Transition-metal-free synthesis of (*Z*)-3-ylidenephthalides from 2-acyl-benzoic acids

Xinhua He, Fengtian Xue

PII: S0040-4039(14)00233-0
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.02.012
Reference: TETL 44199

To appear in: *Tetrahedron Letters*

Received Date: 14 January 2014

Please cite this article as: He, X., Xue, F., Transition-metal-free synthesis of (*Z*)-3-ylidenephthalides from 2-acyl-benzoic acids, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.02.012

Transition-metal-free synthesis of (*Z*)-3-ylidenephthalides from 2-acyl-benzoic acids

Xinhua He[a] and Fengtian Xue[a,*]

[a]*Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 Penn Street, Baltimore, Maryland 21201*

**Correspondence to Professor Fengtian Xue at the Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 Penn Street, Baltimore, Maryland 21201*

Phone: 410-706-8521

Email: fxue@rx.umaryland.edu

Keywords:

(*Z*)-3-Ylidenephthalides

2-Acyl-benzoic acid

Intramolecular cyclization

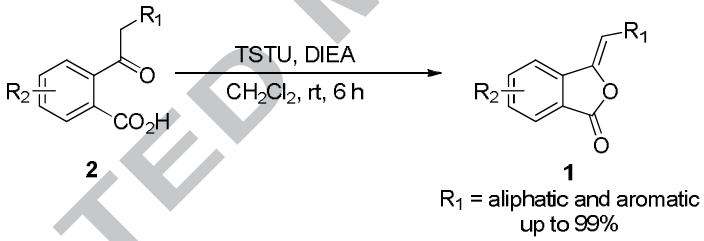
Enol

n-Butylphthalide

Abstract

We report a highly efficient method for the synthesis of (*Z*)-3-ylidenephthalides via intramolecular cyclization of readily available 2-acyl-benzoic acids mediated by TSTU at room temperature. Using this method, diversely substituted (*Z*)-3-ylidenephthalides have been generated in good to excellent yields. The application of the method is highlighted by gram-scale preparation of the antiplatelet drug *n*-butylphthalide.

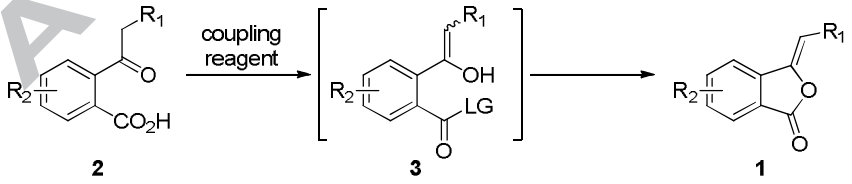
Graphic Abstract



(*Z*)-3-Ylidenephthalides show broad biological activities including inhibitory activity for COX2 as anti-inflammatory agents,[1] anti-platelet activity for cardiovascular diseases,[2] and modulatory activity for transient receptor potential channel TRPA1 and TRPM8 as potential treatment of pain.[3] Therefore, the preparation of (*Z*)-3-ylidenephthalides has attracted significant efforts.

The synthesis of (*Z*)-3-ylidenephthalides was first reported using the modified Perkin reaction.[4] Recently synthesis of (*Z*)-3-ylidenephthalides has been reported using a variety of catalytic protocols including Pd-catalyzed cyclocarbonylation of 2-triflyloxyacetophenones,[5] Pd-catalyzed cyclization of alkenoic acids,[6] Wittig-Horner reaction of phthalide-3-phosphonates with ketones,[7] Ag-catalyzed heteroannulation of 2-(1-alkynyl)benzoic acids,[8] Au (I)-catalyzed cyclization of alkyne acids,[9] organo-base catalyzed intramolecular cyclization,[10] Oxidative cyclization of ortho-alkynylbenzaldehydes using $NaClO_2$,[11] NHC-catalyzed oxidative cyclization,[12] and Pd/C-mediated coupling-cyclization of *o*-bromobenzoic acids.[1] Although these available methods have been useful in preparing various (*Z*)-3-ylidenephthalides, they usually suffer from limitations such as the involvement of metal catalysts, generation of significant amount of side products, complex purification procedure, and low isolation yields.

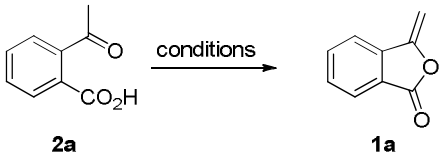
Since the bloom of peptide synthesis in 1990s, various coupling reagents has been described,[13] which, by activating the carboxylic acid group, can assist the formation of a new amide bond or an ester bond.[13] We hypothesize that activation of 2-acyl-benzoic acids (**2**) by coupling reagents can generate intermediate **3**, which will subsequently undergo an intramolecular cyclization via the enol OH group to yield (*Z*)-3-ylidenephthalide **1**.



Scheme 1. Synthetic plan to (*Z*)-3-ylidenephthalides **1** from 2-acyl-benzoic acids **2**.

To test this idea, a solution of 2-acetyl-benzoic acids (**2a**) in CH_2Cl_2 was treated with HBTU in the presence of TEA (Table 1, entry 1). The reaction went smoothly at room temperature, generating compound **1a** in good yields after 12 h. This encouraging result prompted us to screen other coupling reagents. Reactions employing carbodiimide-based coupling reagents DIC (Table 1, entry 2) and EDC (Table 1, entry 3) gave no desired product. When EDC was combined with HOBt, the reaction yielded 3-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)oxy)-3-methylisobenzofuran-1(3*H*)-one (**4**, Scheme 2) as the only product in high yields (Table 1, entry 4). Reaction using DPPA as the coupling reagent generated trace amount of compound **1a** (Table 1, entry 5), along with 4-methylene-1*H*-benzo[*d*][1,3]oxazin-2(4*H*)-one **5** as the major product in high yields (Scheme 3).[14] Improved yields of compound **1a** were observed when uranium-based coupling reagents HATU (Table 1, entry 6) and TSTU (Table 1, entry 7) were used. For both reactions, compound **1a** was generated in excellent yields. Next, we chose TSTU as the coupling reagent to screen other organic solvents (Table 1, entries 8-12), and found that the reaction yields dropped when CH_2Cl_2 was replaced by other tested solvents including THF, CH_3CN, toluene, EtOAc and DMF. Accordingly, CH_2Cl_2 was selected as the solvent for further optimization of bases used in the reaction (Table 1, entries 13-16). We found that DIEA was superior to other tested bases including DMAP, K_2CO_3, and NMM. After a short screening of reaction time, we found that the optimal reaction time was 6 h (Table 1, entries 17-18). The decrease of the amount of DIEA will lead to the decrease of yields of compound **1a** (Table 1, entries 19-21).

Table 1. Optimization of Reaction Conditions for 1a[a]

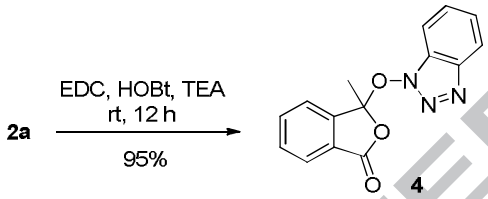


2a **1a**

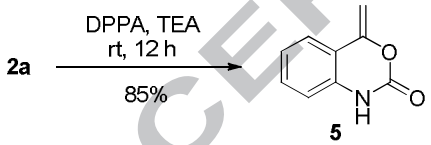
entry	reagent[b]	base[c]	solvent[d]	T., t	Yield **1a**, %[e]
1	HBTU	TEA	CH_2Cl_2	rt, 12 h	74
2	DIC	TEA	CH_2Cl_2	rt, 12 h	0
3	EDC	TEA	CH_2Cl_2	rt, 12 h	0
4	EDC/HOBt	TEA	CH_2Cl_2	rt, 12 h	0[f]
5	DPPA	TEA	CH_2Cl_2	rt, 12 h	trace[g]
6	HATU	TEA	CH_2Cl_2	rt, 12 h	91
7	TSTU	TEA	CH_2Cl_2	rt, 12 h	93
8	TSTU	TEA	THF	rt, 12 h	57
9	TSTU	TEA	CH_3CN	rt, 12 h	88
10	TSTU	TEA	toluene	rt, 12 h	68
11	TSTU	TEA	EtOAc	rt, 12 h	22
12	TSTU	TEA	DMF	rt, 12 h	61
13	TSTU	DMAP	CH_2Cl_2	rt, 12 h	0
14	TSTU	K_2CO_3	CH_2Cl_2	rt, 12 h	27
15	TSTU	NMM	CH_2Cl_2	rt, 12 h	70
16	TSTU	DIEA	CH_2Cl_2	rt, 12 h	99
17	TSTU	DIEA	CH_2Cl_2	rt, 6 h	99
18	TSTU	DIEA	CH_2Cl_2	rt, 1 h	83
19	TSTU	DIEA (1.0 equiv)	CH_2Cl_2	rt, 6 h	86
20	TSTU	DIEA (0.5 equiv)	CH_2Cl_2	rt, 6 h	56

21	TSTU	DIEA (0.1 equiv)	CH_2Cl_2	rt, 6 h	38

[a]The reaction was carried out at room temperature with 1.0 mmol of **2a**, 1.0 mmol of coupling reagent and 2.0 mmol of the base in 5.0 mL of solvent. [b]HBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyl uronium hexafluoro phosphate, DIC = *N*,*N*′-diisopropylcarbodiimide, EDC = *N*-(3-dimethylamino propyl)-*N*′-ethylcarbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole hydrate, DPPA = diphenylphosphoryl azide, HATU = 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluoro-phosphate, TSTU = *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(*N*-succinimidyl) uroniumtetrafluoro borate. [c]TEA = triethylamine, DMAP = 4-(dimethylamino)pyridine, K_2CO_3 = potassium carbonate, NMM = 4-methylmorpholine, DIEA = diisopropyl ethylamine. [d]DCM = dichloromethane, THF = tetrahydrofuran, CH_3CN = acetonitrile, EtOAc = ethyl acetate, DMF = *N*,*N*-dimethyl formamide. [e]Determined by ^{1}H NMR. [f]Compound **4** was isolated in 95% yield, [g]<5%.



Scheme 2. Formation of compound **4**.

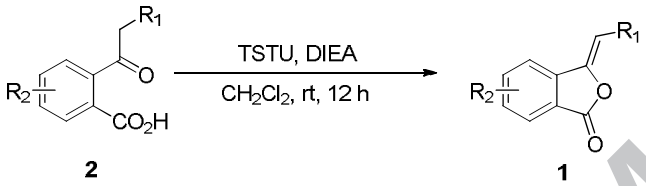


Scheme 3. Formation of compound **5**.

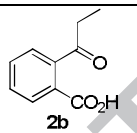
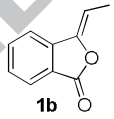
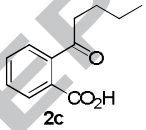
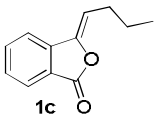
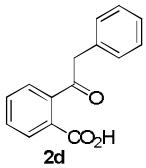
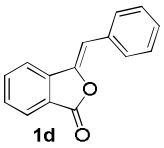
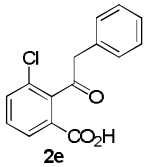
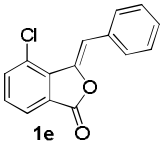
Next, we explored the substrate scope of this method using the optimized conditions. A collection of (*Z*)-3-ylidenephthalides with diverse R_1 and R_2 substituents were prepared as shown in Table 2. 2-Propionylbenzoic acid **2b** was cyclized well to give the thermodynamic product (*Z*)-3-methyliene phthalide **1b** in good yields (Table 2, entry 1). The stereochemistry of compound **1b** was confirmed by

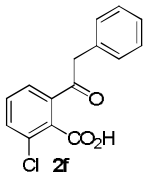
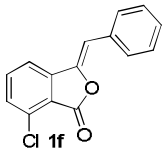
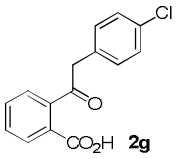
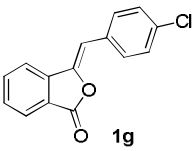
comparing its ^{1}H NMR to published result.[2] Similar good yields of (*Z*)-propylienephthalide **1c** were obtained when 2-pentanoyl benzoic acid **2c** was used as the starting material (Table 2, entry 2). When the phenyl-acetyl substrates (**2d**, **2e**, **2f** and **2g)** were treated with TSTU, the corresponding (*Z*)-3-ylidenephthalides **1d**, **1e**, **1f** and **1g** were generated all in high yields (Table 2, entry 3-6). It was noted that for these reactions, the products were obtained by a simple extraction, which provides a much more efficient way for the isolation of the (*Z*)-3-ylidenephthalides.

Table 2. Reactions of Other 2-Acyl-Benzoic Acids[a]



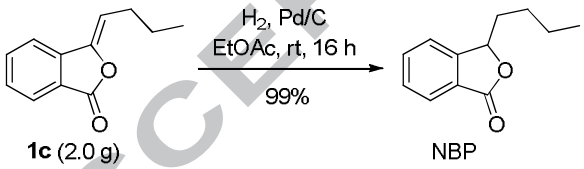
2 **1**

entry	substrate **2**	product **1**	R_1	R_2	yield, %[b]
1	 **2b**	 **1b**	CH_3	H	83
2	 **2c**	 **1c**	H	*n*-Bu	82
3	 **2d**	 **1d**	Ph	H	98
4	 **2e**	 **1e**	Ph	4-Cl	99

5			Ph	7-Cl	81
6			*p*-Cl-Ph	H	91

[a] Reaction was carried out at room temperature with 1.0 mmol of **2**, 1.0 mmol of TSTU, 2.0 mmol of DIEA in 5.0 mL of DCM. [b] Isolated yields.

With the ability to access diversely substituted 3-ylidenephthalide core structures in high efficiency, we next show the transformation of compound **1c** into *n*-butylphthalide (NBP, Scheme 4). NBP is a widely used antiplatelet drug for the treatment of ischemia[15] and stroke.[2, 16] Recently NBP has been reported to be an intriguing neuroprotective agent in the brain,[17] as well as a potential therapeutic agent for the treatment for Alzheimer's diseases.[18] Clinical use of NBP was approved by the State Food and Drug Administration (SFDA) of China in 2002. As shown in Scheme 4, gram-scale synthesis of NBP by catalytic hydrogenation of compound **1c** using Pd/C gave almost quantitative yields in one step.[19]



Scheme 4. Synthesis of NBP.

In summary, we described, for the first time, that 2-acyl-benzoic acids can be transformed into (*Z*)-3-ylidenephthalides using a TSTU-mediated intramolecular cyclization.[20] The value of this method has been shown in the preparation of various (*Z*)-3-ylidenephthalides in good to excellent yields. In particular, the practical gram-scale synthesis of the antiplatelet drug NBP.

Acknowledgements

We gratefully acknowledge funding from the Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy.

Supplementary data

Supplementary data associated with this article can be found in the online version.

References

1. Rambabu, D.; Kumar, G. P.; Kumar, B. D.; Kapavarapu, R.; Rao, M. V. B.; Pal, M. *Tetrahedron Lett.* **2013,** *54*, 2989-2995.

2. Yang, H.; Hu, G. Y.; Chen, J.; Wang, Y.; Wang, Z. H. *Bioorg. Med. Chem. Lett.* **2007,** *17*, 5210-5213.

3. Ortar, G.; Moriello, A. S.; Morera, E.; Nalli, M.; Di Marzo, V.; De Petrocellis, L. *Bioorg. Med. Chem. Lett.* **2013,** *23*, 5614-5618.

4. Mowry, D. T.; Ringwald, E. L.; Renoll, M. *J. Am. Chem. Soc.* **1949,** *71*, 120-122.

5. Ciattini, P. G.; Mastropietro, G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1993,** *34*, 3763-3766.

6. Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993,** *58*, 5298-5300.

7. Watanabe, M.; Morimoto, H.; Tomoda, M.; Iwanaga, U. *Synthesis-Stuttgart* **1994,** *10*, 1083-1086.

8. Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000,** *56*, 2533-2545.

9. Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; van de Weghe, P. *Tetrahedron* **2007,** *63*, 9979-9990.

10. Kanazawa, C.; Terada, M. *Tetrahedron Lett.* **2007,** *48*, 933-935.

11. Li, J.; Chin, E.; Lui, A. S.; Chen, L. J. *Tetrahedron Lett.* **2010,** *51*, 5937-5939.

12. Park, J. H.; Bhilare, S. V.; Youn, S. W. *Org. Lett.* **2011,** *13*, 2228-2231.

13. Han, S. Y.; Kim, Y. A. *Tetrahedron* **2004,** *60*, 2447-2467.

14. Ishida, T.; Kikuchi, S.; Tsubo, T.; Yamada, T. *Org. Lett.* **2013,** *15*, 848-851.

15. Wang, X. L.; Wang, L. N.; Li, T. T.; Huang, Z. J.; Lai, Y. S.; Ji, H.; Wan, X. L.; Xu, J. Y.; Tian, J. D.; Zhang, Y. H. *J. Med. Chem.* **2013,** *56*, 3078-3089.

16. (a) Wang, X. L.; Wang, L. N.; Huang, Z. J.; Sheng, X.; Li, T. T.; Ji, H.; Xu, J. Y.; Zhang, Y. H. *Bioorg. Med. Chem. Lett.* **2013,** *23*, 1985-1988; (b) Li, L.; Zhang, B.; Tao, Y. Q.; Wang, Y.; Wei, H.; Zhao, J.; Huang, R. X.; Pei, Z. *Brain Res.* **2009,** *1290*, 91-101.

17. (a) Li, J. M.; Li, Y.; Ogle, M.; Zhou, X.; Song, M. K.; Yu, S. P.; Wei, L. *Brain Res.* **2010,** *1359*, 216-226; (b) Sun, B.; Feng, M. J.; Tian, X. Y.; Lu, X. W.; Zhang, Y. Y.; Ke, X. J.; Huang, S. S.; Cao, J. J.;

Ding, X. S. *Neurosci. Lett.* **2012,** *516*, 247-252; (c) Zhao, W. H.; Xu, S. F.; Peng, Y.; Ji, X. C.; Cao, D. X.; Li, J.; Liu, B.; Shi, Q. Q.; Wang, L.; Wang, X. L. *Neurosci. Lett.* **2013,** *541*, 155-160.

18. Peng, Y.; Hu, Y. L.; Xu, S. F.; Feng, N.; Wang, L.; Wang, X. L. *Neurosci. Lett.* **2011,** *487*, 211-216.

19. Kuethe, J. T.; Maloney, K. M. *Tetrahedron* **2013,** *69*, 5248-5258.

20. Typical procedure for the synthesis of (*Z*)-3-ylidenephthalide **1a.** To a solution of 2-acetyl-benzoic acid (164 mg, 1.0 mmol) and TSTU (301 mg, 1.0 mmol) in CH_2Cl_2 (5.0 mL) was added DIEA (2.0 mmol). The reaction was allowed to stir at room temperature for 6 h. Then, the reaction mixture was poured into water (10 mL), extracted using EtOAc (3 × 10 mL). The combined organic layers were washed by brine with water (3 × 10 mL) and $NaHCO_3$ aqueous (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation to yield (*Z*)-3-ylidenephthalide **1a** as a white solid (144 mg, 0.99 mmol, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (d, *J* = 8.0 Hz, 1H), 7.71-7.70 (m, 2H), 7.58-7.53 (m, 1H), 5.21 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 151.8, 139.0, 134.5, 130.5, 125.2, 120.6, 91.3. LC-MS ($M+Na^+$) calcd for $C_9H_6NaO_2$ 169, found 169.