Tetrahedron Letters 58 (2017) 1098–1101

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ruthenium-catalyzed selective synthesis of monoalkylated barbituric acids through "borrowing hydrogen" methodology

Anggi Eka Putra [a], Yohei Oe [a,b,*], Tetsuo Ohta [a,b]

[a] Graduate School of Life and Medical Sciences, Doshisha University, 1-3 Tatara Miyakodani, Kyotanabe-shi, Kyoto 610-0394, Japan
[b] Department of Biomedical Information, Faculty of Life and Medical Sciences, Doshisha University, 1-3 Tatara Miyakodani, Kyotanabe-shi, Kyoto 610-0394, Japan

ARTICLE INFO

Article history:
Received 22 November 2016
Revised 13 January 2017
Accepted 23 January 2017
Available online 7 February 2017

Keywords:
Barbituric acids
Alkylation
Alcohol
Borrowing hydrogen
Ruthenium catalysis

ABSTRACT

An environmentally benign alkylation of barbituric acids via "borrowing hydrogen" process with ruthenium catalysis has been established. The corresponding 5-(alkyl)barubituric acids were obtained in good to excellent yields with low catalyst loading. Various substrates including aliphatic alcohols were tolerated in the present catalytic system. A novel method for construction of barbituric acid-fused benzopyrane derivatives was also demonstrated.

Nitrogen-containing heterocyclic compounds are skeletons of various biologically active substances.[1] Barbituric acid is one of the most important nitrogen-containing heterocyclic systems; it is found in various natural and synthesized compounds of anesthetics, anti-inflammatory drugs, analgesics, anxiolytics, anti-cancer drugs, HIV/AIDS protease inhibitors, and others.[2,3] Among them, its 5-alkylated motifs are an important class of barbituric acid derivatives for medicines (Fig. 1). Therefore, the development of an efficient method for selective alkylation of barbituric acids is very important for synthetic purposes.

The use of alkyl halides should be avoided from the viewpoint of green chemistry, and traditional alkylation method using alkyl halides for the alkylation of barbituric acids is ineffective because of unexpected multiple alkylations.[4] The Tsuji-Trost reaction of barbituric acids with allyl alcohols or their derivatives has been reported for the alternative barbituric acid alkylation, though multiple alkylations occurred.[5] Reaction of barbituric acids with aldehydes or ketones followed by reduction was found to be a more efficient way to install an alkyl group on the barbituric acids; however, a two-step reaction and external hydrogen sources were required.[6,7] A simpler method was found to be treatment of the barbituric acids with aldehydes (or ketones) followed by hydrogenation in the presence of a Pt/C or Pd/C catalyst in a one-pot scheme.[8] Afterward, ethidines were found to be useful hydrogen donors in the presence of organocatalyst.[9] However, these two reactions also required the use of additional hydrogen donors.

Alkylation of nucleophilic reagents with alcohols using transition metal catalysts has been paid much attention.[10,11] Although alcohol is a relatively inert electrophile, it is a useful alkylating reagent under the "borrowing hydrogen" conditions. This methodology also enabled us to achieve environmentally benign alkylation of barbituric acids. Grigg reported microwave-assisted alkylation of 1,3-dimethylbarbituric acids with alcohol by using $[Cp*IrCl_2]_2$ as a catalyst, but the generality of the barbituric acids was not investigated.[12] We also reported Pd/C-catalyzed alkylation of 1,3-dimethylbarbituric acid and barbituric acid with alcohols, but found that only benzylic alcohols could be used.[11m] Therefore, an efficient catalytic system that tolerates a variety of barbituric acids and alcohols is desired. Here, we report a general alkylation of barbituric acids with alcohols via the hydrogen borrowing method with a Ru catalyst, tolerating a variety alcohol substrates including the aliphatic one (Scheme 1).

We tested a reaction of 1,3-dimethylbarbituric acid (**1a**) and benzyl alcohol (**2a**) with several catalysts (Table 1). Although it has been reported that $[Cp*IrCl_2]_2$ afforded a high yield of the corresponding product **3aa** under microwave irradiation,[12] this catalyst failed to give a full conversion even for a long reaction time under conventional thermal heating (entry 1). $Pd(OAc)_2$ and Pd/C showed good catalytic activities, respectively obtaining **3aa** in

* Corresponding author at: Graduate School of Life and Medical Sciences, Doshisha University, 1-3 Tatara Miyakodani, Kyotanabe-shi, Kyoto 610-0394, Japan.
E-mail address: yoe@mail.doshisha.ac.jp (Y. Oe).

http://dx.doi.org/10.1016/j.tetlet.2017.01.070
0040-4039/

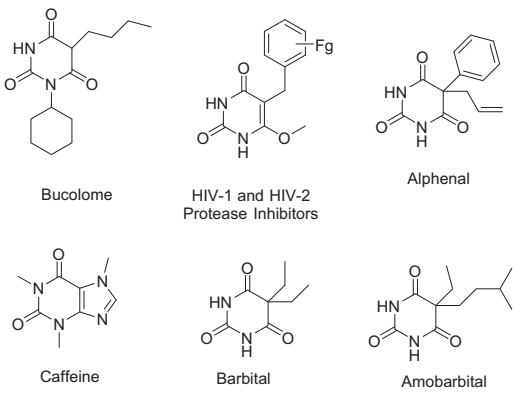
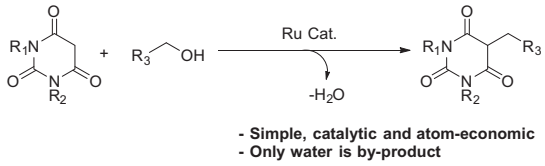


Fig. 1. Examples of 5-alkylated barbituric acids motif on biologically active molecules.



Scheme 1. This work.

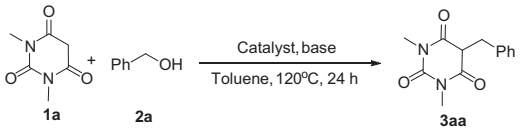
68% and 77% yield (entries 2 and 3). Although $[RuCl_2(p\text{-cymene})]_2$ itself afforded **3aa** in moderate yield, addition of dppf improved the catalytic efficiency, obtaining **3aa** in 88% yield (entries 4 and 5). With this result, we tested several ruthenium complexes (entry 5–7) and found that $RuCl_2(PPh_3)_3$ was superior than the others, affording **3aa** in 96% yield (entry 7). $RuCl_2(PPh_3)_3$ also showed the highest turnover frequency (TOF) among we tested. When K_2CO_3 was used instead of KOH, the catalytic efficiency slightly improved (entry 8). Although reducing the catalyst loadings to 0.5 mol% Ru led to a decrease in the product yield, high reaction efficiency was obtained even with 5 mol% of K_2CO_3 (entries 9–11). A small excess of **2a** (1.2 eq.) was enough to yield **3aa** in sufficient yield (entry 12). Finally, it was found that the reaction completed after 8 h (entry 13).[13]

With the optimized reaction condition in hand, we tested the scope of alcohol substrates (Table 2). To our delight, all of the benzylic alcohols having an electron donating group such as a methyl and hydroxymethyl group at any position (*ortho*, *para* and *meta*) **2a-2f** afforded good to excellent yields of the corresponding alkylated products **3aa-3af** (entries 2–6). As well as benzylic alcohol having an electron withdrawing group **2g** and **2h**, the reaction using benzylic alcohol containing an electron withdrawing group also gave a very satisfying result (entries 7–8); even a very strong electron withdrawing group such as a trifluoromethyl group was tolerated (entry 8). Although the reaction time had to be prolonged to 24 h, 2-naphthylmethanol (**2i**) was found to give an excellent yield of the corresponding product **3ai** (99% yield, entry 9). Unfortunately, the yield was lower (72%) when 1-napthpthylmethanol (**2j**) was used (entry 10). Alcohols such as piperonyl alcohol (**2k**) and furanyl alcohol (**2l**) bearing a heterocyclic substituent to give the corresponding products **3ak** and **3al** in 97% and 94% yield (entries 11 and 12). We were pleased to find that the aliphatic alcohols were also usable in the present catalytic transformation (entries 13–15). The reaction of 1,3-dimethylbarbituric acid (**1a**) with 1-hexanol (**2m**) and 1-octanol (**2n**) nicely proceeded to afford high yields of the corresponding 5-alkylbarbituric acids **2am** and **2an** (entries 13 and 14).

Next, we moved our attention to the influence of substituents on nitrogen atoms of barbituric acids (Scheme 2). Both reactions of **2a** with *N*-cyclohexyl **1b** and *N*-phenyl **1c** took place to afford the corresponding alkylated products **3ba** and **3ca** in 84% and 99% yield. Of note is that the reaction of barbituric acid (**1d**) with **2a** provided 5-benzylated product **3da** in 83% yield without accompanying formation of the corresponding *N*- and *O*-alkylated by-products.

It was considered that the present "borrowing hydrogen" alkylation of barbituric acid with salicyl alcohols **2p-r** followed by the intramolecular cyclization with the acid catalyst would afford the corresponding benzopyrane derivatives (Scheme 3), which is the key structure of bioactive compounds such as antagonists for neuropeptide S receptor (NPSR),[14] and we found that this type of heterocyclic compounds were efficiently synthesized via the

Table 1
Optimization of reaction condition.[a]



Entry	Catalyst (mol% metal)	Base (mol%)	**2a** (eq.)	Yield (%)[b]	TOF (h^{-1})[c]
1	$[Cp*IrCl_2]_2$ (1)	KOH (20)	2	78	25
2	$Pd(OAc)_2$ (1)	KOH (20)	2	68	32
3	Pd/C (1)	KOH (20)	2	77	22
4	$[RuCl_2(p\text{-cymene})_2]_2$ (1)	KOH (20)	2	26	–
5	$[RuCl_2(p\text{-cymene})_2]_2$/ 2dppf (1)	KOH (20)	2	88	37
6	$RuHCl(CO)(PPh_3)_3$ (1)	KOH (20)	2	84	51
7	$RuCl_2(PPh_3)_3$ (1)	KOH (20)	2	96	53
8	$RuCl_2(PPh_3)_3$ (1)	K_2CO_3 (20)	2	98	–
9	$RuCl_2(PPh_3)_3$ (0.5)	K_2CO_3 (20)	2	42	–
10	$RuCl_2(PPh_3)_3$ (1)	K_2CO_3 (5)	2	99	–
11	$RuCl_2(PPh_3)_3$ (1)	–	2	30	–
12	$RuCl_2(PPh_3)_3$(1)	K_2CO_3 (5)	1.2	99	–
13[d]	$RuCl_2(PPh_3)_3$ (1)	K_2CO_3 (5)	1.2	95	–

[a] Reaction condition: mixture of **1a** (1 mmol), **2a**, catalyst (1 mol% metal), and base were heated at 120 °C in toluene for 24 h.
[b] Determined by ^1H NMR.
[c] Determined at initial conversion points after 30 min.
[d] for 8 h.