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A solvent-free catalytic protocol for the Achmatowicz rearrangement†

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Reported here is the development of an environmentally friendly catalytic (KBr/oxone) and solvent-free protocol for the Achmatowicz rearrangement (AchR). Different from all previous methods is that the use of chromatographic alumina (Al_2O_3) allows AchR to proceed smoothly in the absence of any organic solvent and therefore considerably facilitates the subsequent workup and purification with minimal environmental impacts. Importantly, this protocol allows for scaling up (from milligram to gram), recycling of the Al_2O_3, and integrating with other reactions in a one-pot sequential manner.

The Achmatowicz rearrangement (AchR) is the choice reaction for the synthesis of versatile dihydropyranone acetals,[1–5] key synthetic precursors for functionalized tetrahydropyrans, dihydropyranones, oxidopyrylium, δ-lactones, and pyranoses.[6–15] Therefore, the AchR continues to attract much attention from the synthetic and medicinal communities and to find wide applications in the total synthesis of natural products, including >17 natural products from our lab.[16–25] The increasing importance of the AchR has led to the development of many new efficient methods by identifying new oxidants,[26–41] and two oxidants, namely *N*-bromosuccinimide (NBS)[42] and *m*-chloroperoxybenzoic acid (*m*-CPBA),[43] were found to be among the most efficient ones. However, the use of these stoichiometric oxidants produces quantitative amounts of the organic byproduct of *m*-chlorobenzoic acid or succinimide, which usually requires immediate column chromatography for purification. To address this problem associated with the environmental concern from the organic byproducts, we previously developed a green catalytic protocol[44] for the AchR by the identification of 5 mol% KBr as the catalyst and oxone as the stoichiometric terminal oxidant. In this new protocol, a THF/H_2O (4/1) solution was identified as the most effective solvent system, partially due to the optimal solubility of both organic substrates (furfuryl alcohols) and inorganic reagents used (oxone and KBr). From the point of view of green chemistry, the THF/H_2O solvent system is still not ideal and precludes subsequent transformations such as *O*-acetylation and *O*-Boc protection, in a one-pot manner. Herein, we report our recent efforts that led to the development of a solvent-free catalytic protocol for the AchR (Fig. 1). This new protocol represents the first example of a solvent-free catalytic AchR with broad substrate scope, and importantly enables us for the first time to further functionalize the AchR products in a one-pot sequential manner, which tremendously reduces the use of organic solvents in the liquid–liquid extraction workup and purification.

The development of a solvent-free[45] process for organic reactions is a green chemistry approach because organic solvents are ecologically harmful and the largest contributors to the magnitude of the *E* factor.[46] The additional advantages of solvent-free conditions include low cost and reduced reaction time.[47,48] In particular, catalytic processes under solvent-free conditions greatly reduce the environmental impact and economic cost.[49] Nevertheless, there are relatively few processes using catalysis under solvent-free conditions. This paucity is not unexpected because catalyst efficiency is usually very sensitive to the solvent properties and concentration.[50] In this context, we sought a solid reaction medium that could support our solid catalyst (KBr) and oxidant (oxone) for the reaction with liquid substrates (furfuryl alcohols). A literature search

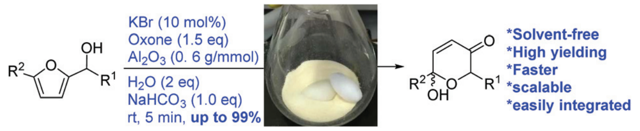

Fig. 1 Our new solvent-free catalytic protocol for the Achmatowicz rearrangement (AchR).

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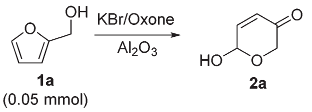
and our initial experimental attempts led us to identify chromatographic neutral alumina (Al_2O_3, Merck KGaA, 70–230 mesh, and pH = 6.8–7.8) as the ideal medium.[51,52]

We first examined and optimized the AchR reaction of **1a** using Al_2O_3 as the reaction medium (Table 1). To our delight, 82.7% yield of the AchR product **2a** was obtained in only 5 min when **1a** suspended in Al_2O_3 was mixed and stirred with KBr (10 mol%), oxone (1.5 equiv.), H_2O (10 eq.) and $NaHCO_3$ (6 eq.) at room temperature (entry 1). Control experiments suggested that Al_2O_3 (entry 2), H_2O (entry 3), KBr (entry 4) and $NaHCO_3$ (entry 5) were indispensable for good yields. Notably, the reaction time was significantly reduced from 30 min (THF/H_2O/oxone/KBr) to 5 min (Al_2O_3/oxone/KBr). Further optimizations (entries 6–12) allowed for the substantial reduction of the quantity of oxone, Al_2O_3, $NaHCO_3$ and H_2O without compromising the high yield. The product **2a** was isolated from the reaction mixture by simple filtration with ethyl acetate and the ^{1}H-NMR spectrum of the concentrated filtrate (crude **2a**) was very clean (Fig. 2). Therefore, this new protocol could eliminate the liquid–liquid extraction (and drying) used in the workup/purification of all prior methods.

With the optimized conditions in hand, we set out to examine the substrate scope (Table 2). Generally, a variety of furfuryl alcohols could be employed for the AchR under these solvent-free conditions, which demonstrated comparable efficiency and generality to those solvent-mediated processes. Furfuryl alcohol derivatives bearing ester (**1j**, **1o**, and **1w**), alkene (**1f–i**), ketone (**1m**), Weinreb amide (**1k**), electron-rich arenes (**1x–ac**), and sulfonamide (**1n** and **1p**) at the 2- or 5-position of furan were excellent substrates for the AchR to provide the corresponding dihydropyranone acetals in good to excellent yields (72–97%). Notably, there were no potentially competing side reactions, including arene bromination,[53,54] alkene dibromination,[55] and alcohol oxidation,[56] all of which have been reported when the combination of oxone and stoichio-

Table 1 Optimization of the AchR reaction of **1a** under the solvent-free conditions



1a
(0.05 mmol)

2a

Entry[a]	Al_2O_3 [b] (mg)	H_2O (eq.)[c]	KBr (eq.)[c]	Oxone (eq.)[c]	$NaHCO_3$ (eq.)[c]	Yield[d] (**2a**, %)
1	100	10	0.1	1.5	6	82.7
2	0	10	0.1	1.5	6	20.7
3	100	0	0.1	1.5	6	0
4	100	10	0	1.5	6	31.9
5	100	10	0.1	1.5	0	50.7
6	100	10	0.1	1	6	81.4
7	100	10	0.1	0.6	6	55.9
8	30	10	0.1	1	6	82.3
9	20	10	0.1	1	6	56.7
10	30	2	0.1	1	6	84.3
11	30	1	0.1	1	6	78.4
12	30	2	0.1	1	1	91

[a] The reaction was carried out at room temperature: **1a** (0.05 mmol) suspended in Al_2O_3 was mixed and stirred vigorously with H_2O, KBr and $NaHCO_3$ for 5 min. [b] Al_2O_3 was activated at 120 °C for 48 h. [c] The equivalent of different materials to **1a**. [d] Yield was determined by ^{1}H-NMR of the crude reaction mixture using CH_2Br_2 as the internal reference.

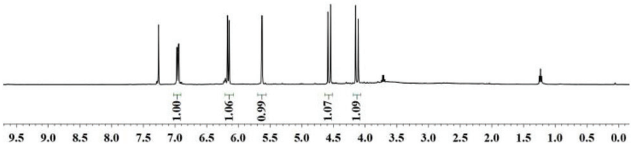
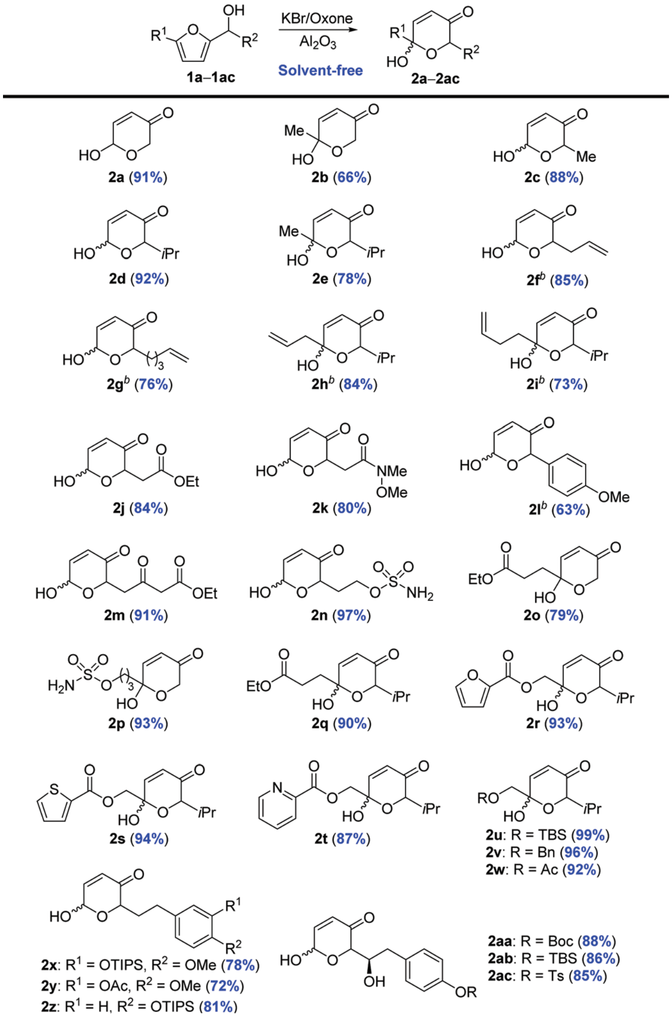


Fig. 2 ^{1}H-NMR spectrum of the crude **2a**.

Table 2 The substrate scope for the solvent-free AchR[a]



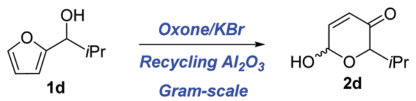
[a] Reaction conditions: Furfuryl alcohol (0.2 mmol), KBr (0.1 eq.), oxone (1.0 eq.), H_2O (2.0 eq.), $NaHCO_3$ (1.0 eq.), Al_2O_3 (120 mg), room temperature, 5 min, and isolated yield. [b] Reaction conditions: Furyl alcohol (0.2 mmol), KBr (0.4 eq.), oxone (2.0 eq.), H_2O (8.0 eq.), $NaHCO_3$ (2.0 eq.), Al_2O_3 (240 mg), room temperature, and 10 min.

metric alkali bromide was used. Heterocycles (**1r–t**) and the widely used protecting groups like TIPS (**1z**), TBS (**1ab** and **1u**), Boc (**1aa**) and Bn (**1v**) were also well tolerated in our solvent-free, catalytic AchR to afford the desired products in excellent yields (81–96%).

To demonstrate the additional value (environmental benefit) of our solvent-free catalytic protocol over the corresponding solvent-mediated process, we recycled the alumina (Al_2O_3) six times without any noticeable decrease of the efficiency for the gram-scale reaction (Table 3). It was noted, however, that more water and a longer reaction time (25–35 min) were needed to achieve the high yield for the recycling system. Remarkably, the recycling process was very simple (Fig. 3): after the completion of the reaction, the reaction mixture (solid) was transferred to a Buchner funnel (or a short chromatography column with cotton plug) for filtration washed with ethyl acetate; the filter cake containing Al_2O_3 and inorganic salts (K_2SO_4, KBr, and an excess of oxone) could be reused directly without further activation or purification. This easy recycling operation largely benefited from the use of oxone and KBr, which did not produce organic byproducts. Additionally, these solvent-free conditions did not require specialized equipment such as a ball mill/mixer used in mechanochemistry.[57–59]

To further exploit the synthetic advantages of our protocol over solvent-assisted methods, we were attracted to explore the possibility of solvent-free, one-pot, sequential reactions. We selected four important transformations of the AchR products, *i.e.*, oxidation, *O*-acetylation, *O*-Boc protection, and *O*-allylation, to examine such a possibility (Scheme 1). Oxidation of the AchR product **2d** to 5-hydroxy-2-pyrone **3** was successfully achieved in a one-pot, solvent-free manner by using oxone/TEMPO (cat).[60] Of note, KBr was used as the dual-role catalyst for both the AchR and subsequent oxidation. The sequential reactions were performed as follows: treatment of furfuryl alcohol **1d** (0.2 mmol) suspended in Al_2O_3 (120 mg) with oxone (123 mg, 1.0 eq.), KBr (7.1 mg, 0.3 eq.), H_2O (7.2 μL, 2.0 eq.), and $NaHCO_3$ (16.8 mg, 1.0 eq.) and the reaction mixture was stirred vigorously at room temperature for 2 min, then to this reaction mixture were added oxone (246 mg, 2.0 eq.) and catalytic TEMPO (6.25 mg, 0.2 eq.), the solid reaction mixture was stirred for 10 min, and then filtered through a pad of silica gel with ethyl acetate to remove the solid byproduct and Al_2O_3, and concentrated in a vacuum, to provide **3** in 84% overall yield. This is remarkable because we have realized two solvent-free catalytic reactions in a one pot. Next, we derivatized **2d** as acetate **4** and *tert*-butyl carbonate **5** in excellent yields (89% and 86% for two steps) by adding Ac_2O/DMAP and $(Boc)_2O$/DMAP, respectively, to the reaction vessel of the AchR. *O*-Acetylation and *O*-Boc protection are among the most used direct transformations of the AchR products since they afford substrates for *O*-glycosylation,[61,62] [5 + 2]-cycloaddition, and *C*-arylation. Surprisingly, these transformations have been conventionally performed with the purified AchR products in a separate reaction vessel because the stoichiometric byproduct from the oxidant (*m*-CPBA, NBS, *tert*-BuOOH, Br_2/MeOH, *etc.*) or aqueous reaction medium of the AchR did not permit a one-pot anhydrous acetylation. The final example of our sequential reactions was *O*-alkylation of **2d** in 73% yield by adding Ag_2O (92.7 mg, 2.0 eq.) and allyl bromide (69 μL, 4.0 eq.) to the solvent-free AchR mixture. Importantly, no aqueous workup was needed for all these two-step, one-pot, solvent-free reactions and the products (**3–6**) could be purified easily by transferring the solid reaction mixture to the top of the silica gel in a chromatography column eluting with hexane/ethyl acetate.

Table 3 Recycling use of Al_2O_3 (4.28 g) for the gram-scale AchR of **1d**



Entry[a]	H_2O (eq.)	Time (min)	Yield (%)
1	3 eq.	10	92
2	6 eq.	10	91.6
3	6 eq.	15	91.2
4	6 eq.	20	91
5	9 eq.	25	90.9
6	9 eq.	35	90.2

[a] After filtration with ethyl acetate, the filtrate cake (Al_2O_3) was air-flushed to dryness for re-use.

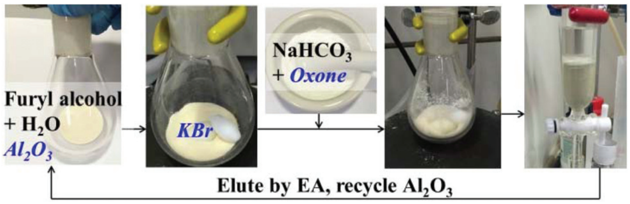
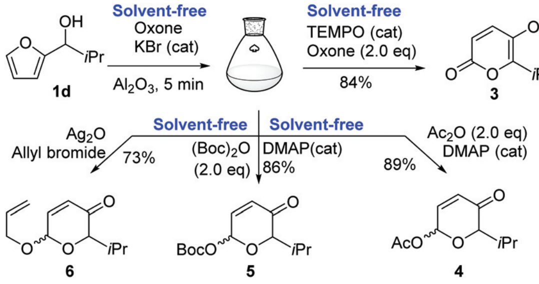
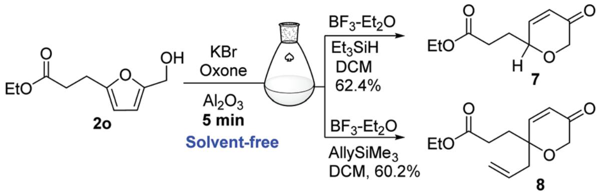


Fig. 3 Workflow diagram of the gram-scale, solvent-free AchR with recycling of Al_2O_3.



Scheme 1 Solvent-free, one-pot, two-step reactions involving the AchR.

Nevertheless, we recognized that the one-pot, solvent-free conditions could not be extended to the AchR–Kishi reduction or AchR–Ferrier allylation. Since the Kishi reduction and Ferrier-type allylation have been widely used for the synthesis of tetrahydropyrans from the AchR products, we aimed to



Scheme 2 One-pot sequential AchR/Kishi reduction and AchR–Ferrier allylation.

achieve the one-pot reaction goal (Scheme 2). Fortunately, we found that an excess of BF_3–Et_2O (8.0 eq.) could effect the Kishi reduction and Ferrier-type allylation of the AchR products in the same reaction vessel by adding solvent dichloromethane, Et_3SiH (12.0 eq.) and allyltrimethylsilane (12.0 eq.), respectively. The presence of neutral alumina might reduce the BF_3–Et_2O acidity and thus an excess of BF_3–Et_2O was required for both the Kishi reduction and Ferrier allylation. It was also noted that without the addition of dichloromethane, the AchR product was rapidly decomposed by BF_3–Et_2O. Nevertheless, the one-pot process of two reactions still presented sufficient greenness, cost, and time advantages over the two-pot operation.

Conclusions

In summary, we have established a solvent-free catalytic protocol for the AchR, representing the greenest conditions to date. The efficiency and utility of this new protocol was demonstrated with (1) 29 examples, (2) six-times recycling of Al_2O_3 on a gram scale, (3) the successful integration of oxidation, *O*-acylation or *O*-allylation as a one-pot solvent-free reaction, and (4) one-pot AchR/Kishi reduction and AchR–Ferrier allylation. The most striking advantages of this protocol over all previous methods include no solvent, no stoichiometric organic byproduct generated from the oxidant, no liquid–liquid extraction in the workup, and no column chromatography for purification. Furthermore, this new protocol is operationally simple and does not require specialized equipment (ball mill). It is expected that this new green protocol will aid the application of the AchR in organic synthesis and drug discovery.

Conflicts of interest

There are no conflicts of interest to declare.

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