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One pot rhodium catalyzed, base and solvent-free synthesis of 2-(bromomethyl)furan derivatives and synthesis of Hashmi phenol through platinum catalyzed cascade cyclization

Mahalingam Sivaraman, Doraiswamy Muralidharan, Paramasivan T. Perumal *

Organic Chemistry Division, CSIR-Central Leather Research Institute, Adyar, Chennai 600020, Tamilnadu, India

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ABSTRACT

A novel rhodium catalyzed one pot synthetic strategy was developed to construct fused furan scaffolds via in situ generation of dicarbonyl iodonium ylide and its application to the synthesis of Hashmi phenol is described.

Fused furan derivatives are found to be the core structure in numerous natural products and pharmaceutical scaffolds (Fig. 1).[1] Because of the wide range of biological activities and pharmaceutical applications, organic chemists are interested in the synthesis of this privileged structure.[2] Many synthetic approaches to this skeleton have been disclosed in the literature, of particular value is transition metal catalyzed cyclization of alkyne.[3] Although these methods offer some advantages, typically they require the preparation of starting materials. Therefore, there is still scope for the development of new methods, especially one pot reaction which do not require starting material preparation. 1,3-Dicarbonyl iodonium ylide is relatively stable which is equivalent to the carbene precursors and a safe alternative to the diazo compounds.[4] The ylide behaves as an excellent 1,3-dipole and undergoes [3+2]-cycloadditon with suitable acceptors to provide a wide range of five-membered heterocycles.[4c,5] From previous reports we observed the interesting chemistry of ylide with phenyl acetylenes, ketenes, nitriles, isocyanates, isothiocyanates, dienes, and carbodiimides leading to five-membered fused heterocycles.[4–6]

We were interested in the one pot and cascade reactions to develop a green approach to avoid the toxic waste to the environment. So we planned an one pot synthesis of 2-(bromomethyl)furans directly through the [3+2]-cycloaddition of 1,3-cyclic diketones and propargyl bromide without isolation of ylide and to functionalize C–Br bond further. To test this strategy first we chose the known 5,5-dimethyl-1,3-cyclohexanedione phenyliodonium ylide (**1a**′) as a substrate, which is easily synthesized by condensation of $PhI(OAc)_2$ with dimedone under basic condition.[7] $Rh_2(OAc)_4$ catalyzed reaction of **1a**′ and propargyl bromide (**2**) under the solvent-free condition leads to 2-(bromomethyl)-6,7-dihydro-6,6-dimethylbenzofuran-4(5*H*)-one (**3a**) with an isolated yield of 53% (Scheme 1).

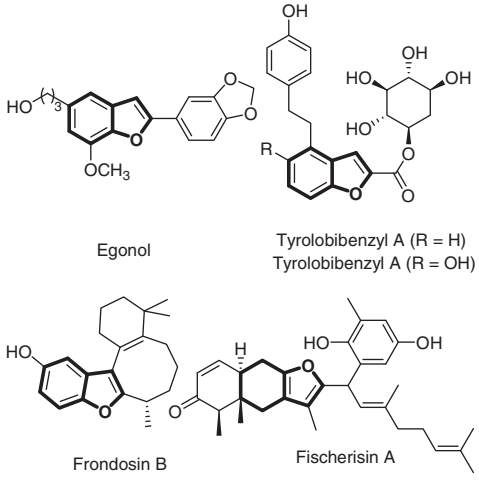

Figure 1. Fused furan containing natural products.

* Corresponding author.
E-mail address: ptperumal@gmail.com (P.T. Perumal).

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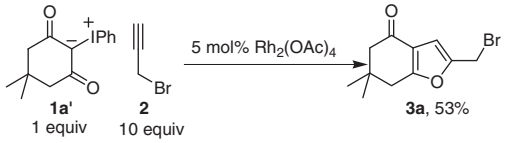


Scheme 1. Reaction of iodonium ylide (**1a**′) and propargyl bromide.

With this encouraging result we examined the one pot reaction of dimidone (**1a**), propargyl bromide (10 equiv), $PhI(OAc)_2$ (1.1 equiv), K_2CO_3 (1.1 equiv), and $Rh_2(OAc)_4$ (10 mol %) and obtained **3a** in 65% yield (Table 1, entry 1). When the reaction was carried out in the absence of base, we observed a slight increase in the yield from 65% to 67% (Table 1, entry 2). The reaction when performed in the absence of either $Rh_2(OAc)_4$ or $PhI(OAc)_2$, was found to be inefficient (Table 1, entries 3 and 4). On further optimization of reaction conditions, we found that only 2 equiv of propargyl bromide, 1.1 equiv of $PhI(OAc)_2$, and 1 mol % $Rh_2(OAc)_4$ were enough for this effective transformation to yield 76% of **3a** (Table 1, entry 8). When the reaction was carried out in the presence of $PhI(CF_3CO_2)_2$ instead of $PhI(OAc)_2$ we got a reduced yield (30%, Table 1, entry 9), and the $Cu(acac)_2$ catalyzed reaction also yielded only 37% (Table 1, entry 10). Finally we achieved an one pot rhodium catalyzed base and solvent free in situ generation of dicarbonyl iodonium ylide which with propargyl bromide lead to the 2-(bromomethyl)furan derivatives. Product **3a** is unequivocally confirmed by 1D and 2D NMR techniques. After confirmation of the product and optimum reaction conditions (Table 1, entry 8) in hand, we examined the scope of this transformation and the results are presented in Table 2.

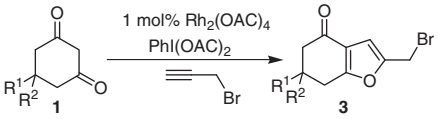
Plausible reaction pathways are summarized for the formation of 2-(bromomethyl)furans in Scheme 2, wherein the in situ generated iodonium ylide serves as the source of initial carbene (or carbenoid), which is transferred to the triple bond of propargyl bromide via rhodium complexes **4** and **5**. The formation of **3a** may involve a [3+2]-cycloaddition of the carbenoid mechanism (path A), which is already well documented.[4c,5] And also, we are not omitting the possibility of cyclopropenation followed by cyclization (path B).[8]

Table 1
Optimization of reaction conditions of **3a**

Entry	Catalyst (mol %)	Additives (equiv)	Yield[b] (%)	Time (min)
1	$Rh_2(OAc)_4$ (10)	$PhI(OAc)_2$ (1.1) + K_2CO_3 (1.1)	65	30
2	$Rh_2(OAc)_4$ (10)	$PhI(OAc)_2$ (1.1)	67	30
3	—	$PhI(OAc)_2$ (1.1)	—	120
4	$Rh_2(OAc)_4$ (10)	—	—	120
5	$Rh_2(OAc)_4$ (5)	$PhI(OAc)_2$ (1.1)	71	60
6	$Rh_2(OAc)_4$ (1)	$PhI(OAc)_2$ (1.1)	73	60
7[c]	$Rh_2(OAc)_4$ (1)	$PhI(OAc)_2$ (1.1)	73	60
8[d]	**$Rh_2(OAc)_4$ (1)**	**$PhI(OAc)_2$ (1.1)**	**76**	**60**
9[d]	$Rh_2(OAc)_4$ (1)	$PhI(CF_3CO_2)_2$ (1.1)	30	120
10[d]	$Cu(acac)_2$ (1)	$PhI(OAc)_2$ (1.1)	37	120

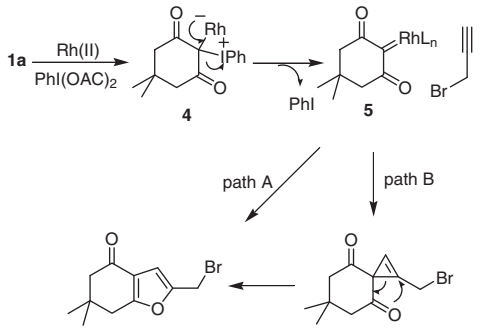
[a] One equivalent of dimedone, 10 equiv of propargyl bromide at room temperature, unless otherwise mentioned.
[b] Isolated yield.
[c] Five equivalents of propargyl bromide.
[d] Two equivalents of propargyl bromide.

Table 2
Substrate scope of the reaction

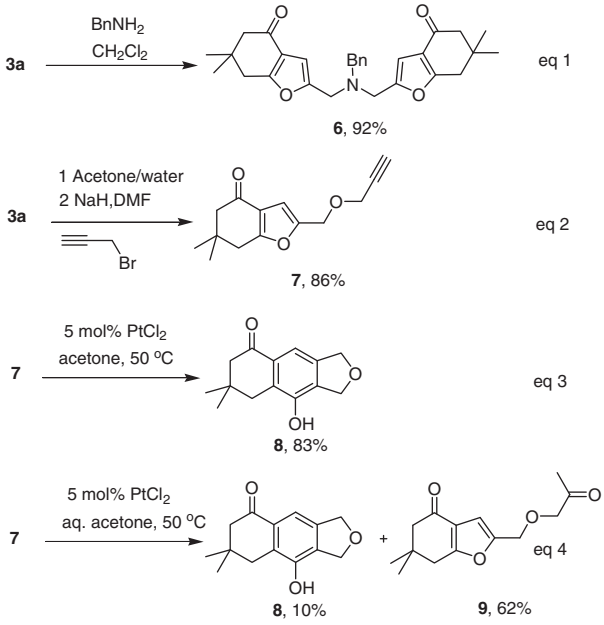


Entry	R^1	R^2	Product	% Yield[a] (Time)[b]
1	CH_3	CH_3	**3a**	76 (1.0)
2	H	CH_3	**3b**	78 (1.0)
3	H	H	**3c**	56 (1.5)
4	H	C_6H_5	**3d**	54 (2.0)
5	H	4-CH_3O–C_6H_4	**3e**	67 (1.5)
6	H	3,5-$(CH_3O)_2$–C_6H_3	**3f**	70 (1.0)
7	H	3,4,5-$(CH_3O)_3$–C_6H_2	**3g**	72 (1.0)
8	H	4-Br–C_6H_4	**3h**	52 (2.0)
9	H	4-Cl–C_6H_4	**3i**	65 (1.5)
10	H	2,6-Cl_2–C_6H_3	**3j**	66 (1.5)
11	H	4-F–C_6H_4	**3k**	72 (1.0)
12	4,4-dimethylcyclohexane-1,3-dione		**3l**, **3l**′ (1:1)	80 (1.0)

[a] Isolated yield.
[b] Time in hour.



Scheme 2. Plausible reaction mechanism for **3a**.



Scheme 3. Chemical transformation of 2-(bromomethyl)furans.

We planned further transformation of 2-(bromomethyl)furans (**3a**), where the presence of the C–Br bond provided an easy access to other useful organic scaffolds. The product **3a** is easily aminated by treatment with $BnNH_2$ in CH_2Cl_2 at room temperature to afford **6** in 92% yield (Scheme 3, Eq. 1).[9] The product **3a** when treated with acetone and water followed by propargylation led to 6,7-dihydro-6,6-dimethyl-2-((prop-2-ynyloxy)methyl)benzofuran-4(5*H*)-one (**7**) with overall yield 86% (Scheme 3, Eq. 2).[9,10] From the literature review we found that the ring transformation of 2-((prop-2-ynyloxy)methyl)furan lead to the Hashmi phenol.[10,11] To examine this, we have chosen $PtCl_2$ as the catalyst for this transformation. Treatment of **7** with 5 mol % of $PtCl_2$ in acetone at 50 °C affords 7,8-dihydro-9-hydroxy-7,7-dimethylnaphtho[2,3-c]furan-5(1*H*,3*H*,6*H*)-one (Hashmi phenol, **8**), isolated yield 83% (Scheme 3, Eq. 3). The treatment of **7** with 5 mol % of $PtCl_2$ in aq acetone at 50 °C afforded 62% of hydrated product **9** along with 10% of **8** (Scheme 3, Eq. 4).

In conclusion, we have developed a facile one pot, base and solvent-free pathway for the synthesis of 2-(bromomethyl)furans directly from in situ generated 1,3-dicarbonyl iodonium ylide. This reaction involves readily available starting materials, high atom-economy, low catalyst loading, and tolerates a wide scope of substrates to afford medium to good yield. The product **3a** is a useful key intermediate in the synthesis of furoscrobiculin B[12] and further transformation of **3a** is also achieved. Subsequent research will focus on application of this methodology to access five-membered heterocycles.

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Supplementary data

Supplementary data (experimental procedures, analytical data and scanned copies of ^1H and ^{13}C NMR of compound **3a**–**l**, **3l′**, **6**, **7**, **8**, **9**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.108.

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