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Ruthenium-catalyzed synthesis of 1,3,5-triazin-2(1*H*)-ones and dihydro[1,3,5]triazino[1,2-*a*]-benzimidazoles from alcohols and guanides†

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An efficient ruthenium-catalyzed synthesis of tri-substituted 1,3,5-triazinones from alcohols and guanylureas under mild conditions has been developed. The scope of both the alcohols and guanylureas in the reaction is demonstrated. This ruthenium-catalyzed ring-forming process can be successfully extended to 2-guanidinobenzimidazoles to afford substituted dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles.

Introduction

A triazine fragment is a ubiquitous structure that displays several biological activities, such as antibacterial, anti-HSV-1, anticancer and anti-HIV activities.[1–4] Among the triazine derivatives reported, 1,3,5-triazinones, with particular reference to 3,4-dihydro-triazin-2(1*H*)-ones, have been reported as the first class of BACE-1 and GSK-3β dual-target inhibitors in the search for innovative Alzheimer's disease (AD) modifiers.[5] However, there are few reports on the synthesis of these compounds at present.[5,6] For this reason, the development of synthetic protocols and biological activities for functionalized 1,3,5-triazinones has always been an active area of research. Additionally, heterocyclic compounds with a 1,3,5-triazino[1,2-*a*]-benzimidazole nucleus have been reported to possess a variety of biological effects, such as antibacterial and dihydrofolate reductase (DHFR) inhibitory effects.[4] The most common synthetic methods of 1,3,5-triazino[1,2-*a*]-benzimidazoles that have been reported are fundamentally based on the formation of a triazinic ring of 2-guanidinobenzimidazole with aldehydes and isocyanates.[7] On the other hand, transition metal catalysts have more recently been found to bring about *C*- and *N*-alkylation reactions with alcohols as alkylating agents *via* a hydrogen autotransfer pathway, exemplifying the efficiency of this bond construction.[8] Compared to other alkylating agents, alcohols are readily available and are considered potential agents. Recently, we independently discovered a $Ru_3(CO)_{12}$ catalyzed reaction of alcohols and biguanides to access tri-substituted 1,3,5-triazines.[9] As a continuation of our studies on metal-catalyzed atom-economical reactions, in this paper, we wish to develop ruthenium-catalyzed alcohols with guanylureas and 2-guanidinobenzimidazoles to synthesize 1,3,5-triazin-2(1*H*)-ones and dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles.[10]

Results and discussion

Under our previously established conditions for ruthenium-catalyzed synthesis of 1,3,5-triazines, the reaction of benzyl alcohol (**1a**) with (*N*′-phenylcarbamimidoyl)urea (**2a**) with $Ru_3(CO)_{12}$ (2 mol%) and *t*-BuOK (3 equiv.) produced 1,3,5-triazin-2(1*H*)-one product **3a** in 30% yield after 20 h at 100 °C (Table 1, entry 1).[9] Subsequently, we evaluated the utility of several commercially available ruthenium complexes. The data from Table 1 indicate that moderate yields can be obtained under our previously established reaction conditions. Gratifyingly, the optimal yield was obtained when using $RuCl_2(COD)$ as a catalyst (Table 1, entry 4). We observed that lowering the reaction temperature to 80 °C or increasing the reaction temperature to reflux resulted in a lower yield (Table 1, entries 5 and 6). The formation of **3a** was related to the reaction time, and changing the reaction time to 28 h or 10 h resulted in a lower yield (Table 1, entries 7 and 8). Further studies on the loading of the catalyst and base revealed that the reaction conducted with 1 mol% of the Ru complex or 4 mol% of the Ru complex gave **3a** in a slightly lower yield (Table 1, entries 9 and 10). Reducing and increasing the amount of *t*-BuOK resulted in yields of 17% and 21%, respectively (Table 1, entries 11 and 12). Different solvents were screened, and dioxane was found to be the best one (Table 1, entries 4, 13 and 14). Notably, other bases such as MeONa, NaH, and DBU gave no desired product as we have previously reported.[9]

With the optimized conditions in hand, we first explored the scope of the process with respect to the aromatic unit of aliphatic alcohols **1** (Table 2). A broad range of arenes with

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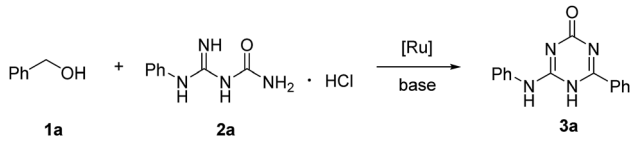
Table 1 Optimization of the reaction conditions

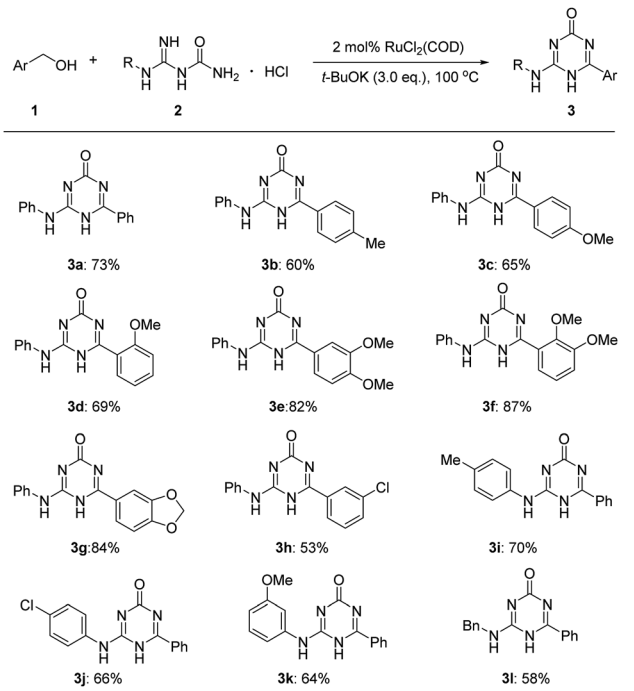


1a 2a 3a

Entry	Catalyst	Base	Time (h)	Temp. (°C)	Solvent	Yield[a] (%)
1	$Ru_3(CO)_{12}$	*t*-BuOK	20	100	Dioxane	30
2	$RuCl_2(PPh_3)_3$	*t*-BuOK	20	100	Dioxane	48
3	$RuCl(PPh_3)_2(Cp)$	*t*-BuOK	20	100	Dioxane	41
4	$RuCl_2$(COD)	*t*-BuOK	20	100	Dioxane	73
5	$RuCl_2$(COD)	*t*-BuOK	20	Reflux	Dioxane	12
6	$RuCl_2$(COD)	*t*-BuOK	20	80	Dioxane	53
7	$RuCl_2$(COD)	*t*-BuOK	10	100	Dioxane	18
8	$RuCl_2$(COD)	*t*-BuOK	28	100	Dioxane	34
9[b]	$RuCl_2$(COD)	*t*-BuOK	20	100	Dioxane	52
10[c]	$RuCl_2$(COD)	*t*-BuOK	20	100	Dioxane	61
11[d]	$RuCl_2$(COD)	*t*-BuOK	20	100	Dioxane	17
12[e]	$RuCl_2$(COD)	*t*-BuOK	20	100	Dioxane	21
13	$RuCl_2$(COD)	*t*-BuOK	20	Reflux	THF	37
14	$RuCl_2$(COD)	*t*-BuOK	20	100	DMSO	Trace

[a] Reaction conditions: **1a** (0.75 mmol), **2a** (0.5 mmol), catalyst (2 mol%), base (3.0 equiv.), solvent (3 mL); isolated yields are shown. [b] $RuCl_2$(COD) (1 mol%). [c] $RuCl_2$(COD) (4 mol%). [d] *t*-BuOK (2.0 equiv.). [e] *t*-BuOK (4.0 mmol).

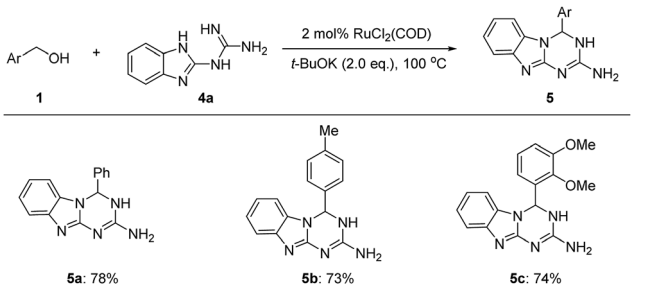
Table 2 Scope of the synthesis of **3**[a]



[a] All reactions were performed with 0.75 mmol of **1** and 0.5 mmol of **2** using $RuCl_2$(COD) (2 mol%), *t*-BuOK (3.0 equiv.), and dioxane (3 mL) at 100 °C for 20 h; isolated yields are shown.

electron-rich groups are tolerated to give the corresponding 1,3,5-triazin-2(1*H*)-ones (*e.g.*, **3b–g**) in good yields. For benzyl alcohols with electron-withdrawing groups, reaction to **3h** could be achieved, but the yield of the process was lower than that for the other examples.

Table 3 Ru-Catalyzed synthesis of 2-amino-*s*-triazino[1,2-*a*]benzimidazoles **5**[a]



[a] All reactions were performed with 0.5 mmol of **1** and 0.5 mmol of **4a** using Ru(COD)Cl_2 (2 mol%), *t*-BuOK (2.0 equiv.), and dioxane (3 mL) at 100 °C for 25 h; isolated yields are shown.

Next, this reaction also occurred with benzyl alcohol (**1a**) and a variety of (*N*′-aryl substituted carbamimidoyl)ureas (**2**) (Table 2). Both electron-donating and electron-withdrawing substituents (such as methoxy, methyl, and chloro) on the aryl ring are well-tolerated in this transformation, affording good yields of the products (*e.g.*, **3i–k**). The coupling reaction of (benzyl-substituted carbamimidoyl)urea also proceeds smoothly to give the desired product (**3l**).

The catalytic protocol can be similarly applied to form dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles from aryl alcohol compounds with 2-guanidinobenzimidazole. It was found that benzyl alcohol, *p*-tolylmethanol, and (2,3-dimethoxyphenyl)-methanol can be easily accessed under standard reaction conditions, providing the corresponding products **5a–5c** in good yields (Table 3).

Conclusions

In summary, we have demonstrated a Ru(II)-catalyzed synthesis of di-substituted 1,3,5-triazin-2(1*H*)-ones from aryl alcohols with guanylureas in combination with a base *via* a hydrogen autotransfer pathway. The new method is compatible with various aryl alcohols containing both electron-donating and electron-withdrawing substituents. *N*′-Aryl and benzyl carbamimidoylureas are tolerated in this transformation. Additionally, the reactions were successfully applied to the formation of densely substituted dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles. Biological testing is currently underway and will be presented in due course.

Experimental

General remarks

Unless otherwise noted, the materials were obtained from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was performed using silica gel 60 F254 and visualized using UV light. Column chromatography was performed with silica gel (mesh 300–400). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer in $CDCl_3$ and DMSO-d_6 with Me_4Si as

an internal standard. Data were reported as follows: chemical shifts in parts per million (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, and m = multiplet), coupling constant in Hertz (Hz) and integration. IR spectra were recorded on an FT-IR spectrometer and only major peaks are reported in cm^{-1}. HRMS and mass data were recorded by ESI on a TOF mass spectrometer.

General procedure for synthesis of 1,3,5-triazin-2(1*H*)-ones

To a mixture of alcohols (0.5 mmol), guanides (0.75 mmol), and *t*-BuOK (1.5 mmol) in dioxane (3 mmol) was added $RuCl_2$(COD) (2 mol%). The resulting mixture in a tube reactor was then sealed and stirred for 20 h at 100 °C. After completion of the reaction, MeOH was added and filtered. The crude residue was obtained after evaporation of the solvent under vacuum, and the residue was purified by flash chromatography with CH_2Cl_2 and CH_3OH as eluents to give the pure product.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) S. Nishigaki, F. Yoneda, H. Matsumoto and K. Morinaga, *J. Med. Chem.*, 1969, **12**, 39; (*b*) V. Dubey, M. Pathak, H. R. Bhat and U. P. Singh, *Chem. Biol. Drug Des.*, 2012, **80**, 598; (*c*) Z. Brzozowski, F. Saczewski and M. Gdaniec, *Eur. J. Med. Chem.*, 2000, **35**, 1053.

2 (*a*) F. E. Goda, A. S. Tantawy, L. A. Abou-Zeid, S. M. Badr and K. B. Selim, *Saudi Pharm. J.*, 2008, **16**, 103; (*b*) D. K. Basedia, B. Shrivastava, B. K. Dubey and P. Sharma, *World J. Pharm. Res.*, 2014, **3**, 2789.

3 (*a*) X. Chen, P. Zhan, X. Liu, Z. Cheng, C. Meng, S. Shao, C. Pannecouque, E. De Clercq and X. Liu, *Design Bio. Med. Chem.*, 2012, **20**, 3856; (*b*) K. Koizumi, N. Kuboyama, K. Tomono, K. Wakabayashi and P. Boger, *Pestic. Sci.*, 1999, **55**, 642.

4 (*a*) F. Sączewski, A. Bułakowska, P. Bednarski and R. Grunert, *Eur. J. Med. Chem.*, 2006, **41**, 219; (*b*) T. Toyoda, R. K. B. Brobey, G. Sano, T. Horii, N. Tomioka and A. Itai, *Biochem. Biophys. Res. Commun.*, 1997, **235**, 515; (*c*) A. V. Dolzhenko, W.-K. Chui, A. V. Dolzhenko and L.-W. Chan, *J. Fluorine Chem.*, 2005, **126**, 759.

5 F. Prati, A. D. Simone, P. Bisignano, A. Armirotti, M. Summa, D. Pizzirani, R. Scarpelli, D. I. Perez, V. Andrisano, A. Perez-Castillo, B. Monti, F. Massenzio, L. Polito, M. Racchi, A. D. Favia, G. Bottegoni, A. Martinez, M. L. Bolognesi and A. Cavalli, *Angew. Chem., Int. Ed.*, 2015, **54**, 1578.

6 (*a*) A. Ostrogovich, *Gazz. Chim. Ital.*, 1909, **39**, 540; (*b*) A. Ostrogovich and V. B. Median, *Gazz. Chim. Ital.*, 1929, **59**, 181; (*c*) A. Ostrogovich and V. B. Median, *Gazz. Chim. Ital.*, 1929, **59**, 198; (*d*) R. Bacaloglu, F. L. Neamtiu, I. Bacaloglu and G. Ostrogovich, *Rev. Roum. Chim.*, 1972, **17**, 747; (*e*) E. Degener, H.-G. Schmelzer and H. Holtschmidt, *Angew. Chem., Int. Ed.*, 1966, **5**, 960; (*f*) S. Shinya Kohra, K. Ueda and Y. Tominaga, *Heterocycles*, 1996, **43**, 839.

7 (*a*) A. V. Dolzhenko and W.-F. Chui, *J. Heterocycl. Chem.*, 2006, **43**, 95; (*b*) A. V. Dolzhenko, W.-K. Chui and A. V. Dolzhenko, *J. Heterocycl. Chem.*, 2006, **43**, 1513; (*c*) A. M. Soliman, S. K. Mohamedb, M. A. A. El Remaily and H. Abdel-Ghany, *Eur. J. Med. Chem.*, 2012, **47**, 138; (*d*) A. V. Dolzhenko, W.-K. Chui and A. V. Dolzhenko, *Synthesis*, 2006, 597; (*e*) L. Capuano, H. J. Schrepfer, M. E. Jaeschke and H. Porschen, *Chem. Ber.*, 1974, **107**, 62; (*f*) D. Martin, H. Graubaum, G. Kempter and W. Ehrlichmann, *J. Prakt. Chem.*, 1981, **323**, 303; (*g*) M. Furukawa, K. Kawanabe, A. Yoshimi, T. Okawara and Y. Noguchi, *Chem. Pharm. Bull.*, 1983, **31**, 2473.

8 (*a*) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit and N. Tongpenyai, *J. Chem. Soc., Chem. Commun.*, 1981, 611; (*b*) M. G. Edwards, R. F. R. Jazzar, B. M. Paine, D. J. Shermer, M. K. Whittlesey, J. M. J. Williams and D. D. Edney, *Chem. Commun.*, 2004, 90; (*c*) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555; (*d*) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (*e*) S. Pan and T. Shibata, *ACS Catal.*, 2013, **3**, 704; (*f*) Y. Obora, *ACS Catal.*, 2014, **4**, 3972; (*g*) T. Suzuki, *Chem. Rev.*, 2011, **111**, 1825; (*h*) G. Guillena, D. J. Ramyn and M. Yus, *Angew. Chem., Int. Ed.*, 2007, **46**, 2358; (*i*) G. Guillena, D. J. Ramyn and M. Yus, *Chem. Rev.*, 2010, **110**, 1611; (*j*) M. Zeng, C. Song and D.-M. Cui, *Chin. J. Org. Chem.*, 2017, **37**, 1352; (*k*) K. Raghuvanshi, D. Zell and L. Ackermann, *Org. Lett.*, 2017, **19**, 1278; (*l*) V. S. Thirunavukkarasu, K. Raghuvanshi and L. Ackermann, *Org. Lett.*, 2013, **15**, 3286; (*m*) K. Raghuvanshi, D. Zell, K. Rauch and L. Ackermann, *ACS Catal.*, 2016, **6**, 3172.

9 M. Zeng, T. Wang, D.-M. Cui and C. Zhang, *New J. Chem.*, 2016, **40**, 8225.

10 (*a*) J. J. Li, C. Song, D.-M. Cui and C. Zhang, *Org. Biomol. Chem.*, 2017, **15**, 5564; (*b*) C. Zhang, M.-T. Ban, K. Zhu, L.-Y. Zhang, Z.-Y. Luo, S.-N. Guo, D.-M. Cui and Y. Zhang, *Org. Lett.*, 2017, **19**, 3947; (*c*) C. Song, T. Wang, T. T. Yu, D.-M. Cui and C. Zhang, *Org. Biomol. Chem.*, 2017, **15**, 7212; (*d*) J. J. Li, K. Wu, W. Zhou, H. Wang, D.-M. Cui and C. Zhang, *Synlett*, 2016, 1993; (*e*) C. Zhang, B. Huang, A.-Q. Bao, X. Li, S.-N. Guo, J.-Q. Zhang, J.-Z. Xu, R.-H. Zhang and D.-M. Cui, *Org. Biomol. Chem.*, 2015, **13**, 11432.