expected to undergo activation with $AuCl_3$ and the subsequent elimination of MeOH to afford **9** through the [3 + 2 + 1] cycloaddition.

In conclusion, we have demonstrated the first example to use aldehyde as a carbon monoxide-like one carbon synthon for a triple C–C coupled [3 + 2 + 1] cycloaddition strategy. $AuCl_3$ catalyzed multi C–H bond activated formal cycloaddition leads to the construction of valuable tricyclic *N*-heterocycles such as 5*H*-benzopyrano[4,3-*c*]pyridine and benzofurano[4,3-*b*]pyridine in a single operation. The new [3 + 2 + 1] cycloaddition approach, use of aldehyde for triple C–C coupling one carbon synthon and powerful C–H activation capability of $AuCl_3$ will find important applications in synthetic chemistry.

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