HETEROCYCLES, Vol. 100, No. 7, 2020, pp. 1065 - 1071. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 19th December, 2019, Accepted, 14th May, 2020, Published online, 18th May, 2020
DOI: 10.3987/COM-19-14196

RECYCLABLE TRIPHENYLBISMUTH(V) BISPERFLUORO-OCTANESULFONATE CATALYZED SYNTHESIS OF DIHYDROPYRIMIDINONES

Ablimit Abdukader,* Rong Wang,* and Marhaba Mamat

School of Chemistry and Chemical Engineering, Xinjiang University, Urumqi 830046, China;*Corresponding authors E-mail: ablimit1970@126.com

Abstract – Triphenylbismuth(V) bisperfluorooctanesulfonate $Ph_3Bi(OSO_2C_8F_{17})_2$ was successfully synthesized by treatment of Ph_3BiCl_2 with $C_8F_{17}SO_2OAg$, and was found to have the nature of air-stability, water tolerance, high thermal stability and strong Lewis acidity. This complex showed high catalytic efficiency for the synthesis of dihydropyrimidinones (DHPMs) via three-component reaction of aromatic aldehydes, 1,3-dicarbonyl compound and urea under mild conditions. Furthermore, it can be reused without loss of activity in a test of five cycles. Hence, here we provide a convenient and efficient method for preparation of dihydropyrimidinones.

Dihydropyrimidinones (DHPMs) are important nitrogen-containing compounds because of their biological and pharmacological activity as well as their enormous value in terms of drug research.[1] They can be used not only as excellent synthetic intermediates for antihypertensive drugs and antineoplastic drugs, but also widely used in sterilization and antiviral drugs.[2] Meanwhile, owing to their calcium antagonistic action in the cardiovascular system, DHPMs are often used as calcium antagonists to inhibit the influx of calcium ions through plasma membrane channels.[3] Hence, the development of a facile method for rapid construction of DHPMs has attracted immense interest. The Biginelli reaction between aromatic aldehydes, 1,3-dicarbonyl compounds and urea is a classical protocol for the preparation of DHPMs.[4] Consequently, considerable effort has been devoted to the assembly of substituted DHPMs by employing Lewis acid as the catalyst, such as $InCl_3$,[5] $LaCl_3$,[6] $Mn(OAc)_3$,[7] $SnCl_3$,[8] BF_3,[9] $FeCl_3/Si(OEt)_4$.[10] However, these catalysts have some disadvantages, such as low yield, poor selectivity, using of organic solvents, applications of expensive reagents, drastic reaction conditions, long reaction time, various side products, unsatisfactory yields, and complicated procedure. Hence, the discovery of novel protocols that are cost-effective and sustainable for the synthesis of DHPMs is still highly desirable.

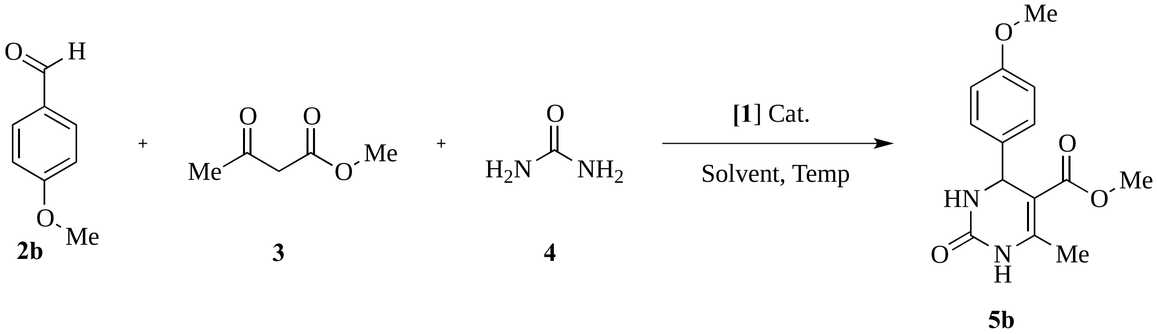
As we all know, bismuth is low in toxicity and price.[11] In recent years, bismuth compounds have attracted much attention, due to their specific activity, properties and environmental concerns. Various inorganic bismuth(III) compounds were employed as catalyst in organic reaction.[12] While the application of organobismuth complexes in the field of catalysis was rarely studied by scientists in the past few decades, partly because of the instability of the Bi-C bond as well as their unsatisfactory catalytic activity. Fortunately，cationic group organometallic compounds as Lewis acid catalysts have greatly attracted the interest of scientists recently. Bosnich and Collins have introduced triflic acid to the metal atom centre of anhydrous metallocene complexes to synthesize the metallocene bis(triflate)s complexes of titanium and zirconium $Cp_2M(OTf)_2$($Cp = C_5H_5$; M = Ti, Zr), which show excellent catalytic activity for the reaction of carbon-carbon bond formation.[13] However, these compounds are sensitive to air and water that greatly limited their application in organic reactions. Lately, Otera and co-workers found that long perfluorooctanesulfonate groups could be used as effective counter anions to provide organometallic species that are air-stable and water-tolerant, in sharp contrast to the corresponding hygroscopic organometallic triflates.[14] Through literature investigation, we found that the synthesis of air-stable organometallic complexes containing large electron-withdrawing perfluoroalkyl(aryl)sulfonate groups and their applications in organic synthesis.[15] We report herein synthesis and characterization of an air-stable triphenylbismuth(Ⅴ) bisperfluorooctanesulfonate **1**, and its high catalytic efficiency and good recyclability in the synthesis of DHPMs.

Shown in Scheme 1 is the synthetic route for the organobismuth compound **1**. Treatment of Ph_3BiCl_2 with $C_8F_{17}SO_2OAg$ in CH_2Cl_2 afforded triphenylbismuth(V) bisperfluorooctanesulfonates **1** quantitatively. And, in this reaction system, we found that the complex **1** has the nature of air-stability, water tolerance, thermally-stability and strong Lewis-acidity. Based on the specific physicochemical properties and strong Lewis acidity of $Ph_3Bi(OSO_2C_8F_{17})_2$, we adopted it as a catalyst for the synthesis of DHPMs.

$$2AgOSO_2C_8F_{17} + Ph_3BiCl_2 \xrightarrow[CH_2Cl_2,\ 2\text{-}3\ h]{N_2,\ rt} \underset{1}{Ph_3Bi(OSO_2C_8F_{17})_2}$$

Scheme 1. Synthesis of organobismuth compound **1**

Table 1. Optimization of the reaction conditions[a]

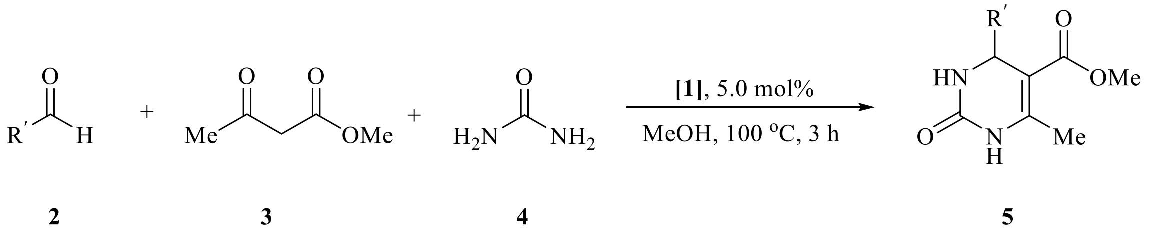


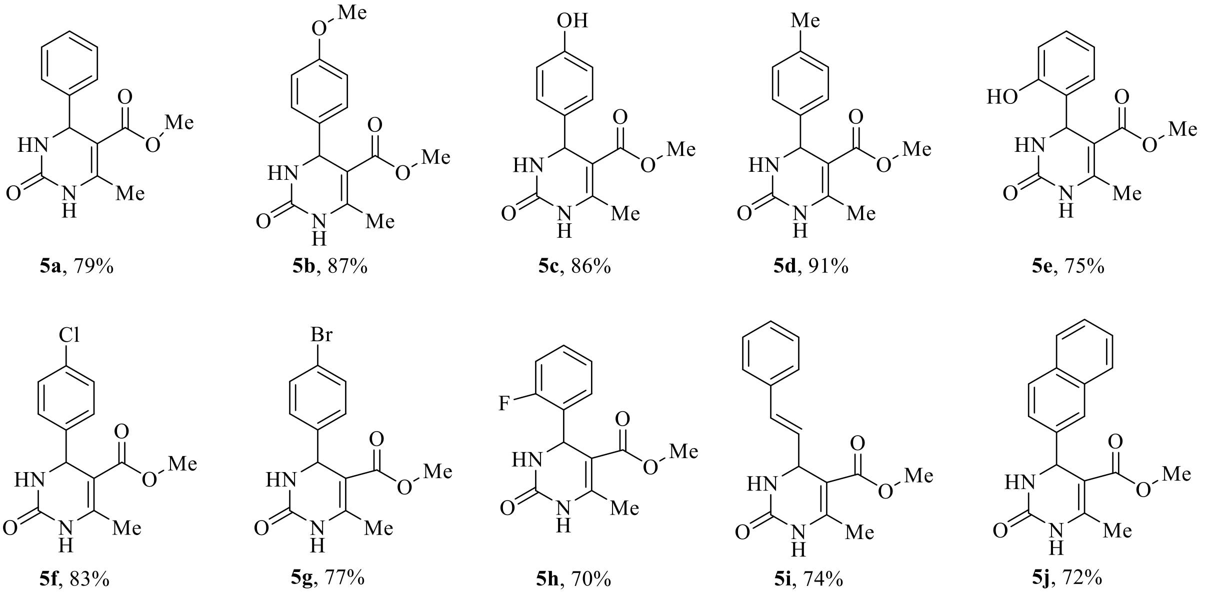
Entry	Solvent	Temp	Catalyst (mol%)	Yield[b] (%)
1	MeOH	100	5	87
2	hexane	100	5	67
3	CH_2Cl_2	100	5	81
4	THF	100	5	73
5	MeCN	100	5	79
6	none	100	5	63
7	MeOH	80	5	74
8	MeOH	100	0	0
9	MeOH	100	6	88

[a]Reaction conditions: **2b** (0.5 mmol), **3** (0.5 mmol), **4** (0.6 mmol), catalyst **1** (5 mol%), solvent (0.5 mL), 100 °C, 3 h, [b]isolated yield.

At first, the reaction was carried out with commercially available *p*-anisaldehyde (**2**), methyl acetoacetate (**3**) and urea (**4**) with 5 mol% of triphenylbismuth(V) bisperfluorooctanesulfonates **1** as the catalyst at 100 °C (Table 1). Obviously, the solvent has a significant influence on the reaction. MeOH was found to be the most suitable choice, giving dihydropyrimidinone **5b** in 87% yield (Table 1, entry 1), considering that other solvent (CH_2Cl_2, THF, MeCN, hexane) gave inferior results (Table 1, entries 2-5). In contrast, only 63% yield of desired product was obtained under solvent-free conditions (Table 1, entry 6). Evaluation of the effect of temperature showed that the reaction could occur effectively at 100 °C, whereas, at 80 °C, the yield of the product was significantly lower to 74% (Table 1, entry 7). Then, we investigated the loading of catalyst and found that the optimal dosage of $Ph_3Bi(OSO_2C_8F_{17})_2$ was 5.0 mol% (Table 1, entries 8-9). Thus, the best results were obtained employing 5 mol% of $Ph_3Bi(OSO_2C_8F_{17})_2$ as the catalyst in MeOH at 100 °C.

Table 2. Preparation of dihydropyrimidinones catalyzed by **1**[a]





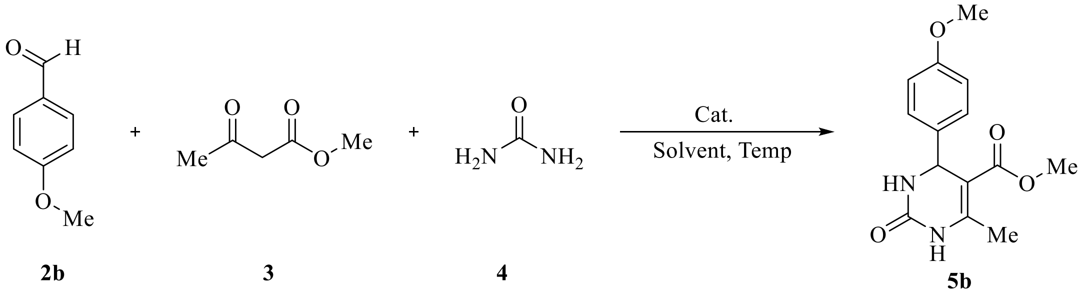
5a, 79% | **5b**, 87% | **5c**, 86% | **5d**, 91% | **5e**, 75%

5f, 83% | **5g**, 77% | **5h**, 70% | **5i**, 74% | **5j**, 72%

[a] **2** (0.5 mmol), **3** (0.5 mmol), **4** (0.6 mmol), catalyst **1** (5 mol%), MeOH (0.5 mL), 100 °C, 3 h, isolated yields.

Subsequently, we applied the optimized reaction conditions to a variety of aldehydes (Table 2). Satisfactory yields were observed regardless of the electronic nature of substituents on the aryl ring of aldehydes, including Me, OMe, OH, and Cl, Br, F groups (Table 2, **5a-5h**). In these reactions, the aromatic aldehydes with electron-donating groups (Table 2, **5b-5d**) afford slightly higher yields of desired products than those with electron-withdrawing groups (**5f-5h**). It is worth mentioning that the *o*-hydroxy-substituted aldehyde give inferior results compared to *p*-hydroxy-substituted aldehyde (**5e vs 5c**). In addition, cinnamic aldehyde undergoes successful Biginelli reaction with methyl acetoacetate and urea under the adopted conditions to afford the corresponding product **5i** in 74% yield . Furthermore, the catalyst system can also be applied to polycyclic aromatic aldehydes (**5j**).

Table 3. Catalyst recovery investigation[a]



Number of uses	1	2	3	4	5	6
Yield[b](%)	95	93	90	90	87	80

[a] **2** (0.5 mmol), **3** (0.5 mmol), **4** (0.6 mmol), catalyst **1** (5 mol%), MeOH (0.5 mL), 100 °C, 3 h, [b] isolated yields.

To test the reusability of the catalyst and reproducibility of catalytic performance, $Ph_3Bi(OSO_2C_8F_{17})_2$ was subject to recycling experiments of the Biginelli reaction between aromatic aldehydes, 1,3-dicarbonyl compound and urea (Table 3). The change in product yield was negligible in a trial of five recycling experiments, demonstrating that the catalyst was stable and suitable for reuse.

In summary, we have demonstrated a convenient and efficient method for preparation of dihydropyrimidinones via Biginelli reaction between aromatic aldehydes, 1,3-dicarbonyl compounds and urea adopting triphenylbismuth(V) bisperfluorooctanesulfonates as catalyst. The approach has merits of high yield, simple operation, mild conditions, low toxicity, and good recyclability of the catalyst. On account of its stability as well as storability, the complex should find a broad range of utility.

EXPERIMENTAL

1. General Considerations

All chemicals were purchased from Aldrich. Co. Ltd and used as received unless otherwise indicated. The preparation of catalyst was carried out under a N_2 atmosphere with freshly distilled solvents unless otherwise noted. THF and Et_2O were distilled from sodium/benzophenone. CH_2Cl_2 was distilled from CaH_2. The NMR spectra were recorded at 25 °C on INOVA-400M (USA) calibrated with tetramethylsilane (TMS) as an internal reference.

2. Synthesis of $Ph_3Bi(OSO_2C_8F_{17})_2$

$AgOSO_2C_8F_{17}$ (0.61 g, 1.0 mmol) was added to a solution of $Ph_3Bi(Cl)_2$ (0.26 g, 0.5 mmol) in 10 mL CH_2Cl_2, and the resulting solution was stirred in the dark at room temperature for 3 h. Then the reaction mixture was filtered, and 1.0 mL of dry hexane was added dropwise to the filtrate until the solution appeared turbid. A white crystal was obtained after the solution was kept in a refrigerator overnight. (590 mg, 82%). Mp 158-160 °C; ^{1}H NMR(400 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 8.0 Hz, 6H), 7.90 (t, *J* = 7.4 Hz, 6H), 7.72 (t, *J* = 7.2 Hz, 3H); ^{19}F NMR(400 MHz, $CDCl_3$) δ: -80.73~-80.80(t, 3F), -112.84(s, 2F), -120.63(s, 2F), -121.63~-121.89(d, 6F), -122.72(s, 2F), -126.12(s, 2F).

ACKNOWLEDGEMENTS

We thank the National Natural Science Foundation of China (No. 21562039) and Xinjiang University Doctoral Science Foundation (BS150227) for financial supports.

SUPPORTING INFORMATION

Supplementary (synthesis of 9-spirofluorenes, IR, ^{1}H and ^{13}C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26574/100/7.

REFERENCES AND NOTES

1. a) B. C. Ranu, A. Hajra, and S. S. Dey, *Org. Process Res. Dev.*, 2002, **6**, 817; b) Y. Ma, C. T. Qian, L. M. Wang, and M. Yang, *J. Org. Chem.*, 2000, **65**, 3864; c) M. Oliverio, P. Costanzo, M. Nardi, I. Rivalta, and A. Procopio, *ACS Sustainable Chem. Eng.*, 2014, **2**, 1228; d) M. Puripat, R. Ramozzi, M. Hatanaka, W. Parasuk, V. Parasuk, and K. Morokuma, *J. Org. Chem.*, 2015, **80**, 6959.
2. J.-P. Wan and Y. Y. Liu, *Synthesis*, 2010, 3943.
3. L. H. S. Matos, F. T. Masson, L. A. Simeoni, and M. Homem-de-Mello, *Eur. J. Med. Chem.*, 2018, **143**, 1779.
4. Z. L. Shen, X. P. Xu, and S. J. Ji, *J. Org. Chem.*, 2010, **75**, 1162.
5. B. C. Ranu, A. Hajra, and U. Jana, *J. Org. Chem.*, 2000, **65**, 6270.
6. J. Lu, Y. J. Bai, Z. J. Wang, B. Q. Yang, and H. R. Ma, *Tetrahedron Lett.*, 2000, **41**, 9075.
7. K. A. Kumar, M. Kasthuraiah, C. S. Reddy, and C. D. Reddy, *Tetrahedron Lett.*, 2001, **42**, 7873.
8. I. Cepanec, M. Litvić, M. Filipan-Litvić, and I. Grüngold, *Tetrahedron Lett.*, 2007, **63**, 11822.
9. E. H. Hu, D. R. Sidler, and U.-H. Dolling, *J. Org. Chem.*, 1998, **63**, 3454.
10. I. Cepanec, M. Litvić, A. Bartolinčić, and M. Lovrić., *Tetrahedron Lett.*, 2005, **61**, 4275.
11. a) X. W. Zhang, J. Xia, H. W. Yan, S. L. Luo, S. F. Yin, C-T. Au, and W-Y. Wong, *J. Organomet. Chem.*, 2009, **694**, 3019; b) X. Zhang, X. Y. Gu, Y. H. Gao, S. P. Nie, and H. F. Lu, *Appl. Organometal. Chem.*, 2017, **31**, e3590.
12. a) J. A. R. Salvador and S. M. Silvestre, *Tetrahedron Lett.*, 2005, **46**, 2581; b) D. H. Aggen, J. N. Arnold, P. D. Hayes, N. J. Smoter, and R. S. Mohan, *Tetrahedron*, 2004, **60**, 3675; c) E. M.

Keramane, B. Boyerp, and J.-P. Roque, *Tetrahedron*, 2001, **57**, 1917; d) S. F. Yin, J. P. Maruyama, T. Yamashita, and S. Shimada, *Angew. Chem. Int. Ed.*, 2008, **47**, 6590.

13. a) T. K. Hollis, N. P. Robison, and B. Bosnich, *Tetrahedron Lett.*, 1992, **33**, 6423; b) T. K. Hollis and B. Bosnich, *J. Am. Chem. Soc.*, 1995, **117**, 4570; c) J. Jaquith, J. Guan, S. Wang, and S. Collins, *Organometallics*, 1995, **14**, 1079; d) S. Lin, G. V. Bondar, C. J. Levy, and S. Collins, *J. Org. Chem.*, 1998, **63**, 1885; e) E. I. Gkaniatsuo, C. N. Banti, N. Kourkoumelis, S. Skoulika, M. Manoli, A. J. Tasiopoulos, and S. K. Hadjikakou, *J. Inorg. Biochem.*, 2015, **150**, 108.
14. a) X. S. Li, A. Kurita, S. Man-e, A. Orita, and J. Otera, *Organometallics*, 2005, **24**, 2567; b) D. L. An, Z.-H. Peng, A. Orita, A. Kurita, S. Man-e, K. Ohkubo, X.-S. Li, and S. Fukuzumi, and J. Otera, *Chem. Eur. J.*, 2006, **12**, 1642; c) S. F. Yin and S. Shimada, *Chem. Commun.*, 2009, 1136; d) T. Ana, I. R. Ciprian, S. Anca, R. Tobias, L. Heinrich, and M. Michael, *J. Organomet. Chem.*, 2016, **806**, 5.
15. a) F. Kheira, B. Abdelkarim, C. Abdelkader, M. Abdellah, B. Gerard, and EI. A. Douniazed, *Cryst. Struct. Theory Appl.*, 2013, **2**, 28; b) A. Islam, B. L. Rodrigues, I. M. Marzano, E. C. Perreira-Maia, D. Dittz, M. T. P. Lopes, M. Ishfaq, F. E Frezard, and C. Demicheli, *Eur. J. Med. Chem.*, 2016, **109**, 254; c) Y. P. Liu, J. Lei, L. W. Tang, Y. Peng, C.-T. Au, Y. Chen, and S. F. Yin, *Eur. J. Med. Chem.*, 2017, **139**, 826; d) A. Pathak, V.-L. Blair, R.-L. Ferrero, L. Kedzierski, and P.-C. Andrews, *J. Inorg. Biochem.*, 2017, **177**, 266.
16. D. Elhamifar, P. Mofatehnia, and M. Faal, *J. Colloid Interface Sci.*, 2017, **504**, 268.
17. N. B. Li, Y. J. Wang, F. J. Liu, and X. Zhao, *Appl. Organometal. Chem.*, 2020, **34**, e5454.
18. D. Elhamifar, M. Nasresfahani , B. Karimi, R. Moshkelgosha, and A. Shábani, *ChemCatChem*, 2014, **6**, 2593.