Tetrahedron Letters 51 (2010) 5246-5251

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet



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

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ARTICLE INFO

ABSTRACT

Article history: Received 25 April 2010 Revised 14 July 2010 Accepted 22 July 2010 Available online 27 July 2010

Keywords: Amino acids Cascade reactions Ibuprofen analogs Organocatalysis TCRA reactions 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.

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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 alkylation⁵ 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-3aryl-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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^{0040-4039/\$ -} see front matter \circledcirc 2010 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2010.07.131



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. Interest-

Table 1

Preliminary optimization of cascade TCRA reactions^a

ingly 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



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

	Ar + Ph-CHO	► Ph CN Ar			
	1b-h 2a	3c 25-70 °C (1.5 equiv.)	5ba-ha	6ba-ha	
Entry	Ar-CH ₂ -CN (0.5 mmol)	Products 5 or 6	Temperature T/°C	Time (h)	Yield 5 or 6^{b} (%)
1	CN NO ₂ 1b	H NO ₂ 5ba	70	48	5ba (95)
2	CN 1c CO ₂ Me	Ph CN 5ca	70	24	5ca (90)
3	CN 1d	CO ₂ Me Ph CN 6da	70	24	6da (50)
4	CN 1e	CN Ph H CN 5ea	70	48	5ea (—)
5		Ph CN 6fa	25	3	6fa (99)
6		Ph CN 6ga	25	5	6ga (98)
7		Ph CN 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-nitrophenyl)-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-cata-lyzed 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 H₂SO₄-catalysis furnished the 2-(4-nitrophenyl)-3-phenyl-propionic acid 7aa in 75% yield as shown in Scheme 3. Generality of the H₂SO₄-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 H₂SO₄-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 NH₄Cl solution and the aqueous layer was extracted with dichloromethane (2×20 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. Pure TCRA products **6** were obtained by column chromatography [silica gel, mixture of hexane/ethylacetate (90/10)].

3. H₂SO₄-Catalyzed hydrolysis reactions of 6

A solution of substituted 2-aryl-propionitrile **6** (0.5 mmol) and H₂SO₄ (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 $CH_2Cl_2(2 \times 5 \text{ mL})$. Then the aqueous layer was acidified with 10% H₂SO₄ and the compound was extracted with $CH_2Cl_2(3 \times 10 \text{ mL})$. The combined in CH_2Cl_2 extract was washed with brine and dried (anhydrous Na₂SO₄). 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 ¹³C NMR, and analytical data (see Supplementary data).

Acknowledgments

This work was made possible by a grant from the Department of Science and Technology (DST), New Delhi [Grant No.: DST/SR/S1/OC-65/2008]. M.S.P. thanks CSIR (New Delhi) for his research fellowship.

A. Supplementary data

General experimental procedures, compound characterization, X-ray crystal structure and analytical data (IR, ¹H NMR and ¹³C NMR) for all new compounds. Copies of the ¹H NMR and ¹³C 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.

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- 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.