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Successively Recycle Waste as Catalyst: A One-Pot Wittig/1,4-Reduction/Paal–Knorr Sequence for Modular Synthesis of Substituted Furans

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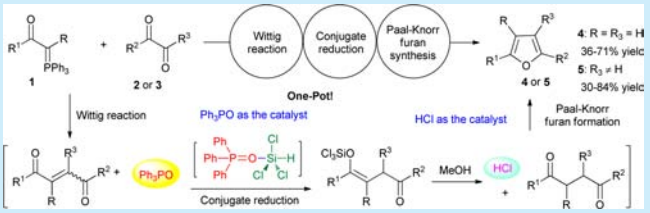
Supporting Information

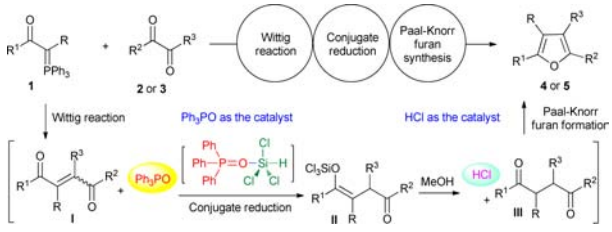
ABSTRACT: A one-pot tandem Wittig/conjugate reduction/Paal–Knorr reaction is reported for the synthesis of di- or trisubstituted furans. This novel sequence first demonstrates the possibility of successively recycling waste from upstream steps to catalyze downstream reactions.



Waste prevention is the central task of green chemistry.[1] To reduce waste generation, an effective strategy attracting ever-increasing attention is to develop a one-pot tandem synthesis, which is also able to effectively save time, labor, energy, and materials and minimize yield losses relating to the isolation of intermediates as well.[2] During the past decade, new concepts continue to be exploited for the design of tandem reactions, such as organocatalytic cascade[3] and multicatalyst-promoted tandem reactions.[4] In this context, a new type of tandem reaction emerges, aiming at internal recycling waste produced in the upstream step as catalyst or cocatalyst for the downstream steps.[5] Such sustainable tandem reactions can improve atom-utilization of a multistep synthesis for waste prevention, as the internal reuse of byproduct reduces the use of extra substance. Since Alaimo first demonstrated the feasibility of the concept,[6a] a variety of rationally designed tandem sequences that internally recycle waste as catalyst or cocatalyst have been independently developed by the Tian,[6b,c] Wu,[6d] Toy,[6e,f] and Coeffard and Greck[6g] groups for efficient and cost-effective synthesis of value-added products from simple substrates. Despite ongoing processes, all of the known protocols could only recycle waste one time, namely the reuse of waste from one upstream step.[5,6] It remains unexplored whether it is possible to successively recycle waste from two more upstream steps to catalyze the following reactions within a tandem sequence.

We are engaged in the development of tandem reactions for the efficient synthesis of interesting targets for chemistry, biology, and medicinal research.[7] In particular, we are interested in improving the atom-efficiency of synthetically useful reactions suffering from low atom-economy by coupling them into tandem reactions to internally recycle the corresponding byproducts to benefit the downstream step.[8] We have developed two tandem sequences to improve the atom-utilization of the Wittig reaction: one is Wittig-conjugate reduction reaction reusing Ph_3PO to activate $HSiCl_3$ for conjugate reduction of enones and the other is a Wittig-cyanosilylation reaction reclaiming Ph_3PO as a cocatalyst for asymmetric cyanosilyaltion of enones.[8a] The tandem Wittig-reduction reaction further enabled the synthesis of α-CF_3 γ-keto esters via chemoselective 1,4-reduction of β-CF_3 substituted enones, a task difficult to realize by other methods.[8b] Most recently, we reported a tandem substitution–Krapcho reaction, reusing byproduct metal halide for dealkoxycarbonylative synthesis of α-fluorinated esters.[8c] On the basis of these results, we considered a one-pot tandem Wittig/conjugate reduction/Paal–Knorr reaction for modular syntheses of substituted furans (Scheme 1). A remarkable feature of this

Scheme 1. Working Model



sequence is to recycle waste twice: (i) reuse waste Ph_3PO from the Wittig reaction of phosphorane **1** with 1,2-dicarbonyl compounds **2** or **3** to catalyze 1,4-reduction of enone intermediate **I** using $HSiCl_3$[9] and (ii) reclaim waste HCl produced from quenching trichlorosilyl intermediate **II** to promote the furan synthesis.[10] Here, we report our initial

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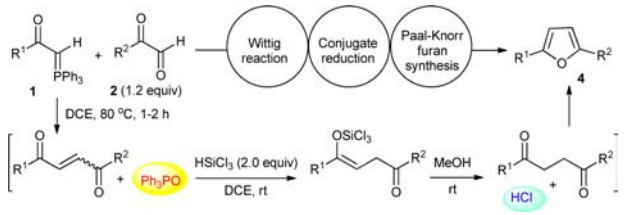
application of this triple sequence for the modular synthesis of di- and trisubstituted furans.

Substituted furans represent a type of prominent structural motif in bioactive compounds that have attracted considerable attention.[11] While a number of elegant metal-catalyzed[12] or organocatalytic methods[13] have been invented, new and efficient methods for modular synthesis of polysubstituted furans are still in demand. Because phosphorane, 1,2-dicarbonyl compounds, and $HSiCl_3$ were readily available, our sequence constituted an attractive new approach with broad substrate scope. For example, 2,5-disubstituted furans **4**, with different alkyl or aryl groups, were obtained in reasonable yield from phosphorane **1** and glyoxal derivatives **2** (Table 1).

Table 1. Tandem Reaction to Furans 4a−z



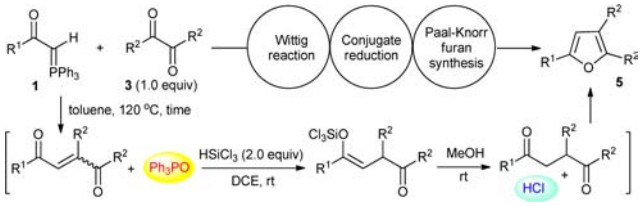
entry[a]	R^1	R^2	4	yield[b] (%)
1	**1a**: Ph	**2a**: Ph	**4a**	63
2	**1a**: Ph	**2b**: 4-$MeOC_6H_4$	**4b**	60
3	**1a**: Ph	**2c**: 4-MeC_6H_4	**4c**	69
4	**1a**: Ph	**2d**: 4-ClC_6H_4	**4d**	71
5	**1a**: Ph	**2e**: 4-FC_6H_4	**4e**	64
6	**1a**: Ph	**2f**: 4-BrC_6H_4	**4f**	65
7	**1a**: Ph	**2g**: 4-$NO_2C_6H_4$	**4g**	67
8	**1a**: Ph	**2h**: 4-CNC_6H_4	**4h**	69
9	**1a**: Ph	**2i**: 4-$CF_3C_6H_4$	**4i**	63
10	**1a**: Ph	**2j**: 3-ClC_6H_4	**4j**	60
11	**1a**: Ph	**2k**: 2-BrC_6H_4	**4k**	62
12	**1a**: Ph	**2l**: 2-naphthyl	**4l**	49
13	**1a**: Ph	**2m**: 2-thienyl	**4m**	58
14	**1b**: 4-$MeOC_6H_4$	**2d**: 4-ClC_6H_4	**4n**	55
15	**1c**: 4-ClC_6H_4	**2d**: 4-ClC_6H_4	**4o**	57
16	**1d**: 4-FC_6H_4	**2d**: 4-ClC_6H_4	**4p**	56
17	**1e**: 4-$NO_2C_6H_4$	**2d**: 4-ClC_6H_4	**4q**	53
18	**1f**: 3-$MeOC_6H_4$	**2d**: 4-ClC_6H_4	**4r**	64
19	**1g**: 2-ClC_6H_4	**2d**: 4-ClC_6H_4	**4s**	48
20	**1h**: 2-naphthyl	**2d**: 4-ClC_6H_4	**4t**	48
21	**1i**: 2-thienyl	**2d**: 4-ClC_6H_4	**4u**	32
22	**1j**: Me	**2d**: 4-ClC_6H_4	**4v**	57
23	**1k**: Et	**2d**: 4-ClC_6H_4	**4w**	64
24	**1l**: ^{i}Pr	**2d**: 4-ClC_6H_4	**4x**	59
25	**1m**: ^{t}Bu	**2d**: 4-ClC_6H_4	**4y**	61
26	**1n**: cyclohexyl	**2d**: 4-ClC_6H_4	**4z**	36

[a]Run on a 0.25 mmol scale. [b]Isolated yield.

Since the Wittig reaction of **1** and **2** worked well in 1,2-dichloroethane (DCE) and was suitable for 1,4-reduction, the one-pot procedure was very simple. The initial Wittig step was run in a screw-capped pressure tube using DCE as the solvent at 80 °C. At almost full conversion of **1**, $HSiCl_3$ was added, and the conjugate reduction was run at 25 °C until completion, followed by addition of two drops of MeOH. The resulting mixture was vigorously stirred to promote the final furan synthesis.

When 1,2-diketones **3** were used for the synthesis of trisubstituted furans, the reaction development was not as easy as it first appeared since the Wittig step worked inefficiently in halogenated solvents required for the reduction step. After condition optimization (see Table S1 of the Supporting Information), it was determined that the initial Wittig step was run in toluene at 120 °C using a screw-capped pressure tube. After full consumption of diketone, toluene was removed, followed by addition of anhydrous DCE and $HSiCl_3$. The rest of the procedure was similar to that described above. This protocol allowed various substituted phosphoranes **1a−m** to readily react with symmetric diketones **3** to give trisubstituted furans **5** in reasonable yield (Table 2). Both aryl and alkyl symmetric

Table 2. Tandem Reaction to Furans 5a−v



entry[a]	R^1	R^2	time (h)	5	yield[b] (%)
1	**1a**: Ph	**3a**: Ph	48	**5a**	84
2	**1a**: Ph	**3b**: 4-MeC_6H_4	48	**5b**	80
3	**1a**: Ph	**3c**: 4-$MeOC_6H_4$	41	**5c**	57
4	**1a**: Ph	**3d**: 4-ClC_6H_4	17	**5d**	71
5	**1a**: Ph	**3e**: 4-FC_6H_4	36	**5e**	67
6	**1a**: Ph	**3f**: 4-$CF_3C_6H_4$	12	**5f**	59
7	**1a**: Ph	**3g**: 3-FC_6H_4	18	**5g**	52
8	**1a**: Ph	**3h**: 2-naphthyl	23	**5h**	54
9	**1a**: Ph	**3i**: 2-thienyl	36	**5i**	71
10	**1a**: Ph	**3j**: Me	24	**5j**	60
11	**1b**: 4-$MeOC_6H_4$	**3a**: Ph	48	**5k**	63
12	**1c**: 4-ClC_6H_4	**3a**: Ph	36	**5l**	70
13	**1d**: 4-FC_6H_4	**3a**: Ph	36	**5m**	69
14	**1e**: 4-$NO_2C_6H_4$	**3a**: Ph	24	**5n**	57
15	**1f**: 3-$MeOC_6H_4$	**3a**: Ph	48	**5o**	64
16	**1g**: 2-ClC_6H_4	**3a**: Ph	48	**5p**	58
17	**1h**: 2-naphthyl	**3a**: Ph	36	**5q**	66
18	**1i**: 2-thienyl	**3a**: Ph	24	**5r**	47
19	**1j**: Me	**3a**: Ph	2	**5s**	52
20	**1k**: Et	**3a**: Ph	24	**5t**	53
21	**1l**: ^{i}Pr	**3a**: Ph	24	**5u**	45
22	**1m**: ^{t}Bu	**3a**: Ph	24	**5v**	30

[a]Run on a 0.25 mmol scale. [b]Isolated yield.

diketones **3a−j** afforded the desired products **5a−j** in good yield. On the other hand, aryl phosphoranes **1b−h** provided furans **5k−q** in higher yield than heteroaryl or alkyl ones **1i−m**, which afforded the corresponding products **5r−v** in moderate yield. The bulky *tert*-butyl phosphorane **1m** could also work but gave product **5v** in only 30% yield.

The use of symmetric 1,2-diketones inevitably gave trisubstituted furans with two identical substituents, and the synthesis of those with three different groups from unsymmetric 1,2-diketone met with problems due to the poor regioselectivity of Wittig reaction. Helpfully, tandem reactions from α-substituted phosphorane **1o** and glyoxal derivatives **2** fulfilled this task, as evidenced by the synthesis of trisubstituted furans **5aa−ah** in Table 3.

We tried in vain to access tetrasubstituted furans, as the reaction of α-substituted phosphorane and diketone failed. Only

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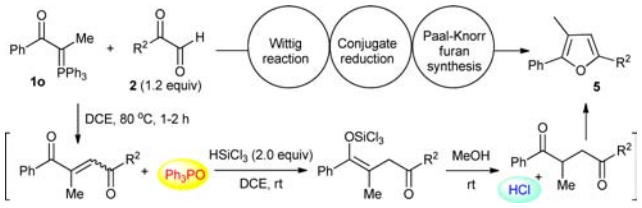
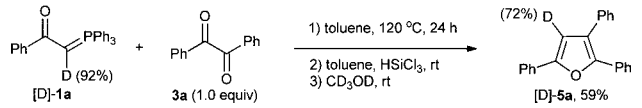
Table 3. Tandem Reaction to Furans 5aa−ah



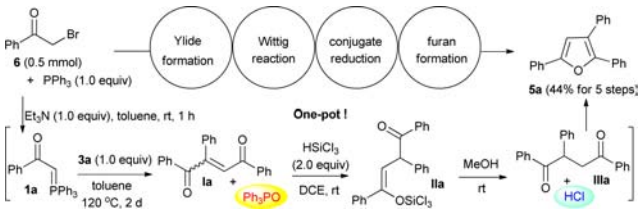
entry[a]	2	R^2	5	yield[b] (%)
1	**2a**	Ph	**5aa**	58
2	**2b**	4-$MeOC_6H_4$	**5ab**	54
3	**2f**	4-BrC_6H_4	**5ac**	45
4	**2i**	4-$CF_3C_6H_4$	**5ad**	59
5	**2g**	4-$NO_2C_6H_4$	**5ae**	61
6	**2l**	2-naphthyl	**5af**	70
7	**2m**	2-thienyl	**5ag**	56
8	**2n**	3-$MeOC_6H_4$	**5ah**	56

[a]Run on a 0.25 mmol scale. [b]Isolated yield.

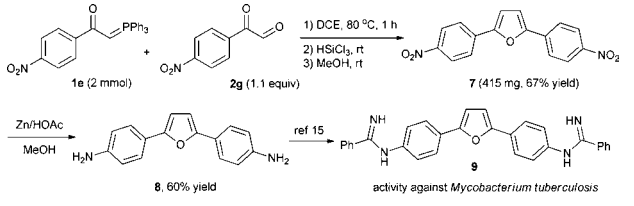
α-deuterated phosphorane [D]-**1a** (92% labeled) could react with diketone **3a** to give furan [D]-**5a** in 59% yield, with 72% deuterium incorporation. This suggested that our sequence might be used for the synthesis of deuterated furans on demand.[14]



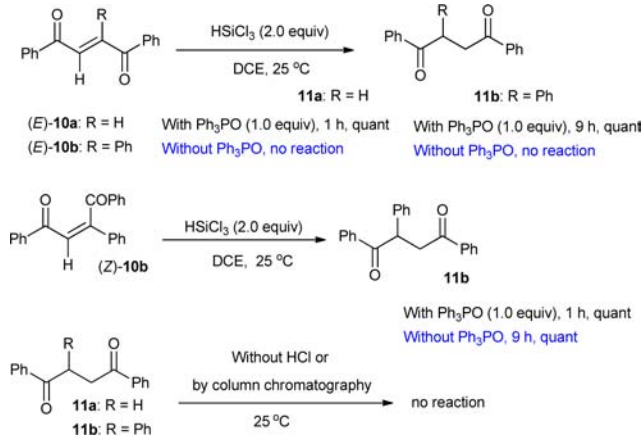
Inspired by Toy's one-pot Wittig-reductive aldol reaction from bromides and PPh_3,[6e,f] we further developed a more efficient procedure starting from bromide **6** and Ph_3P. The desired product **5a** was obtained in an impressive overall 44% yield, as this sequence was essentially composed of five distinct steps, including phosphorous alkylation, phosphonium salt deprotonation, Wittig reaction, conjugate reduction, and furan synthesis, and high yield (average 85%) was achieved for every step.



The utility of our sequence was further shown by the facile synthesis of 2,5-bis(4-nitrophenyl)furan **7**, the precursor to compound **9** that displayed activity versus *Mycobacterium tuberculosis*. Previously, furan **7** was obtained by Pd-catalyzed Stille coupling of 2,5-bis(tri-*n*-butylstannyl)furan and 4-bromonitroarene.[15] Our metal-free protocol was an attractive alternative, as the use of expensive Pd catalyst and toxic tin reagent was avoided.



To confirm the role of Ph_3PO and HCl in 1,4-reduction and furan synthesis, respectively, we attempted the following experiments. As the Wittig reaction of glyoxal derivative **2** showed excellent *E*-selectivity but that of diketone **3** gave poor selectivity, we examined the performance of Ph_3PO in the 1,4-reduction of (*E*)-**10a** and both isomers of enone **10b**, respectively. Without the presence of Ph_3PO, the conjugate reduction of either (*E*)-**10a** or (*E*)-**10b** by $HSiCl_3$ failed at 25 °C. However, in the absence of Ph_3PO, the reduction of (*Z*)-**10b** using $HSiCl_3$ could reach completion within 9 h; nevertheless, the addition of Ph_3PO accelerated the reduction to finish within 1 h. These results clearly showed the necessity of Ph_3PO in the conjugate reduction. On the other hand, without the presence of HCl, both diketone **11a** and **11b** failed to give the desired furans, as expected. In addition, no cyclization occurred during flash column chromatography. This confirmed the indispensible role of waste HCl in furan synthesis.



In conclusion, we have developed a one-pot tandem Wittig/1,4-reduction/Paal−Knorr reaction for the modular synthesis of a wide range of 2,5-substituted and trisubstituted furans from easily available substrates. This not only demonstrates the possibility of successively recycling the waste from distinct steps to catalyze two or more downstream steps within a tandem sequence but also shows the potential of one-pot tandem sequences that take advantage of the internally generated waste in the synthesis of value-added products from easily available starting materials.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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