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Preparation of Functional Phosphorus Zwitterions from Activated Alkanes, Aldehydes, and Tributylphosphine: Synthesis of Polysubstituted Furo[3,2-*c*]coumarins

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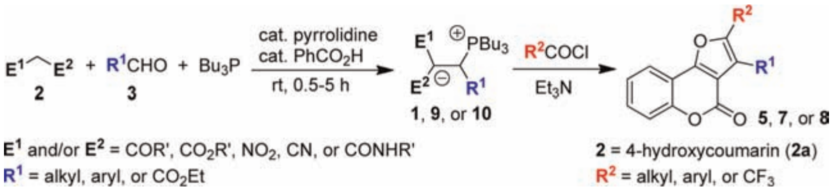
ABSTRACT



A general preparation of new types of highly functional phosphorus zwitterions is realized via tandem three-component reactions using the corresponding functional alkanes, aldehydes, and Bu_3P. Starting from our novel zwitterions as synthetic reagents with commercially available acid chlorides in a one-step procedure provides an attractive approach toward furo[3,2-*c*]coumarins.

Zwitterions with phosphine moieties attract much attention from scientists because of not only the special interest in their specific structures and properties[1] but also their potential application in organic synthesis.[2] The presence of various functionalities in zwitterionic compounds such as **1** allows further functional group transformation and should be possibly served as precious building blocks or useful reagents. Furthermore, the phosphine moieties with a positive formal charge allow zwitterions **1** to be the precursors of Wittig reagents, which have long been recognized as one of the most powerful reagents to construct carbon–carbon double bonds.[3] However, for the study of zwitterions **1**, little has been reported in literature probably due to the limited demonstrated synthetic methodologies.[1a,4] Herein, we wish to report the general preparation of zwitterions **1** using the corresponding functional alkanes **2**, aldehydes **3**, and Bu_3P (Scheme 1). The reaction mechanism of this tandem three-component reaction was proposed to be via the Michael addition of Bu_3P toward Michael acceptors **4** resulting from **2** and **3**. Besides, we developed a facile synthesis for highly functional furo[3,2-*c*]coumarins **5** and furan-containing heterocycles starting from the corresponding zwitterions **1** and acid chlorides **6**.

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(1) (a) Zhu, X.-F.; Henry, C. E.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 6722. In this work, the authors reported a method to prepare the phosphonium enolate zwitterions of type **1** starting from tertiary phosphines, 4-pyridinecarboxaldehyde, and alkynoates; for other selected examples such as a phosphirenium-borate zwitterion, see: (b) Ekkert, O.; Kehr, G.; Fröhlich, R.; Erker, G. *Chem. Commun.* **2011**, *47*, 10482. (c) Geier, S. J.; Dureen, M. A.; Ouyang, E. Y.; Stephan, D. W. *Chem.—Eur. J.* **2010**, *16*, 988. (d) Fukazawa, A.; Yamada, H.; Yamaguchi, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 5582.

(2) For selected reviews, see: (a) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520. (b) Nair, V.; Menon, R. S.; Biju, A. T.; Abhilash, K. G. *Chem. Soc. Rev.* **2012**, *41*, 1050. For recent selected examples using phosphorus zwitterions as reactive intermediates, see: (c) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337. (d) Jung, C.-K.; Wang, J.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4118.

(3) For selected reviews of Wittig reactions, see: (a) Edmonds, D.; Abell, A. In *Modern Carbonyl Olefinations*; Takeda, T., Ed.; Wiley-VCH: Weinheim; 2004, pp 1–17. (b) Abell, A.; Edmonds, D. M. K.; *Organophosphorus Reagents*; Murphy, P. J., Ed.; Oxford University Press: Oxford, 2004; pp 99–127. (c) *Phosphorus Ylides: Chemistry and Applications in Organic Chemistry*; Kolodiazhnyi, O. I., Ed.; Wiley-VCH: New York, 1999. Please also see: (d) Chen, K.-W.; Syu, S.; Jang, Y.-J.; Lin, W. *Org. Biomol. Chem.* **2011**, *9*, 2098. (f) Syu, S.; Lee, Y.-T.; Jang, Y.-J.; Lin, W. *Org. Lett.* **2011**, *13*, 2970.

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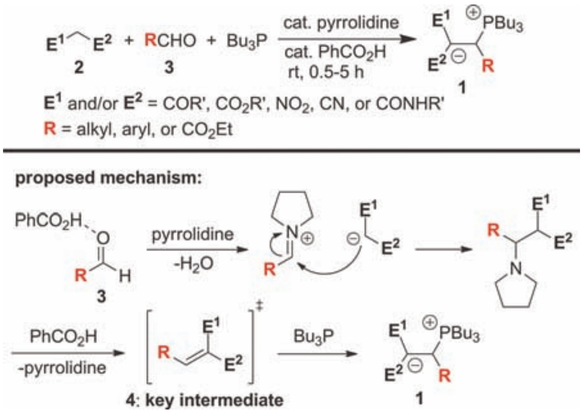
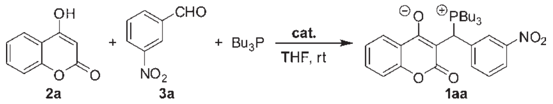
To the best of our knowledge, it is the first time that a general procedure for the formation of **1** from **2**, **3**, and Bu_3P and their further applications for the synthesis of such heterocycles are reported.

Scheme 1. Preparation of Functional Zwitterions **1** via Tandem Three-Component Reactions of Alkanes **2**, Aldehydes **3**, or Bu_3P



First, 4-hydroxycoumarin (**2a**) and *m*-nitrobenzaldehyde (**3a**) were selected as testing substrates to react with Bu_3P under different reaction conditions (Table 1). We found that a secondary amine such as pyrrolidine and an acidic additive such as benzoic acid are beneficial for the formation of the corresponding adduct **1aa** (entries 1−6). The best result was given when both pyrrolidine and benzoic acid were present in our designed reaction (entry 6). We also tried to carry out this three-component reaction in a two-step procedure, in which the addition of Bu_3P was performed only after the conversion of **2a** with **3a** to the desired Michael acceptor **4aa** was complete (entry 7). However, from this catalytic process, there was no formation of **4aa**, and only a competitive side reaction proceeded from the addition of **2a** toward the corresponding intermediate **4aa**.

Table 1. Optimization of Reaction Conditions for Synthesis of **1aa**[a]

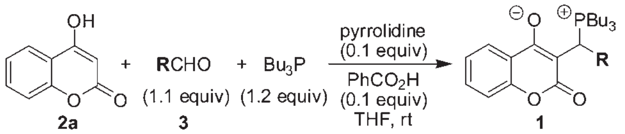


entry	pyrrolidine (equiv)	$PhCO_2H$ (equiv)	time (h)	yield of **1aa**(%)[b]
1	–	–	6	88
2	0.1	–	1.5	83
3	Et_3N (0.3)[c]	–	9	85
4	0.3	0.1	2	95
5	–	0.1	6	88
6	0.1	0.1	1.5	95 (91)[d]
7[e]	0.1	0.1	nd	nd

[a] Reactions were performed with **2a** (0.5 mmol), **3a** (1.1 equiv), and Bu_3P (1.2 equiv) in dry THF (0.5 mL) under nitrogen. [b] NMR yield. [c] Et_3N was used instead of pyrrolidine. [d] Isolated yield. [e] In this two-step, controlled experiment, the expected Michael acceptor **4aa** resulting from **2a** and **3a** was not formed within 24 h in the absence of Bu_3P.

The broad reaction scope of our optimized protocol for substrates **2a** with **3** is demonstrated in Table 2.[5] Under the catalytic reaction conditions (0.1 equiv of pyrrolidine; 0.1 equiv of benzoic acid), highly chemoselective three-component reactions of various aryl- or heteroaryl-substituted aldehydes such as **3b**−**k** (1.1 equiv) completed efficiently at room temperature within 0.5−2.5 h, leading to the corresponding adducts **1ab**−**1ak** in excellent yields (entries 1−10). Interestingly, an ester-substituted aldehyde such as **3l** reacted with **2a** and Bu_3P requiring a prolonged reaction time (16 h) according to our protocol, affording the corresponding adduct **1al** in moderate yield (entry 11). The reaction of an alkyl-substituted aldehyde, such as **3m**, **3n**, or **3o**, Bu_3P, and **2a** also took place nicely to provide the corresponding zwitterion **1am**, **1an**, or **1ao** in excellent yields (entries 12−14). Terephthalaldehyde (**3p**) reacted less chemoselectively with **2a** and Bu_3P, furnishing the adduct **1ap** in merely 50% yield (entry 15).

Table 2. Synthesis of Zwitterions **1**[a]



entry	**R** (**3**)	time (h)	yield of **1** (%)[b]
1	*p*-$NO_2C_6H_4$ (**3b**)	2.5	**1ab**, 96
2[c]	*o*-$NO_2C_6H_4$ (**3c**)	2.5	**1ac**, 94
3	*p*-$CF_3C_6H_4$ (**3d**)	1.5	**1ad**, 90
4	*p*-CNC_6H_4 (**3e**)	2	**1ae**, 88
5	*p*-BrC_6H_4 (**3f**)	0.5	**1af**,[d] 98
6	C_6H_5 (**3g**)	0.5	**1ag**, 97
7	*p*-$OMeC_6H_4$ (**3h**)	0.5	**1ah**, 91
8	1,3-benzodioxol-5-yl (**3i**)	0.5	**1ai**, 98
9	2-furyl (**3j**)	0.5	**1aj**, 98
10	2-thienyl (**3k**)	0.5	**1ak**, 97
11[e]	CO_2Et (**3l**)	16	**1al**, 69
12	*n*-butyl (**3m**)	0.5	**1am**, 98
13	*i*-propyl (**3n**)	0.5	**1an**, 98
14	cyclohexyl (**3o**)	0.5	**1ao**, 95
15	*p*-$CHOC_6H_4$ (**3p**)	0.5	**1ap**, 50

[a] Reactions were performed with **2a** (0.5 mmol) in dry THF (0.5 mL) under nitrogen. [b] Isolated yield. [c] 1.3 equiv of **3c** was used. [d] The structure of **1af** was determined by X-ray analysis.[6] [e] 1.5 equiv of **3l** was used.

We then turn our attention to examine the reactivity of different functional alkanes with an aldehyde and Bu_3P according to our designed catalytic protocol (Scheme 2).[7] It demonstrates that an aryl- or alkyl-substituted aldehyde

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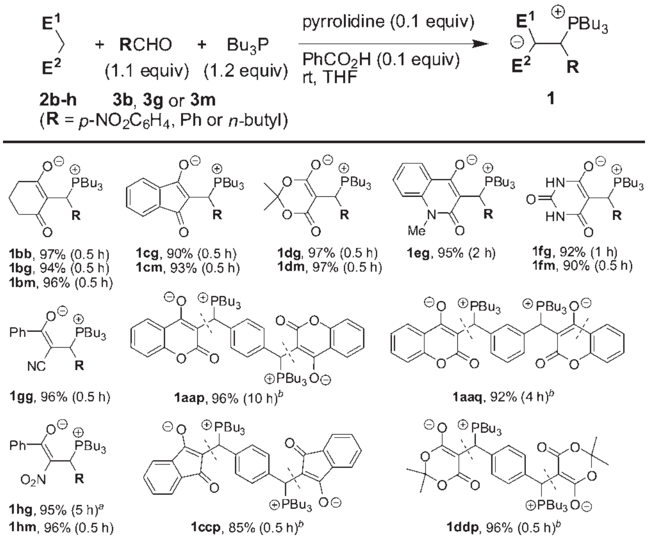
(5) The preparation of the adduct **1**, such as **1aa**, can be easily scaled up (5 mmol of **2a**) with excellent isolated yield (93%) within 1.5 h.

(6) The structures of **1af** and **1hg** were confirmed by X-ray analysis (CCDC number: 853011 and 853017).

(7) It is noteworthy that even some kinds of **1** can be synthesized by direct Michael addition of the corresponding **2** towards the acceptor **4** according to our previous work (see ref 4); however it can still be problematic if the preparation of **4** is difficult.

(**3b**, **3g**, or **3m**; 1.1 equiv) and Bu$_3$P (1.2 equiv) reacted nicely with a wide variety of functional alkanes bearing the ketone, ester, amide, urea, cyano, or nitro functionalities (**2b**–**h**) within 0.5–5 h at room temperature, affording the corresponding phosphorus zwitterions **1** in very high yields. Interestingly, five-component reactions can be performed when the aldehyde **3p** or **3q** was employed in the reaction with a functional alkane such as **2a**, **2c**, or **2d** and Bu$_3$P, giving rise to the corresponding adduct **1aap**, **1ccp**, **1ddp**, or **1aaq** in excellent yields.

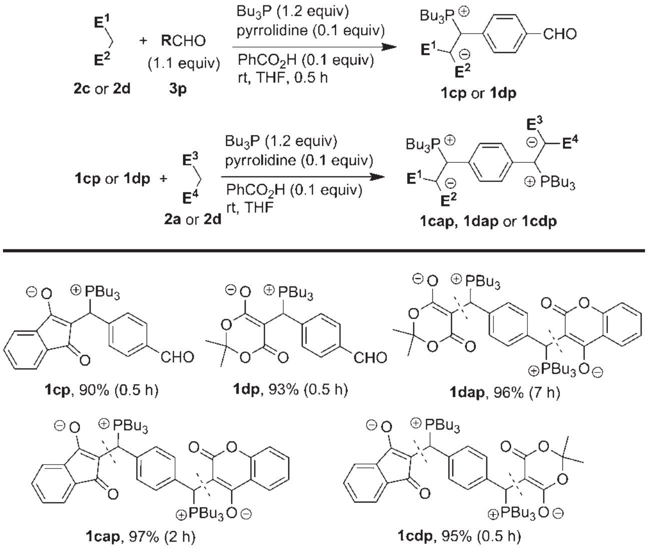
Scheme 2. Synthesis of Zwitterions **1** Starting from **2a**–**h**, **3**, and Bu$_3$P[a]



[a] The structure of **1hg** was determined by X-ray analysis.[6] [b] 0.5 mmol of **3p** and **3q** (**3q** = isophthalaldehyde), 2.1 equiv of **2a**, **2c**, or **2d**, and 2.4 equiv of Bu$_3$P were used.

Surprisingly, under the same proposed reaction conditions, a highly chemoselective three-component reaction of **3p**, Bu$_3$P, and an alkane such as **2c** or **2d** proceeded smoothly and efficiently (Scheme 3). The extra aldehyde functionality can be tolerated, and the corresponding phosphorus zwitterion **1cp** or **1dp** was provided effectively in high yields (90% or 93% yield; 0.5 h). Remarkably, further installation of an additional phosphorus zwitterion as the moiety of the unsymmetrical dizwitterion such as **1dap** (96%; 7 h), **1cap** (97%; 2 h), or **1cdp** (95%; 0.5 h) was very successful, when a different functional alkane such as **2a** or **2d** was employed.

Scheme 3. Synthesis of Zwitterions **1** Starting from **2**, **3p**, and Bu$_3$P



Furo[3,2-*c*]coumarins **5** are important heterocycles well-known as many natural products and exhibit potential biological activity.[8] Among the phosphorus zwitterions **1**, those bearing coumarin as the functional moiety (Table 2) provide an easy access to the preparation of these interesting molecules using the intramolecular Wittig reaction as the key step.[9] After the optimization of reaction conditions,[10] phosphorus zwitterions with the coumarin functionality **1** reacted smoothly with various acid chloride **6**, affording the corresponding furo[3,2-*c*]coumarins **5** in high yields (Table 3). When the aryl-substituted zwitterion such as **1aa** was used, its reaction with aryl-, heteroaryl-, or even alkyl-substituted acid chloride **6** (1.3 equiv) in the presence of Et$_3$N (1.5 equiv) underwent reaction smoothly within 0.25–5 h at room temperature, providing the corresponding adduct **5** in 76–99% yields (entries 1–7). The substitution **R** of zwitterions **1** as well as **R^1** of **6** showed a significant influence on the reactivity for the formation of **5** (entry 2 vs 10 and 14; entry 1 vs 13, 16, 17, and 18). It is also noteworthy that even with the expected long reaction time necessary for the reaction of **1ah** and **6i**, the reaction proceeded successfully under the modified reaction conditions, furnishing the desired product **5k** in high yield (90%; 17 h; entry 11). Remarkably, the zwitterions **1ap** with an aldehyde functionality can be employed successfully with benzoyl chloride (**6a**) in the presence of Et$_3$N, giving the adduct **5r** in 85% yield (entry 18).

Furthermore, our developed protocol provides an efficient route for the facile synthesis of complex heteroaromatic rings, such as **7** and **8**, with both furan and furocoumarin as moieties (Scheme 4). The zwitterion **1gp**, which was prepared from **2g**, **3p**, and Bu$_3$P according to the typical procedure, could be efficiently converted to

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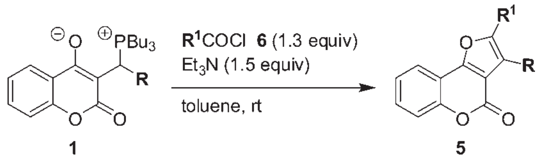
(8) (a) Donnelly, D. M. X.; Boland, G. M. *Nat. Prod. Rep.* **1998**, 241. (b) Wang, X.; Bastow, K. F.; Sun, C.; Lin, Y.; Yu, H.; Don, M.; Wu, T.; Nakamura, S.; Lee, K. *J. Med. Chem.* **2004**, *47*, 5816. (c) Grese, T.; Pennington, L. D.; Sluka, J. P.; Adrian, M. D.; Cole, H. W.; Fuson, T. R.; Magee, D. E.; Phillips, D. L.; Rowley, E. R.; Shetler, P. K.; Short, L. L.; Venugopalan, M.; Yang, N. N.; Sato, M.; Glasebrook, A. L.; Bryant, H. U. *J. Med. Chem.* **1998**, *41*, 1272. (d) Zhao, L.; Brinton, R. D. *J. Med. Chem.* **2005**, *48*, 3463.

(9) For selected examples of furocoumarin synthesis, see: (a) Chen, L.; Li, Y.; Xu, M.-H. *Org. Biomol. Chem.* **2010**, *8*, 3073. (b) Raffa, G.; Rusch, M.; Balme, G.; Monteiro, N. *Org. Lett.* **2009**, *11*, 5254. (c) Cheng, G.; Hu, Y. *J. Org. Chem.* **2008**, *73*, 4732. (d) Cheng, G.; Hu, Y. *Chem. Commun.* **2007**, 3285. For the preparation of furo[3,4-*c*]coumarins starting from the corresponding Michael acceptors via intramolecular Wittig reactions, see: (e) Jang, Y.-J.; Syu, S.; Chen, Y.-J.; Yang, M.-C.; Lin, W. *Org. Biomol. Chem.* **2012**, *10*, 843.

(10) For the optimization of reaction conditions, please see Supporting Information.

Table 3. Synthesis of Furo[3,2-*c*]coumarins **5** from **1**[a]

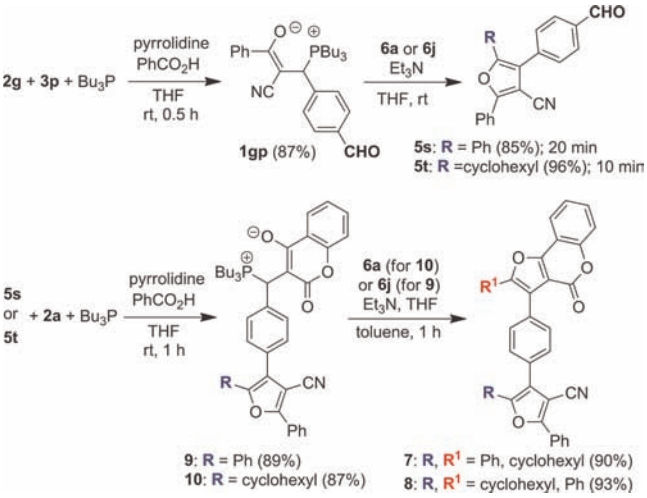


entry	R (1)	R^1 (6)	time (h)	yield of **5** (%)[b]
1	*m*-$NO_2C_6H_4$ (**1aa**)	C_6H_5 (**6a**)	1	**5a**, 99
2	**1aa**	*p*-$OMeC_6H_4$ (**6b**)	1.5	**5b**, 92
3	**1aa**	2-thienyl (**6c**)	5	**5c**, 88
4	**1aa**	nonyl (**6d**)	1	**5d**, 86
5	**1aa**	isopropyl (**6e**)	5	**5e**, 76
6	**1aa**	*tert*-butyl (**6f**)	3	**5f**, 90
7	**1aa**	CF_3 (**6g**)[c]	0.25	**5g**, 88
8	*p*-$CF_3C_6H_4$ (**1ad**)	*p*-BrC_6H_4 (**6h**)	0.5	**5h**, 90
9	*p*-CNC_6H_4 (**1ae**)	**6h**	2	**5i**, 84
10[d]	C_6H_5 (**1ag**)	**6b**	4	**5j**, 93
11[d]	*p*-$OMeC_6H_4$ (**1ah**)	*o*-BrC_6H_4 (**6i**)	17	**5k**, 90
12	*p*-$OMeC_6H_4$ (**1ah**)	cyclohexyl (**6j**)	2	**5l**, 87
13[d]	*o*-$NO_2C_6H_4$ (**1ac**)	**6a**	7	**5m**, 93
14	2-furyl (**1aj**)	**6b**	1	**5n**, 90
15	2-thienyl (**1ak**)	**6h**	1.5	**5o**, 97
16[d]	1,3-benzodioxol-5-yl (**1ai**)	**6a**	10	**5p**, 84
17	CO_2Et (**1al**)	**6a**	0.5	**5q**, 89
18	*p*-$CHOC_6H_4$ (**1ap**)	**6a**	1	**5r**, 85

[a] Reactions were performed with **1** (0.5 mmol) in dry THF (0.5 mL) under nitrogen. [b] Isolated yield. [c] Trifluoroacetic anhydride was used. [d] 2.2 equiv of Et_3N and 1.7 equiv of **6** were used at 65 °C.

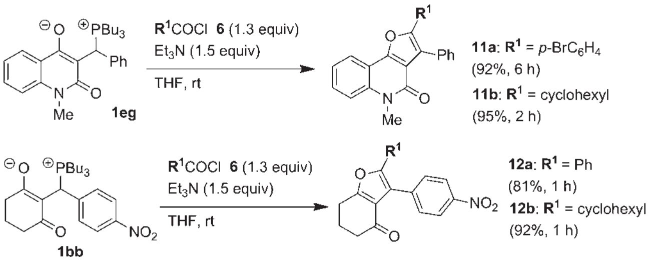
fully substituted furan **5s** (85%) or **5t** (96%) with the corresponding acid chloride **6a** or **6j**, respectively. After the treatment of **2a** and Bu_3P with **5s** or **5t** according to our developed method, the corresponding zwitterion **9** or **10** bearing furan as well as coumarin functionalities was afforded within 1 h in high yield. Finally, the zwitterion **9** or **10** can be employed with an acid chloride such **6j** or **6a**, providing the highly functional aromatic compound **7** or **8** in excellent yields.

Scheme 4. Multistep Syntheses of Heteroaromatic Rings **7** and **8**



In our preliminary studies, not only the zwitterion bearing coumarin functionality but also the other zwitterion such as **1eg** or **1bb** has good reactivity with an acid chloride **6** for the formation of the corresponding interesting heterocycle **11** or **12** via an intramolecular Wittig reaction as the key step (Scheme 5).[11] In the presence of Et_3N (1.5 equiv), an acid chloride such as **6h** or **6j** (1.3 equiv) worked nicely with the zwitterion **1eg** within 6 or 2 h at room temperature, providing the corresponding adduct **11a** or **11b** in 92% or 95% yield, respectively. The reaction of the other phosphorus zwitterion **1bb** and an acid chloride such as **6a** or **6j** in the presence of Et_3N also took place efficiently within 1 h, affording the corresponding furan **12a** or **12b** in 81% or 92% yield, respectively.

Scheme 5. Synthesis of Heterocycles **11** and **12**



In conclusion, a general procedure for new types of highly functional phosphorus zwitterions **1** is developed via tandem three-component reactions using the corresponding functional alkanes **2**, aldehydes **3**, and Bu_3P. The reaction conditions are mild, and numerous highly functional phosphorus zwitterions **1** can be generated very efficiently in high to excellent yields. Additionally, the new phosphorus zwitterions with the coumarin functionality **1** can be applied successfully in the reaction with a wide variety of acid chlorides **6** to afford highly functional furo[3,2-*c*]coumarins **5** in good to excellent yields. Further studies and the application of **1** in organic synthesis, such as the preparation of other heterocycles, are currently underway.

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Supporting Information Available. General experimental procedures, compound characterization data, and X-ray and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] For the formation of the heterocycles **11** and **12** in recent literature, please also see: (a) Zhu, X.; Xu, X.-P.; Sun, C.; Chen, T.; Shen, Z.-L.; Ji, S.-J. *Tetrahedron* **2011**, *67*, 6375. (b) Reddy, C. R.; Vijaykumar, J.; Gree, R. *Synthesis* **2010**, *21*, 3715. (c) Arai, M.; Ishikawa, T.; Saito, S.; Miyauchi, Y.; Miyahara, T. *Synlett* **2009**, *1*, 122. (d) Cadierno, V.; Diez, J.; Gimeno, J.; Nebra, N. *J. Org. Chem.* **2008**, *73*, 5852.

The authors declare no competing financial interest.