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TCT (2,4,6-TRICHLORO-1,3,5-TRIAZINE) PROMOTED SINGLE-STEP SYNTHESIS OF 4,6-DIARYLPYRIMIDIN-2(1*H*)-ONES UNDER MICROWAVE IRRADIATION

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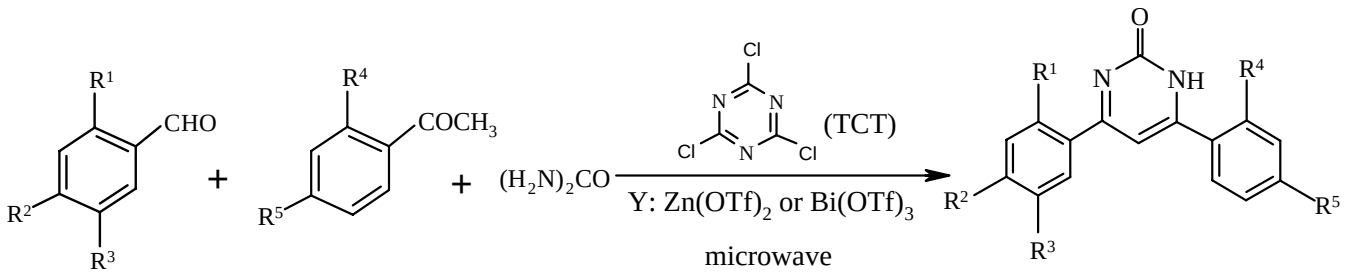
Abstract – An efficient single-step procedure for the synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones promoted by $Zn(OTf)_2$-TCT or $Bi(OTf)_3$-TCT under solvent-free microwave irradiation conditions has been developed.

Pyrimidinone derivatives display various biological[1-3] and pharmacological[4-8] activities such as antitumor action. Therefore, the synthesis of these heterocycles is interesting for both organic synthesis and medicinal chemistry. Many procedures have been reported for the preparation of a variety of pyrimidinone derivatives.[9-14] But little attention has been paid to the synthesis of pyrimidin-2(1*H*)-ones and there are only few methods for the preparation of these compounds.[15] Thus the development of an efficient and convenient method for this purpose is still in demand.

In recent years organic reactions assisted by microwave irradiation have gained special attention. The chief features of the microwave reactions are the enhanced selectivity, much improved reaction rates and milder reaction conditions.[16] Several metal-catalyzed reactions for the synthesis of heterocyclic compounds have been reported in the literature.[17] Among them, multi-component reactions which performed under solvent-free microwave irradiation conditions have received special attentions because of their improved reaction rates and environmentally benign conditions.[18] In the course of our ongoing program to develop environmentally friendly methods using metal triflates under solvent-free microwave irradiation conditions,[19-21] we report a new protocol for the preparation of pyrimidin-2(1*H*)-one derivatives.

Recently Sedova *et al.* reported a new method for the synthesis of pyrimidin-2(1*H*)-ones.[15a] However,

these methods suffer from drawbacks such as long reaction times, unsatisfactory yields and low selectivity that limit these methods to small-scale synthesis. These results led us to develop a simple and efficient procedure for the direct synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones promoted by 2,4,6-trichloro-1,3,5-triazine (TCT) in the presence of $Zn(OTf)_2$ or $Bi(OTf)_3$ under microwave irradiation (Scheme 1).



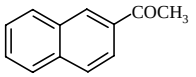
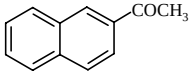
1 2 **Scheme 1** 3

Optimization of the various parameters resulted in two preferred methods. First we observed that when a mixture of an aryl aldehydes (1), an aryl alkyl ketones (2) and urea in the presence of TCT and 10 mol% of $Zn(OTf)_2$ was irradiated by microwave at 450 W under solvent-free conditions, various 4,6-diarylpyrimidin-2(1*H*)-ones (3) were obtained efficiently (Method 1). The results in Table 1 show that the products achieved in high yields with the exception of Entry 9 (64 %).

However, significant improvement in the yield was observed using Method 2. Many recent papers describing the use of bismuth compounds in organic transformations pointed out that their use is environmentally friendly.[22] In addition, bismuth derivatives have been widely used in medicine.[23] They have attracted much attention because they are easy to handle, low cost and are relatively insensitive to air and moisture.[24] In the course of more investigation, we found that utilization of $Bi(OTf)_3$ (only 1 mol%) instead of $Zn(OTf)_2$ was also catalyzed this transformation at 300 W effectively (Table 1). As shown in Table 1, a wide range of substituted and structurally divers aryl aldehydes and aryl alkyl ketones were subjected to this procedure to synthesize the corresponding products in good to excellent yields (Table 1).

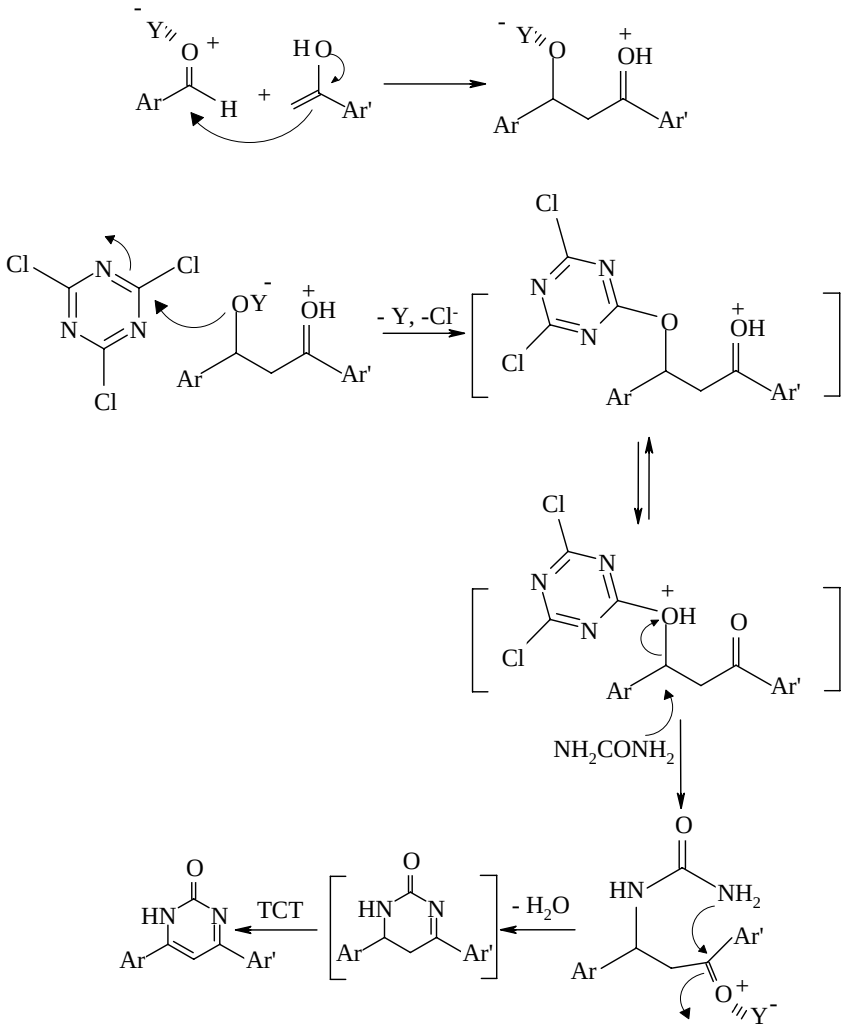
We found that treatment of aryl aldehydes (1) or aryl methyl ketones (2), carrying either electron-withdrawing or electron-donating groups, afforded the corresponding pyrimidinones (3) in high to excellent yields in short reaction times (Table 1). Another important aspect is that various functionalities such as ether, halide, nitro, etc., survived under the present reaction conditions. To the best of our knowledge, this is the first example for the highly efficient single-step synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones (3). These solvent-free single-step reactions which proceeded under microwave irradiation are very fast and clean without the use of any harsh conditions. For comparison,

Table 1. Synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones promoted by $Zn(OTf)_2$[a]-TCT or $Bi(OTf)_3$[b]-TCT under microwave irradiation

Entry	Aldehyde (**1**)				Ketone (**2**)			Product (**3**)[c]	**Y**	Time (min)	Yield (%)[d]
		R^1	R^2	R^3		R^4	R^5				
1	**1a**	H	H	H	**2a**	H	H	**3a**	$Zn(OTf)_2$	12	94
2	**1b**	H	F	H	**2a**	H	H	**3b**	$Zn(OTf)_2$	14	88
3	**1c**	H	Br	H	**2b**	H	Br	**3c**	$Zn(OTf)_2$	14	89
4	**1d**	H	Cl	H	**2c**	H	NO_2	**3d**	$Zn(OTf)_2$	13	73
5	**1a**	H	H	H	**2d**	H	CH_3O	**3e**	$Zn(OTf)_2$	12	91
6	**1d**	H	Cl	H	**2d**	H	CH_3O	**3f**	$Zn(OTf)_2$	15	90
7	**1e**	H	H	NO_2	**2e**	H	Ph	**3g**	$Zn(OTf)_2$	14	81
8	**1f**	CH_3O	H	CH_3O	**2e**	H	Ph	**3h**	$Zn(OTf)_2$	12	88
9	**1g**	CH_3	CH_3	H	**2b**	H	Br	**3i**	$Zn(OTf)_2$	13	64
10	**1g**	CH_3	CH_3	H	**2c**	H	NO_2	**3j**	$Zn(OTf)_2$	14	85
11	**1h**	H	$N(CH_3)_2$	H	**2d**	H	CH_3O	**3k**	$Bi(OTf)_3$	12	82
12	**1d**	H	Cl	H	**2d**	H	CH_3O	**3f**	$Bi(OTf)_3$	15	91
13	**1i**	H	CH_3	H	**2d**	H	CH_3O	**3l**	$Bi(OTf)_3$	10	93
14	**1j**	CH_3O	CH_3O	H	**2a**	H	H	**3m**	$Bi(OTf)_3$	10	84
15	**1k**	H	H	NO_2	**2a**	H	H	**3n**	$Bi(OTf)_3$	15	85
16	**1c**	H	Br	H	**2a**	H	H	**3o**	$Bi(OTf)_3$	15	79
17	**1l**	H	Ph	H	**2b**	H	Br	**3p**	$Bi(OTf)_3$	10	94
18	**1b**	H	F	H	**2b**	H	Br	**3q**	$Bi(OTf)_3$	14	74
19	**1j**	CH_3O	CH_3O	H	**2b**	H	Br	**3r**	$Bi(OTf)_3$	10	90
20	**1j**	H	CH_3O	H	**2f**	H	Cl	**3s**	$Bi(OTf)_3$	11	87
21	**1b**	H	F	H	**2g**	H	CH_3	**3t**	$Bi(OTf)_3$	14	85
22	**1i**	H	CH_3	H	**2e**	H	Ph	**3u**	$Bi(OTf)_3$	10	91
23	**1m**	H	H	Br	**2e**	H	Ph	**3v**	$Bi(OTf)_3$	15	89
24	**1j**	CH_3O	CH_3O	H	**2h**	F	H	**3w**	$Bi(OTf)_3$	14	84
25	**1b**	H	F	H	**2h**	F	H	**3x**	$Bi(OTf)_3$	15	83
26	**1l**	H	Ph	H	**2i**			**3y**	$Bi(OTf)_3$	10	86
27	**1d**	H	Cl	H	**2i**			**3z**	$Bi(OTf)_3$	15	85

[a]Method A; [b]Method B; [c]All products were characterized by ^{1}H-NMR,^{13}C-NMR, IR and mass spectroscopy; [d]Isolated yields.

the reaction of 4-chlorobenzaldehyde and 4-methoxyacetophenone was performed by conventional heating (stirring in an oil-bath at 140 °C) in the presence of $Zn(OTf)_2$-TCT or $Bi(OTf)_3$-TCT and the product was formed in decreased yield (less than 12%) in prolonged reaction times (more than 18h) showing that microwave irradiation plays a critical role in these reactions. It is important to note that in the absence of the catalysts or promoter (TCT) the reaction did not proceed at all. Therefore, the combination of $Zn(OTf)_2$ or $Bi(OTf)_3$ with TCT is essential in this process. According to these results we propose a reaction mechanism for this transformation (Scheme 2).



Scheme 2

In conclusion, we describe a new and highly efficient procedure for the solvent-free single-step synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones promoted by $Zn(OTf)_2$-TCT or $Bi(OTf)_3$-TCT under microwave irradiation. In addition, short reaction times, absence of solvent and mild reaction conditions are noteworthy advantages of this method.

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REFERENCES

1. B. Lagu, D. Tian, G. Chiu, D. Nagarathnam, J. Fang, Q. Shen, C. Forray, R. W. Ransom, R. S. Chang, K. P. Vyas, K. Zhang, and C. Gluchowski, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 175.

2. V. Pomel, J. C. Rovera, A. Godard, F. Marsais, and G. Quéguiner, *J. Heterocycl. Chem.,* 1996, **33**, 1995.
3. S. Karina, A. Matus, J.-L. Fourrey, and P. Clivio, *J. Chem. Soc., Perkin Trans. 1,* 2002, 774.
4. S. M. Vroegop, D. L. Chapman, D. E. Decker, L. A. Galinet, R. J. Brideau, K. A. Ready, C. J. Dunn, and S. E. Buxser, *Int. J. Immunopharmacol.,* 1999, **21**, 647.
5. S. Sasaki, N. Cho, Y. Nara, M. Harada, S. Endo, N. Suzuki, S. Furuya, and M. Fujino, *J. Med. Chem.,* 2003, **46**, 113.
6. V. Pomel, J. C. Rovera, A. Godard, F. Marsais, and G. Quéguiner, *J. Heterocycl. Chem.,* 1996, **33**, 1995.
7. L. H. Li, T. L. Wallace, K. A. Richard, and D. Tracey, *Cancer Research*, 1985, **45**, 532.
8. S. Bartolini, A. Mai, M. Artico, N. Paesano, D. Rotili, C. Spadafora, and G. Sbardella, *J. Med. Chem.,* 2005**, 48**, 6776.
9. S. Arai, T. Sakurai, H. Asakura, S. Fuma, T. Shioiri, and T. Aoyama, *Heterocycles*, 2001, **55**, 2283.
10. N. Nishiwaki, T. Matsunaga, Y. Tohda, and M. Ariga, *Heterocycles*, 1994, **38**, 249.
11. N. Nishiwaki, Y. Mizukawa, M. Ohta, R. Terai, Y. Tohda, and M. Ariga, *Heterocycl. Commun.*, 1996, **2**, 21.
12. N. Nishiwaki, H.-P. Wang, K. Matsuo, Y. Tohda, and M. Ariga, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2261.
13. N. Nishiwaki, E. Wakamura, Y. Nishida, Y. Tohda, and M. Ariga, *Heterocycl. Commun.,* 1996, **2**, 129.
14. A. K. Sharma, S. Jayakumar, M. S. Hundal, and P. M. Mahajan, *J. Chem. Soc., Perkin Trans. 1*, 2002, 774.
15. V. F. Sedova and O. P. Shkurko, *Chem. Heterocycl. Compd.,* 2004, **40**, 194; N. Nishiwaki, Y. Tohda, and M. Ariga, *Synthesis*, 1997, 1277.
16. M. Kidwai, P. Sapra, K. R. Bhushan, P. Misra, *Synthesis*, 2001, 1509; E.S.H. El Ashry, E. Ramadan, A.A. Kassem and M. Hagar, *Adv. Heterocycl. Chem.,* 2005, **88**, 1; E.S.H. El Ashry, A.A. Kassem and E. Ramadan, *Adv. Heterocycl. Chem.,* 2006, **90**, 1; X. Xing, J. Wu, G. Feng and W.-M. Dai, *Tetrahedron*, 2006, **62**, 6774; Y. Ju, R. S.Varma, *J. Org. Chem.* 2006, **71**, 135.
17. B. C. Ranu, R. Jana, and S. S. Dey, *Chem. Lett.*, 2004, **33**, 274; M. C. Bagley, K. Chapaneri, C. Glover, and E. A. Merritt, *Synlett*, 2004, 2615; Y. Xu and Q.-X. Guo, *Heterocycles*, 2004, **63**, 903; B. Desai, T. N. Danks, and G. Wagner, *Tetrahedron Lett.,* 2005, **46**, 955; Y. J. Kim and R. S. Varma, *Tetrahedron Lett.,* 2005, **46**, 1467; R. J. Abdel-Jalil, W. Voelter, and R. Stoll, *Tetrahedron Lett*., 2005, **46**, 1725.
18. A. Kamal, K. S. Reddy, B. R. Prasad, A. H. Babu, and A. V. Ramana, *Tetrahedron Lett*., 2004, **45**,

6517; I. Saxena, D. C. Borah, and J. C. Sarma, *Tetrahedron Lett*., 2005, **46**, 1159; U. K. Nadir and A. Singh, *Tetrahedron Lett*., 2005, **46**, 2083; D. Guzmán-Lucero, J. Guzmán, D. Likhatchev, and R. Martinez-Palou, *Tetrahedron Lett*., 2005, **46**, 1119.

19. A. R. Khosropour, M. M. Khodaei, and K. Ghozati, *Chem. Lett.*, 2004, **33**, 1378; M. M. Khodaei, A. R. Khosropour, and M. Kookhazadeh, *Tetrahedron Lett.*, 2004, **45**, 1725; M. M. Khodaei, A. R. Khosropour, and M. Kookhazadeh, *Synlett*, 2004, 1980; M. M. Khodaei, A. R. Khosropour, and M. Kookhazadeh, *Can. J. Chem.*, 2005, **83**, 209; M. M. Khodaei, A. R. Khosropour, and P. Fattahpour, *Tetrahedron Lett.*, 2005, **46**, 2105; A. R. Khosropour, M. M. Khodaei, and H. Moghannian, *Synlett*, 2005, 955; A. R. Khosropour, M. M. Khodaei, M. Beygzadeh, and M. Jokar, *Heterocycles*, 2005, **65**, 767.
20. I. Mohammadpoor-Baltork, H. Aliyan, and A. R. Khosropour, *Tetrahedron*, 2001, **57**, 5851; I. Mohammadpoor-Baltork and A. R. Khosropour, *Monatsh. Chem.*, 2002, **133**, 189; A. R. Khosropour, M. M. Khodaei, and K. Ghozati, *Tetrahedron Lett*., 2004, **45**, 3525; A. R. Khosropour, M. M. Khodaei, and K. Ghozati, *Russian J. Org. Chem*., 2004, 1332; A. R. Khosropour, M. M. Khodaei, and K. Ghozati, *Z. Naturforsch. B*, 2005, 512; M. M. Khodaei, A. R. Khosropour, and K. Ghozati, *J. Braz. Chem. Soc.*, 2005, **16**, 673.
21. A. R. Khosropour, M. M. Khodaei, and K. Ghozati, *Chem. Lett*., 2004, **33**, 304.
22. S. B. Cunha, R. Lima, and A. R. Souza, *Tetrahedron Lett*., 2002, **43**, 49; E. M. Keramane, B. Boyer, and J. P. Roque, *Tetrahedron*, 2001, **57**, 1909; E. M. Keramane, B. Boyer, and J. P. Roque, *Tetrahedron Lett.*, 2001, **42**, 855.
23. G. Wilkinson, R. D. Gillard, and J. A. McCleverty, '*Comprehensive Coordination Chemistry*,' Vol. 3, Pergamon Press, London, 1987, p. 292.
24. N. Srivastava and B. K. Banik, *J. Org. Chem*., 2003, **68**, 2109; K. J. Eash, M. S. Pulia, L. C. Wieland, and R. S. Mohan, *J. Org. Chem*., 2000, **65**, 8399; H. Suzuki, T. Ikegami, and Y. Matano, *Synthesis*, 1997, 249; J. A. Marshall, *Chemtracts*, 1997, 1064; J. Reglinski, '*Chemistry of Arsenic, Antimony and Bismuth*' ed. by N. C. Norman, Blackie Academic and Professional, New York, 1998, p. 403.
25. *Typical Procedure for the Synthesis of 4-(4-Chlorophenyl)-6-(4-methoxyphenyl)-1H-pyrimidin-2-one promoted by Bi(OTf)$_3$-TCT(Table 1, Entry 12):* 4-Chlorobenzaldehyde (1d) (140.6 mg, 1 mmol), 4-methoxyacetophenone (2d) (150 mg, 1 mmol), urea (90 mg, 1.5 mmol), TCT (184 mg, 1 mmol) and Bi(OTf)$_3$ (7 mg, 0.01 mmol) were taken into a reaction tube and thoroughly mixed with a glass rod. The resulting mixture was placed in the microwave cavity and irradiated for 15 min at 300 w. After completion of the reaction, as indicated by TLC, the mixture was allowed to cool. The precipitate was washed with cooled ethanol (10 ml) and recrystallized by ethyl acetate to give pyrimidinone (3f) in 91% yield. mp 287-290 °C. IR (KBr) 3429, 3100, 2890, 1617, 1582, 810, 600

cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 3.8 (s, 3H, OCH_3), 7.09 (d, *J* =8.4 Hz, 2H, Ar), 7.53 (s, 1H,=CH-), 7.61 (d, *J* = 8.09 Hz, 2H, Ar), 8.17 (m, 4H, Ar), 12.0 (br, 1H, NH); ^{13}C NMR($CDCl_3$, 50MHz) δ 100.4, 115.1, 115.4, 128.8, 129.7, 129.9, 130.2, 130.4, 130.7, 131.2, 137.1, 160.7, 163.0; EIMS *m/z* 314 (M^++2), 312 (M^+), 311, 297, 270, 268, 205, 75.