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Direct amino acid-catalyzed cascade reductive alkylation of arylacetonitriles: high-yielding synthesis of ibuprofen analogs

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ABSTRACT

A novel approach for a one-pot, three-component reductive alkylation (TCRA) reaction of arylacetonitriles-containing electron-withdrawing groups with aldehydes/ketones and 1,4-dihydropyridine via iminium-catalysis has been developed. Many TCRA reaction products have direct applications in agricultural and pharmaceutical chemistry.

1. Introduction

2-Arylpropionic acids are an important class of compounds, which are present in a wide variety of biologically active compounds and are widely used as intermediates in the synthesis of non-steroidal anti-inflammatory drugs (NSAIDs) (Scheme 1).[1] Therefore, the development of new and more general cascade methods for the synthesis of novel NSAIDs is of significant interest.[2]

As part of our research program to engineer direct multi-catalysis cascade (MCC) reactions,[3,4] we have discovered a metal-free methodology for the reductive alkylation[5] of arylacetonitriles **1** containing an electron-withdrawing groups with aldehydes/ketones **2** and 1,4-dihydropyridines **3** by using amino acid-catalyzed cascade three-component reductive alkylation (TCRA) reactions via iminium- and self-catalysis in one-pot (Scheme 2). We propose that, in the first step the catalyst (*S*)-**4a** activates component **2** by iminium ion formation, which then selectively adds to arylacetonitriles **1** via a Mannich and retro-Mannich type reaction to generate active olefin **5**. This is followed by bio-mimetic hydrogenation of active olefin **5** by organic-hydrides **3** to produce **6** through self-catalysis by decreasing HOMO–LUMO energy gap between **3** and **5**, respectively.[5] Further treatment of **6** with an acid would lead to 2-aryl-3-aryl-propionic acids or 2-aryl-3-alkyl-propionic acids **7** as shown in Scheme 2. In this Letter, for the first time we report the soft- or organocatalysis approach to the reductive alkylation of less reactive arylacetonitriles **1** with **2** and **3**.[5]

First we focused on the optimization for high-yielding synthesis of 2-(4-nitro-phenyl)-3-phenyl-propionitrile **6aa** from **1a**, **2a,** and **3a–c** through amine- or amino acid **4**-/self-catalysis, by studying the effect of catalyst **4**, solvent, temperature, and hydrogen donor ability of **3a–c** in the designed TCRA reactions. Interestingly, in L-proline **4a**-/self-catalyzed cascade TCRA reaction of (4-nitro-phenyl)-acetonitrile **1a** and benzaldehyde **2a** with 1.0 equiv of Hantzsch ester **3a** in ethanol at 25 °C for 48 h, neither the expected product **6aa**, nor the olefination product **5aa** was obtained. But the same TCRA reaction in ethanol at 70 °C for 12 h furnished the expected TCRA product **6aa** with 75% yield (Table 1, entries 1 and 2). The TCRA reaction of **1a** and **2a** with 1.5 equiv of **3a** under **4a**-/self-catalysis in ethanol at 70 °C for 12 h furnished the expected product **6aa** with improved (82%) yield (Table 1, entry 3). Interestingly, the TCRA reaction of **1a** and **2a** with 1.5 equiv of **3a** under **4a**-/self-catalysis in DMSO at 25 °C for 20 h furnished the expected product **6aa** in 80% yield (Table 1, entry 5). L-Proline-/self-catalyzed cascade TCRA reaction of **1a** and **2a** with 1.5 equiv of in situ generated organic hydride source, 2-phenyl-2,3-dihydro-1*H*-benzoimidazole **3b** in ethanol at 70 °C for 12 h furnished the expected TCRA product **6aa** in only 50% yield (Table 1, entry 6). L-Proline-/self-catalyzed cascade TCRA reaction of **1a** and **2a** with 1.5 equiv of 2,6-dimethyl-3,5-diacetyl-1, 4-dihydropyridine **3c** in ethanol at 70 °C for 15 h furnished the expected product **6aa** with 75% yield, but the same cascade reaction in DMSO at 25 °C for 24 h furnished the expected product **6aa** with 80% yield (Table 1, entries 7 and 8). To the best of our knowledge, this is the first time that **3c** has been used as organic-hydride in

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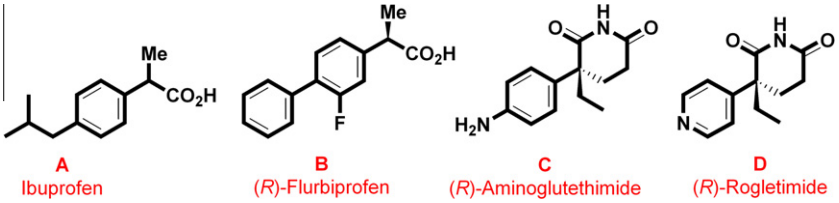
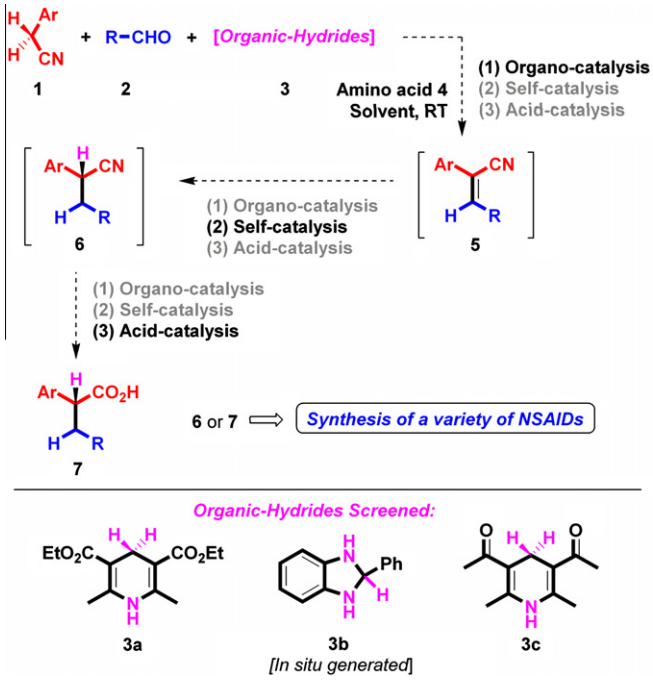


Scheme 1. Pharmaceutically attractive NSAIDs generated from 2-arylpropionic acids and 2-aryl-3-alkyl-propionitriles.



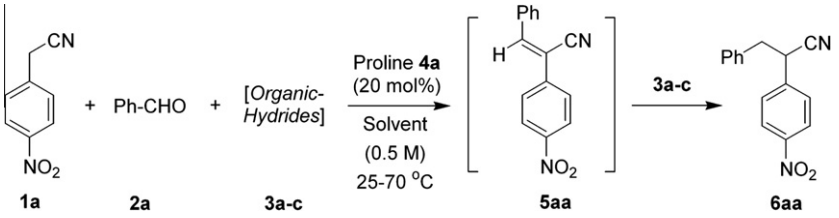
Scheme 2. Cascade TCRA approach to 2-aryl-3-alkyl-propionitriles.

organo-catalytic cascade reactions. **3c** has proved to be a better organic-hydride compared to **3a** due to the easy separation of polar by-product pyridine **3c′** from the crude reaction mixture. Interestingly we observed that the sequential one-pot reaction of **1a**, **2a,** and **3c** in DMSO at 25 °C for 24 h furnished the **6aa** with reduced (58%) yield compared to cascade reaction. This may be due to the absence of self-catalytic nature of **3c** in sequential TCRA reaction (entry 9).[5a] The optimum conditions (Table 1, entries 3, 5, and 8) involved the use of catalyst **4a** in cascade TCRA reaction of **1a**, **2a,** and **3a** or **3c** in EtOH or DMSO at 25/70 °C to furnish **6aa** in very good yield.[6]

We then proceeded to investigate the synthesis of **6aa** from **1a**, **2a,** and **3c** through amine- or amino acid **4**-/self-catalysis, by looking at the structural effect of catalyst **4** in DMSO at 25 °C for 24 h (Table S1, see Supplementary data). As shown in Table S1, amino acid glycine **4b** furnished the product **6aa** in good yield (71%) compared to amine catalysts.

We then decided to investigate the scope and limitations of the TCRA reaction of a range of C–H source molecules **1a**–**h** with aldehydes/ketones **2a**–**t** and **3c** under L-proline **4a**-/self-catalysis at 25–70 °C in EtOH or DMSO (Tables 2 and 3). As shown in Table 2, reaction of (2-nitro-phenyl)-acetonitrile **1b** with **2a** and 1.5 equiv of **3c** under the **4a**-catalysis in EtOH at 70 °C for 48 h furnished the single olefin derivative (*Z*)-**5ba** in 95% yield instead of the expected **6ba** (entry 1). The reaction with 4-cyanomethyl-benzoic acid methyl ester **1c** also furnished the single olefin derivative (*Z*)-**5ca** as major product instead of expected **6ca** from the reaction of **1c**, **2a,** and **3c** (entry 2). Similar results were obtained from the reaction of **1b**–**c**, **2a,** and **3c** under **4a**-catalysis in DMSO at 25 °C for 24 h (results not shown in Table 2). The formation of olefins (*Z*)-**5ba**–**ca** instead of expected alkylation products **6ba**–**ca** from TCRA reactions could be explained based on the steric/electronic factors and also based on the HOMO–LUMO energy gap between **5** and **3c**.[7,5] Interestingly, reaction of 4-cyanomethyl-benzonitrile **1d** with **2a** and 1.5 equiv of **3c** in EtOH at 70 °C for 24 h furnished

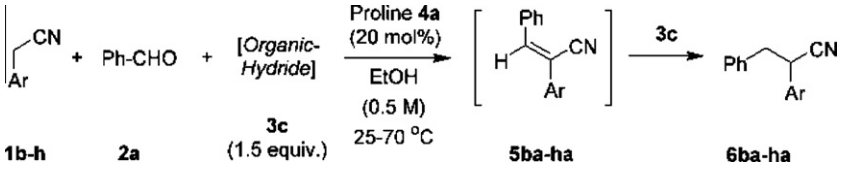
Table 1
Preliminary optimization of cascade TCRA reactions[a]

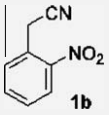
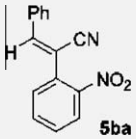
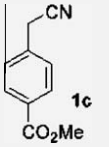
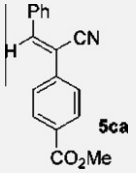
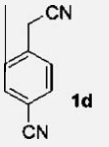
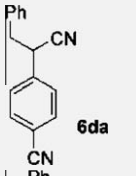
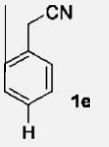
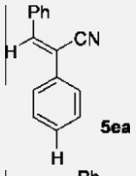
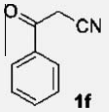
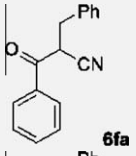
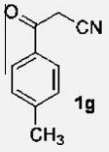
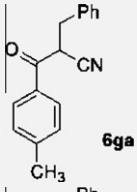
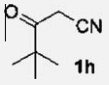
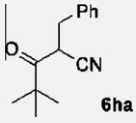


Entry	Solvent (0.5 M)	Organic-hydride (equiv)	Temperature (*T*)/°C	Time (h)	Yield **6aa**[b] (%)
1	EtOH	**3a** (1)	25	48	—
2	EtOH	**3a** (1)	70	12	75
3	EtOH	**3a** (1.5)	70	12	82
4	DMF	**3a** (1.5)	70	16	70
5	DMSO	**3a** (1.5)	25	20	80
6	EtOH	**3b** (1.5)	70	12	50
7	EtOH	**3c** (1.5)	70	15	75
8	DMSO	**3c** (1.5)	25	24	80
9[c]	DMSO	**3c** (1.5)	25	24	58

[a] All reactants **1a**, **2a**, **3a**–**c,** and catalyst **4a** were mixed at the same time in solvent and stirred at 25–70 °C.
[b] Yield refers to the column-purified product.
[c] Reaction is performed in sequential manner.

Table 2
Chemically diverse libraries of cascade TCRA products **6ba–ha**[a]



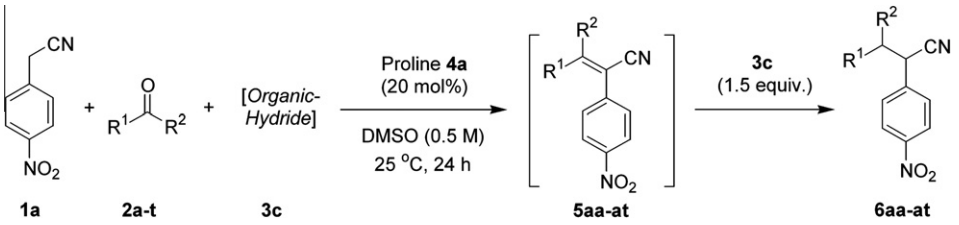
Entry	Ar-CH_2–CN (0.5 mmol)	Products **5** or **6**	Temperature *T*/°C	Time (h)	Yield **5** or **6**[b] (%)
1	 **1b**	 **5ba**	70	48	**5ba** (95)
2	 **1c**	 **5ca**	70	24	**5ca** (90)
3	 **1d**	 **6da**	70	24	**6da** (50)
4	 **1e**	 **5ea**	70	48	**5ea** (—)
5	 **1f**	 **6fa**	25	3	**6fa** (99)
6	 **1g**	 **6ga**	25	5	**6ga** (98)
7	 **1h**	 **6ha**	70	24	**6ha** (81)

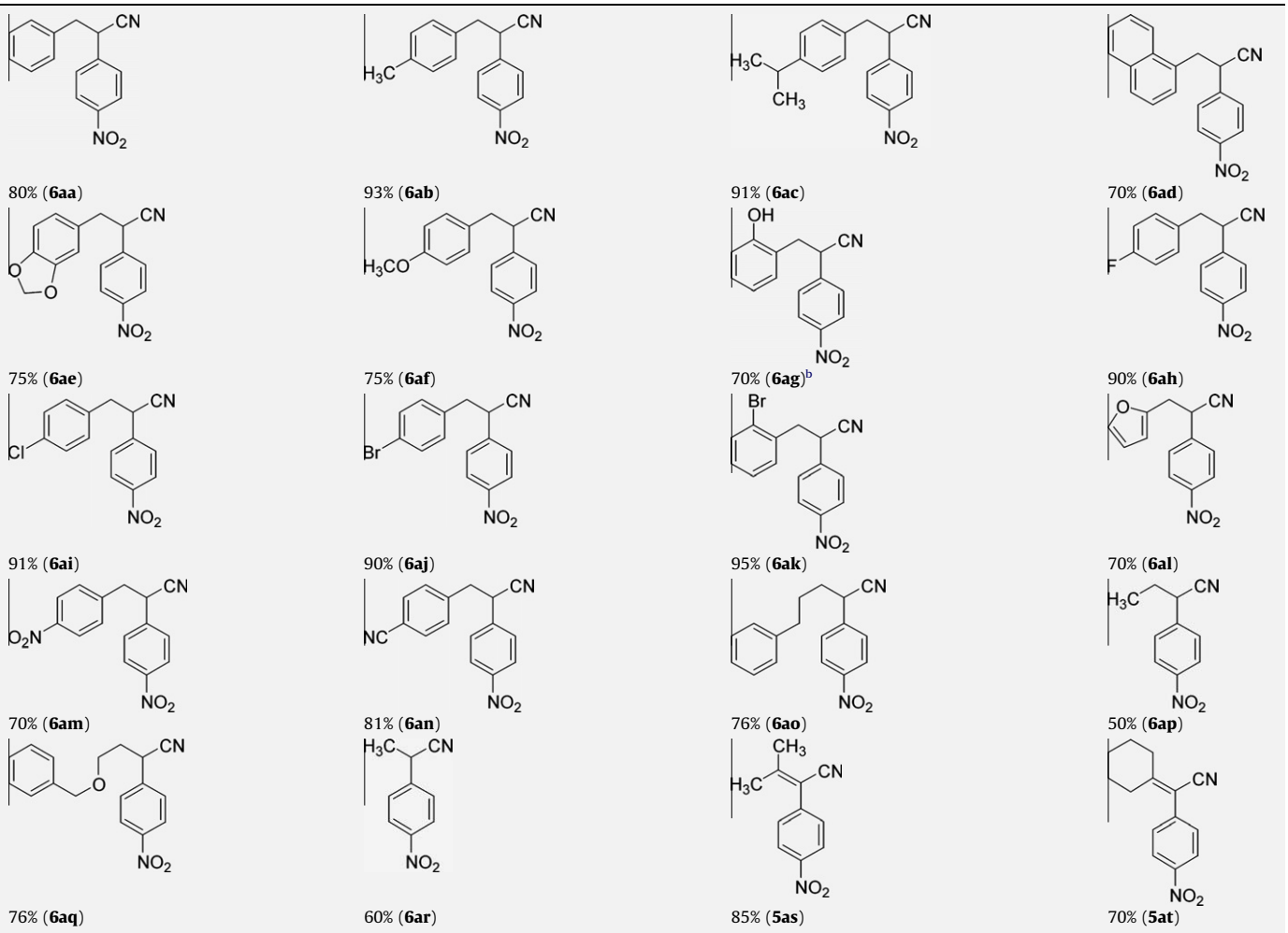
[a] All reactants **1b–h**, **2a**, **3c,** and catalyst **4a** were mixed at the same time in EtOH and stirred at 25–70 °C.
[b] Yield refers to the column-purified product.

the expected product **6da** in 50% yield (entry 3). Unfortunately, the reaction of phenylacetonitrile **1e** with **2a** and **3c** did not furnish the expected **6ea** or the olefin **5ea** as shown in entry 4, Table 2. Formation of selective (*Z*)-olefins **5aa–da** from **1a–d** and **2a** was confirmed by conducting two-component reaction of **1a–d** and **2a** under proline-catalysis at two different optimized conditions [EtOH, 70 °C for 11–48 h or DMSO, 25 °C for 11–71 h] to furnish the (*Z*)-olefins **5** in very good yields as shown in Table S2 (see Supplementary data). Regiochemistry of (*Z*)-olefins **5** was confirmed by X-ray crystal structure analysis on **5aa** as shown in Figure S1 (see Supplementary data).[8] Reaction of 3-oxo-3-phenyl-propionitrile **1f** with **2a** and **3c** under **4a**-/self-catalysis in EtOH at 25 °C for 3 h furnished the product **6fa** in 99% yield as shown in entry 5, Table 2. The generality of the TCRA reactions was further confirmed by two more examples using different C–H source **1g–h** with **2a** and **3c** to furnish the expected products **6ga** in 98% yield and product **6ha** in 81% yield, respectively as shown in Table 2. The structure and stereochemistry of substances **5–6** were confirmed by NMR analysis and also by mass analysis. This one-pot TCRA methodology may be suitable for developing a large number of diverse-compounds of **5** or **6** as intermediates for NSAIDs.

The results in Table 3 demonstrate the broad scope of this reductive methodology covering a structurally diverse group of aldehydes **2a–r** and less reactive ketones **2s–t**.[2] Interestingly, a large number of derivatives of 2-(4-nitro-phenyl)-3-aryl-propionitrile **6** are not known and the present methodology gives a protocol

Table 3
Chemically diverse libraries of cascade TCRA products **6aa–ar**[a]

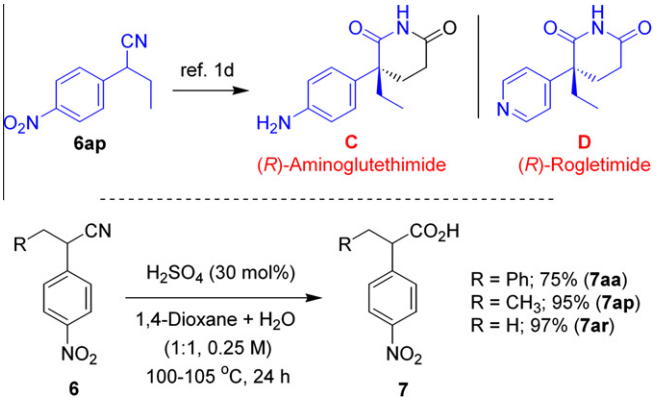




[a] Yield refers to the column-purified product.
[b] Reaction time is 96 h.

to prepare them in good yields. A series of substituted aromatic aldehydes **2a–n**, hetero-aromatic aldehyde **2l**, aliphatic aldehydes **2o–r,** and ketones **2s–t** were reacted with 1.0 equiv of (4-nitro-phenyl)-acetonitrile **1a** and organic-hydride **3c** (1.5 equiv) catalyzed by 20 mol % of proline **4a** in DMSO at 25 °C for 24 h (Table 3). Interestingly, L-proline-/self-catalyzed TCRA reaction of **1a** with 2-hydroxy-benzaldehyde **2g** and **3c** in DMSO at 25 °C took longer reaction time (96 h) to generate the cascade product **6ag** with 70% yield (Table 3). But the same L-proline-/self-catalyzed TCRA reaction of **1a**, and **3c** with 2-bromo-benzaldehyde **2k** at 25 °C in DMSO furnished the expected TCRA product **6ak** within 24 h as shown in Table 3.

TCRA reaction of **1a** with 3-phenylpropionaldehyde **2o** and **3c** under **4a**-/self-catalysis for 24 h in DMSO furnished the expected alkylated product **6ao** in 76% yield. Generality of the **4a**-/self-catalyzed cascade TCRA reactions with aliphatic aldehydes was further confirmed by three more examples using different aldehyde sources **2p–r** with **1a** and **3c** to furnish the expected TCRA products **6ap** in 50% yield, **6aq** in 76% yield, and product **6ar** in 60% yield, respectively, as shown in Table 3. Due to the many synthetic and pharmaceutical applications of 2-(4-nitro-phenyl)-propionitrile **6ar**, we further decided to investigate the improvement of the yield of **6ar** with TCRA reaction of **1a** with 39% aqueous formaldehyde **2r** and **3c** at different conditions as shown in Table S3 (see Supplementary data). We screened a TCRA reaction of **1a** with 1 equiv of 39% aqueous formaldehyde **2r** and 1.5 equiv of **3c** under the amino acid **4a–b**-/self- or amine **4c–h**-/self-catalysis in various solvents at 25 °C. But unfortunately none of the conditions gave better results compared to **4a**-/self-catalysis in DMSO at 25 °C for 24 h as shown in Table 3. Interestingly, when we used the 1.5 equiv of aqueous formaldehyde **2r** in TCRA reaction of **1a** and **3c** with **2r**, we couldn't find the product formation of **6ar**, that may be due to



Scheme 3. Applications of cascade TCRA reactions.

the presence of more water in the reaction (Table S3, see Supplementary data). TCRA products **6aa–ar** and analogs are very important intermediates for the synthesis of NSAIDs (**A–D**) and their drug-analogs.[1] Recently, Jones and co-workers reported the asymmetric synthesis of (*R*)-aminoglutethimide **C** (useful as treatment for the hormone-dependent breast cancer) from key intermediate **6ap**, which was prepared in three-steps starting from 1-chloro-4-nitrobenzene with <40% overall yield.[1d] Utilizing the presently developed TCRA method, we produced the drug intermediate **6ap** in 50% yield in a single step as shown in Table 3 and Scheme 3.

As shown in Table 3, TCRA reaction of (4-nitro-phenyl)-acetonitrile **1a** with 3.0 equiv of acetone **2s** and 1.5 equiv of **3c** under the **4a**-/self-catalysis in DMSO at 25 °C for 24 h furnished the olefin derivative **5as** in 85% yield instead of expected **6as** (entry 19). Same TCRA reaction of **1a**, **3c** (1.5 equiv) with 1.5 equiv of cyclohexanone **2t** also furnished the olefin derivative **5at** as major product instead of expected **6at** (entry 20). Formation of intermediate olefins **5as–at** instead of expected alkylation products **6as–at** from TCRA reactions could be explained based on the steric and electronic factors.[5]

Based on the demand of pharmaceutical applications, we further extended the TCRA products **6** into more useful intermediates **7** as shown in Scheme 3. Hydrolysis products **7** were obtained in very good yields with high selectivity and purity without column purification through acid-catalysis on **6** as shown in Scheme 3. This method will be showing much impact on the synthesis of 2-arylpropionic acids **7**. Compounds **7** have gained importance in recent years as intermediates for the synthesis of NSAIDs.[1] Hydrolysis of **6aa** under 30 mol % of H_2SO_4-catalysis furnished the 2-(4-nitrophenyl)-3-phenyl-propionic acid **7aa** in 75% yield as shown in Scheme 3. Generality of the H_2SO_4-catalyzed hydrolysis of **6** was further confirmed by two more examples using **6ap** and **6ar** to furnish the expected **7ap** in 95% yield and **7ar** in 97% yield, respectively as shown in Scheme 3. For the pharmaceutical applications, high-yielding synthesis of diversity-oriented library of substituted 2-arylpropionic acids **7** could be generated by using our two-step sequence of proline-/self-catalyzed TCRA reaction followed by H_2SO_4-catalyzed hydrolysis reaction.

In summary, we have developed a direct amino acid-/self-catalyzed cascade TCRA reactions of arylacetonitriles **1** containing electron withdrawing groups with aldehydes **2** and organic-hydride **3c**, which has direct applications in drug discovery process. Also we have developed the two-step sequence to synthesize 2-arylpropionic acids **7** with very good yields, which are useful as NSAIDs. Further work is in progress to utilize novel cascade TCRA products **6** as starting materials for the development of asymmetric cascade Michael-aldol reactions.

2. General experimental procedures for the TCRA reactions: proline-catalyzed cascade TCRA reactions

In a glass vial equipped with a magnetic stirring bar, to 0.5 mmol of arylacetonitrile **1**, 0.5 mmol of the aldehyde/ketone **2** and 0.75 mmol of 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine **3c** was added 1.0 mL of DMSO, followed by the catalyst amino acid **4a** (0.1 mmol). The reaction mixture was stirred at 25 °C for the time indicated in Tables 1–3. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure TCRA products **6** were obtained by column chromatography [silica gel, mixture of hexane/ethylacetate (90/10)].

3. H_2SO_4-Catalyzed hydrolysis reactions of 6

A solution of substituted 2-aryl-propionitrile **6** (0.5 mmol) and H_2SO_4 (1.5 mL, 50%) in 1, 4-dioxane solvent (1.0 mL) was stirred at 100 °C for 24 h. The reaction mixture was cooled and aqueous layer was made basic with 1 N aqueous NaOH and then un-reacted starting materials were extracted with CH_2Cl_2 (2 × 5 mL). Then the aqueous layer was acidified with 10% H_2SO_4 and the compound was extracted with CH_2Cl_2 (3 × 10 mL). The combined in CH_2Cl_2 extract was washed with brine and dried (anhydrous Na_2SO_4). Evaporation of the solvent afforded the pure 2-arylpropionic acids **7**.

Many of the TCRA products **6** and **7** are commercially available or have been synthesized previously, and their analytical data match literature values; and new compounds were characterized on the basis of IR, ^1H and ^{13}C NMR, and analytical data (see Supplementary data).

Acknowledgments

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A. Supplementary data

General experimental procedures, compound characterization, X-ray crystal structure and analytical data (IR, ^1H NMR and ^{13}C NMR) for all new compounds. Copies of the ^1H NMR and ^{13}C NMR spectra of all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.131.

References and notes

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8. CCDC-774736 for **5aa** contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; or mailto:deposit@ccdc.cam.ac.uk.