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Phosphotungstic Acidcatalyzed Strecker Three-Component Reaction of Amino Acids, Aldehydes, and Trimethylsilyl Cyanide

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A simple and efficient one-pot, three-component Strecker reaction of protected amino acids, aromatic aldehydes, and trimethylsilyl cyanide has been developed for the synthesis of chiral *α*-amino nitriles. The reaction was carried out in the presence of catalytic amount of phosphotungstic acid ($H_3[P(W_3O_{10})_4]$) as an environmentally friendly catalyst.

Keywords: Strecker reaction, Protected *α*-amino acid, Heteropoly acid, Phosphotungstic acid, Trimethylsilyl cyanide, Environmentally friendly catalyst, Diastereoselectivity

INTRODUCTION

Strecker reaction is one of the most important multicomponent reactions in organic chemistry for direct one-pot synthesis of *α*-amino nitriles and other biologically relevant molecules [1-4]. *α*-Amino nitriles have wide applications in organic synthesis [5-7]. They serve as efficient precursors for the synthesis of natural and unnatural *α*-amino acids, bioactive molecules like clopidogrel, prassugrel, saframycin A [8]. In recent years, development of new processes that achieve stereoselective *α*-amino nitriles has received considerable attention due to growing asymmetric Strecker synthesis [9-10]. Asymmetric Strecker reaction could be done using chiral starting materials or chiral catalysts. Many Lewis acid catalysts have been used for this reaction such as, $NiCl_2$[11], $Cu(OTf)_2$[12], $RuCl_3$[13], $La(NO_3)_3$[14], $InCl_3$[15], $Yb(OTf)_3$[16], $Pr(OTf)_3$[17], $BiCl_3$[18], $CeCl_3$[19], RhI_3[20] and $FeCl_3$[21]. Different metallic species or other catalytic active centers have been often immobilized on inorganic materials such as SiO_2, Al_2O_3, ZrO_2, TiO_2 or MgF_2, synthetic organic polymers or their hybrid materials and nano-ordered heterogeneous catalysts [22]. These catalysts have more advantageous in terms of catalyst/product separation and continuous production. Polymer-supported $Sc(OTf)_3$ [23], montmorillonite-KSF [24], silica-H_2SO_4 [25-26] and poly(4-vinylpyridine)-SO_2 [27] complex are examples of heterogeneous catalysts.

The reaction could be done using both metal-based and metal-free asymmetric catalysts. Many efforts have been directed to the development of catalytic asymmetric approaches to these compounds. Using metal-assisted hydrocyanation of imines and organocatalysts are still in many instances. Lewis acids containing chiral ligands have been used as chiral Lewis acids in asymmetric Strecker synthesis [28-30].

Using a variety of Lewis acids which most of these methods involve the use of strong acidic conditions, expensive reagents, extended reaction times, harsh reaction conditions, fast hydrolysis and tedious work-up leading to the generation of a large amount of waste. Therefore, more general and milder reaction conditions for one-pot multicomponent Strecker reactions would be advantageous. Using of chiral ligands and also carrying out the reaction in the presence of organocatalysts are suitable approaches for the enantiomerically pure synthesis of *α*-amino acids [31-36].

Heteropoly acids (HPAs) have been extensively studied

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as natural acids and catalysts for many reactions and found industrial applications in several processes. HPAs are promising solid acids to replace environmentally harmful liquid acid catalysts such as H_2SO_4. In solutions, the acidic properties of HPAs are quite well documented in terms of dissociation constants and Hammett acidity function [37-39]. Phosphotungstic acid is a heteropoly acid with the chemical formula $H_3PW_{12}O_{40}$. Phosphotungstic acid is used in histology as a component for staining of cell specimens [40].

In the best of our knowledge, there is only a report about the using of *α*-amino acids in Strecker synthesis [41]. Herein, we wish to report a three-component reaction of methyl ester of α-amino acids, trimethylsilyl cyanide and aromatic aldehydes in the presence of phosphotungstic acid as a heteropoly acid as a green acidic catalyst.

EXPERIMENTAL

Commercially available materials were used without further purification. Melting points were determined on an Electrothermal 9100 apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR FTLA 2000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on Bruker DRX-300 AVANCE spectrometers at 300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR. DMSO-d_6 and $CDCl_3$ were used as solvent. High resolution mass spectra were recorded on Mass-ESI-POS (Apex Qe-FT-ICR instrument) spectrometer. Mass spectra data were obtained by using *GC-MS Hewlet Packard* (Agilent Technology 5973, EI, 70 eV) instrument.

General Procedure for the Synthesis of α-Aminonitriles4a-n

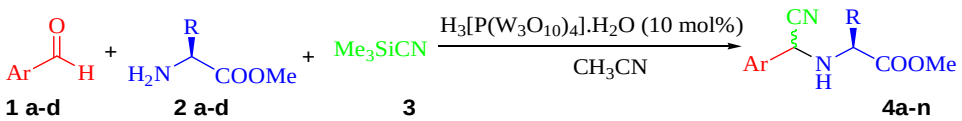
Phosphotungstic acid (0.3 mg, 10 mol%) was added to a solution of *α*-amino acid methyl ester **1** (1 mmol), aromatic aldehyde **2** (1 mmol), and trimethylsilyl cyanide **3** (0.12 mg, 1.2 mmol) in 10 ml acetonitrile. The mixture was heated under reflux conditions. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 1:3), at first the reaction was filtered, then the solvent was removed under vacuum, and the residue was purified using preparative TLC. The yields of *α*-amino nitriles **4a-n** were 48-81%.

Spectral Data for Compounds 4a-n

(4a): Methyl 2(S)-((2-bromophenyl)((R,S)cyano) methylamino)-3-phenylpropanoate, ratio of diastereomers (dr 54:46). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.22 (*brs*, 1H, NH, diastereomer A), 2.50 (*brs*, 1H, NH, diastereomer B), 2.89-2.99 (*m*, 2H, NCH-C$\underline{H}^{\beta}$, mixture of two diastereomers), 3.05 (*dd*, 1H, *J* = 13.7 Hz, *J* = 5.6 Hz, NCH-C$\underline{H}^{\beta}$, diastereomer A), 3.11 (*dd*, 1H, *J* = 13.7 Hz, *J* = 5.7 Hz, NCH-C$\underline{H}^{\beta}$, diastereomerB), 3.67 (*s*, 3H, -OMe, diastereomer A), 3.74 (*s*, 3H, -OMe, diastereomer B), 3.62-3.80 (*m*, 1H, CH^{α}, diastereomer A), 3.85-3.90 (*m*, 1H, CH^{α} diastereomer B), 5.08 (*s*, 1H, C$\underline{H}$CN, diastereomer A), 5.21 (*s*, 1H, C$\underline{H}$CN, diastereomer B), 7.17-7.34 (*m*, 12H, H-Ar, mixture of two diastereomers A, B), 7.48 (*d*, 1H, *J* = 1.6 Hz, H-Ar, diastereomer A), 7.51 (*d*, 1H, *J* = 1.6 Hz, H-Ar, diastereomer B), 7.54 (*t*, 2H, *J* = 1.7 Hz, H-Ar, diastereomer A), 7.57 (*t*, 2H, *J* = 1.6 Hz, H-Ar, CH_2Phe, diastereomer B) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 39.2, 39.6 (CH_2), 52.1, 52.2 (C$\underline{H}$-CN), 52.6, 52.7 (-OMe), 59.7, 60.4 (CHα), 117.8, 118.0 (CN), 126.7, 127.1, 128.1, 128.2, 128.5, 128.7, 129.2, 129.3, 129.4, 129.6, 130.8, 130.9, 133.4, 133.6, 133.7, 133.8 (C-Ar), 173.2, 173.5(C=O) ppm. HR-Mass (ESI) *m/z*: for $C_{18}H_{19}BrN_2O_2$ $[M+H]^+$ found :373.05496, Calcd.: 373.05491.

(4b): Methyl 2(S)-((4-chlorophenyl)((R,S)cyano) methylamino)-3-phenylpropanoate, ratio of diastereomers (dr 64:36). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.32 (*brs*, 2H, NH, mixture of two diastereomers), 2.89 (*dd*, 2H, *J* = 13.7, 8.1 Hz, NCH-C$\underline{H}^{\beta}$, mixture of two



Scheme 1. Strecker reaction of amino acids methyl ester, aldehydes and trimethylsilyl cyanide

diastereomers), 3.09 (*dd*, 2H, *J* = 13.6, 5.2 Hz, NCH-C<u>H</u>$^{\beta}$, mixture of two diastereomers), 3.63 (*dd*, 1H, *J* = 8.3, 5.2 Hz, CH$^{\alpha}$, diastereomer A), 3.73 (*s*, 3H, -OMe, diastereomer A), 3.76 (*s*, 3H, -OMe, diastereomer B), 3.76-3.80 (*m*, 1H, CH$^{\alpha}$, diastereomer B), 4.50 (*s*, 1H, -C<u>H</u>CN, diastereomer A), 4.82 (*s*, 1H, -C<u>H</u>CN, diastereomer B), 7.13 (dd, 2H, *J* = 5.8, 1.9 Hz, H-Ar(Phe) mixture of two diastereomers), 7.19 (*dd*, 4H, *J* = 7.9, 1.6 Hz, H-Ar(Phe) mixture of two diastereomers), 7.26 (dd, 2H, *J* = 4.2, 1.1 Hz, H-Ar, mixture of two diastereomers), 7.30 (d, 10H, *J* = 5.1 Hz, H-Ar, mixture of two diastereomers) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 39.5, 39.7 (CH_2), 52.1, 52.2 (<u>C</u>H-CN), 52.3, 52.6 (-OMe), 59.4, 60.5 (CH$^{\alpha}$), 118.0, 118.3 (<u>C</u>N), 127.0, 127.1, 128.4, 128.6, 128.7, 128.8, 128.9, 129.1, 129.2, 129.4, 129.6, 129.7, 132.7, 132.8, 135.1, 135.2, 136.1, 136.7 (C-Ar), 173.5, 173.6 (C=O) ppm. HR-Mass (ESI) *m/z*: for $C_{18}H_{18}ClN_2O_2$ $[M+H]^+$ found: 329.10544, Calcd.: 329.10537. $C_{18}H_{17}ClN_2NaO_2$ $[M+Na]^+$ found: 351.08740, Calcd.: 351.08734; $C_{18}H_{17}ClKN_2O_2$ $[M+K]^+$ found: 367.06136, Calcd.: 367.06130.

(4c): Methyl 2(S)-((R,S)cyano(4-cyanophenyl) methylamino)-3-phenylpropanoate, ratio of diastereomers (dr 59:41). ^{1}H NMR (300 MHz, CD_3Cl) δ = 3.08 (*dd*, 1H, *J* = 5.3, 1.6 Hz, -NCH-C<u>H</u>$^{\beta}$, diastereomer A), 3.12 (*dd*, 1H, *J* = 5.4, 1.8 Hz, -NCH-C<u>H</u>$^{\beta}$, diastereomer B), 3.83-3.87 (*m*, 2H, CH$^{\alpha}$, mixture of two diastereomers), 3.72 (*s*, 3H, -OMe, diastereomer A), 3.74 (*s*, 3H, -OMe, diastereomer B), 3.85 (*dd*, 1H, *J* = 8.0, 5.4 Hz, CH$^{\alpha}$, diastereomer B), 4.54 (*s*, C<u>H</u>CN, diastereomer A), 4.84 (*s*, C<u>H</u>CN, diastereomer B), 7.14-7.36 (*m*, 10H, H-Ar, mixture of two diastereomers), 7.80 (*s*, 4H, H-Ar, diastereomer A), 7.88 (*d*, 2H, *J* = 8.3 Hz, H-Ar, diastereomer B), 8.29 (*d*, 2H, *J* = 8.3 Hz, H-Ar, diastereomer B) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 39.4, 39.7 (CH_2), 52.2, 52.9 (<u>C</u>H-CN), 53.0, 53.3 (-OMe), 59.6, 60.4 (CH$^{\alpha}$), 110.1 (<u>C</u>$_{Ar}$-CN), 116.7, 117.0 (CH-<u>C</u>N), 118.4, 118.6 (C$_{Ar}$-<u>C</u>N), 127.0, 127.1, 127.4,127.5,128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.1, 129.3, 129.4, 129.7, 131.6, 132.8, 132.9, 133.2, 135.6, 136.1, 136.4, 136.8 (C-Ar), 173.5, 173.6 (C=O) ppm. HR-Mass (ESI) *m/z*: for $C_{19}H_{18}N_3O_2$ $[M+H]^+$ found: 320.12620, Calcd.: 320.12583. $C_{19}H_{17}KN_3O_2$ $[M+K]^+$ found: 358.24045, Calcd.: 358.24062.

(4d): Methyl 2(S)-((R,S)cyano(4-nitrophenyl) methylamino)-3-phenylpropanoate (dr 52:48). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.25 (*dd*, 2H, *J* = 13.6, 9.2 Hz, NCH-C<u>H</u>$^{\beta}$, diastereomer A), 3.56 (*dd*, 2H, *J* = 13.6, 4.3 Hz, NCH-C<u>H</u>$^{\beta}$, diastereomer B), 3.81 (*s*, 6H, -OMe, mixture of two diastereomers), 3.75-3.90 (*m*, 2H, CH$^{\alpha}$, mixture of two diastereomers), 4.87 (*d*, 1H, *J* = 4.4 Hz, C<u>H</u>CN, diastereomer A), 4.90 (*d*, 1H, *J* = 4.4 Hz, -C<u>H</u>CN, diastereomer B), 7.14 (*dd*, 2H, *J* = 7.6, 1.9 Hz, H-Ar, mixture of two diastereomers), 7.25 (*d*, 2H, *J* = 8.1 Hz, H-Ar, mixture of two diastereomers), 7.34 (*dd*, 1H, *J* = 6.5, 2.9 Hz, H-Ar, mixture of two diastereomers), 8.13 (*d*, 2H, *J* = 8.8 Hz, H-Ar, mixture of two diastereomers), 8.32 (*d*, 2H, *J* = 8.8 Hz, H-Ar, mixture of two diastereomers) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 39.7, 39.8 (CH_2), 52.5, 52.6 (<u>C</u>H-CN), 53.4 (-OMe), 71.7 (CHα), 113.3, 114.3 (<u>C</u>N), 123.4, 126.9, 127.0, 128.2, 128.4, 128.6, 128.8, 129.2, 129.3, 129.8, 130.3, 136.3, 136.6 (C-Ar), 173.5, 173.6 (C=O) ppm. HR-Mass (ESI) *m/z*: for $C_{18}H_{19}N_3O_4$ $[M+H]^+$ found: 340.12071, Calcd.: 340.12068.

(4e): Methyl 2(S)-(((2-bromophenyl)((R,S)cyano) methyl)amino)-3-methylbutanoate, ratio of two diastereomers (dr 63:37). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.88 (*d*, 6H, *J* = 6.9 Hz, CH_3, diastereomer A), 0.93 (*d*, 6H, *J* = 6.9 Hz, CH_3, diastereomer A), 1.97 (*heptet*, 1H, CH$^{\beta}$, diastereomer A), 2.35 (*brs*, 1H, CH$^{\beta}$, diastereomer B), 3.13 (*d*, 1H, *J* = 5.6 Hz, CH$^{\alpha}$, diastereomer A), 3.31 (*d*, 1H, *J* = 5.6 Hz, CH$^{\alpha}$, diastereomer B), 3.68 (*s*, 3H, -OMe, diastereomer A), 3.76 (*s*, 3H, -OMe, diastereomer B), 5.12 (*s*, 1H, CHCN, diastereomer A), 5.20 (*s*, 1H, CHCN, diastereomer B), 7.23-7.28 (*m*, 2H, H-Ar, mixture of two diastereomers), 7.36-7.45 (*m*, 2H,H-Ar, mixture of two diastereomers), 7.59 (*d*, 2H, *J* = 7.9 Hz, H-Ar, mixture of two diastereomers), 7.67 (*t*, 2H, *J* = 8.0 Hz, H-Ar, mixture of two diastereomers) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.9, 18.1, 19.2, 19.3 (CH(<u>C</u>H_3)$_2$), 31.6, 32.0 (<u>C</u>H(CH$_3$)$_2$), 51.9, 52.0 (<u>C</u>H-CN), 53.0, 53.5 (-OMe), 64.0, 64.9 (CHα), 118.1, 118.2 (<u>C</u>N), 123.4, 123.9, 128.1, 129.3, 129.9, 130.8, 130.9, 133.4, 133.5, 134.0 (C Ar), 174.1, 174.2 (C=O) ppm. Mass-EI (70 ev) $C_{14}H_{17}BrN_2O_2$ $[M]^{\cdot+}$ = 325.

(4f): Methyl 2(S)-(((4-chlorophenyl)((R,S)cyano) methyl)amino)-3-methylbutanoate (dr 52:48). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.87 (*d*, 3H, *J* = 6.9 Hz, CH_3,diastereomer A), 0.91 (*d*, 3H, *J* = 6.9 Hz, CH_3, diastereomer A), 0.96 (*d*, 3H, *J* = 6.9 Hz, CH_3, diastereomer

B), 0.98 (*d*, 3H, *J* = 6.9 Hz, CH_3, diastereomer B), 1.94-2.07 (m, 1H, C<u>H</u>$(CH_3)_2$, diastereomer A), 2.28-2.31 (m, 1H, C<u>H</u>$(CH_3)_2$, diastereomer B), 3.11 (*brs*, 1H, CH^{α}, diastereomer A), 3.29 (*brs*, 1H, CH^{α}, diastereomer B), 3.76 (*s*, 3H, -OMe, diastereomer A), 3.78 (*s*, 3H, -OMe, diastereomer B), 4.67 (*s*, 1H, C<u>H</u>CN, diastereomer A), 4.77 (*s*, 1H, C<u>H</u>CN, diastereomer B), 7.37 (*d*, 2H, *J* = 2.3 Hz, H-Ar, diastereomer A), 7.40 (*d*, 2H, *J* = 2.3 Hz, H-Ar, diastereomer A), 7.46 (*d*, 2H, *J* = 6.6 Hz, CHAr, diastereomer B), 7.50 (d, 2H, *J* = 6.6 Hz, H-Ar, diastereomer B).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.8, 18.0, 19.2 (CH(<u>C</u>$H_3)_2$), 31.6, 31.9 (<u>C</u>H$(CH_3)_2$), 52.0, 52.8 (<u>C</u>H-CN), 53.4 (-OMe), 63.9, 65.0 (CH^{α}), 118.2, 118.3 (<u>C</u>N), 128.9, 129.1, 129.2, 129.4, 130.9, 133.1, 135.2, 135.3 (C-Ar), 174.2, 174.3 (C=O) ppm. Mass-EI (70 ev) $C_{14}H_{17}ClN_2O_2$ $[M]^{\cdot+}$ = 281.

(4g): Methyl 2(S)-(((R,S)cyano(4-cyanophenyl) methyl)amino)-3-methylbutanoate (dr 51:49). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.99 (*d*, 3H, *J* = 6.6 Hz, CH_3, diastereomer A), 1.02 (*d*, 3H, *J* = 6.6 Hz, CH_3, diastereomer A), 1.25-1.28 (m, 6H, $2CH_3$, diastereomer B), 2.24-2.35 (m, 2H, C<u>H</u>$(CH_3)_2$, mixture of two diastereomers), 3.69-3.77 (m, 1H, CH^{α}, diastereomer A), 3.79 (s, 6H, -OMe, mixture of two diastereomers), 3.81-3.92 (m, 1H, CH^{α}, diastereomer B), 4.76 (d, 1H, *J* = 4.8 Hz, C<u>H</u>CN, diastereomer A), 4.79 (d, 1H, *J* = 4.8 Hz, C<u>H</u>CN, diastereomer B), 7.73 (d, 2H, *J* = 6.7 Hz, H-Ar, diastereomer A), 7.78 (d, 2H, *J* = 7.8 Hz, H-Ar, diastereomer B), 7.91 (d, 2H, *J* = 8.3 Hz, H-Ar, diastereomer A), 8.17 (d, 2H, *J* = 8.3 Hz, H-Ar, diastereomer B) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.8, 17.9, 18.5, 19.2 (CH(<u>C</u>$H_3)_2$), 31.5, 32.0 (<u>C</u>H$(CH_3)_2$), 52.1, 52.7 (<u>C</u>H-CN), 53.7 (-OMe), 63.9, 65.4 (CH^{α}), 113.4 (<u>C</u>$_{Ar}$-CN), 117.5, 117.6 (C_{Ar}-<u>C</u>N), 118.1 (CH-<u>C</u>N), 128.1, 128.3, 128.7, 128.9, 132.3, 132.4, 132.7, 132.8, 139.5, 139.6 (C-Ar), 173.9, 174.2 (C=O) ppm. Mass-EI (70 ev) $C_{15}H_{17}N_3O_2$ $[M]^{\cdot+}$= 271.

(4h): Methyl 2(S)-(((R,S)cyano(4-nitrophenyl)methyl) amino)-3-methylbutanoate (dr 78:22). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.02 (*d*, 3H, *J* = 5.8 Hz, CH_3, diastereomer A), 1.04 (*d*, 3H, *J* = 5.8 Hz, CH_3, diastereomer B), 1.24-1.27 (*brs*, 6H, $2CH_3$, diastereomer B), 1.99-2.03 (*m*, 1H, C<u>H</u>$(CH_3)_2$, diastereomer A), 2.53-2.64 (*m*, 1H, C<u>H</u>$(CH_3)_2$, diastereomer B), 3.30 (*d*, 1H, *J* = 5.4 Hz, CH^{α}, diastereomer A), 3.38 (*d*, 1H, *J* = 5.6 Hz, diastereomer B), 3.75 (*s*, 3H, -OMe, diastereomer A), 3.80 (*s*, 3H, -OMe, diastereomer B), 4.47 (*s*, 1H, C<u>H</u>CN, diastereomer A), 4.51 (*d*, 1H, *J* = 5.4 Hz, C<u>H</u>CN, diastereomer B), 8.17 (*d*, 1H, *J* = 8.5 Hz, H-Ar, diastereomer A), 8.23 (*d*, 1H, *J* = 8.4 Hz, H-Ar, diastereomer A), 8.24 (*d*, 1H, *J* = 9.1 Hz, H-Ar, diastereomer B), 8.35 (*d*, 1H, *J* = 8.6 Hz, H-Ar, diastereomer B) ppm.

^{13}C NMR Data for Pure Diastereomer A

^{13}C NMR (75 MHz, $CDCl_3$) δ = 18.1, 19.4 (CH (<u>C</u>$H_3)_2$), 29.7 (<u>C</u>H $(CH_3)_2$, 52.6 (<u>C</u>H-CN), 64.9 (-OMe), 66.3 (CH^{α}), 109.0, 124.1, 129.0, 138.0, 142.0 (C-Ar), 169.6 (C=O) ppm.

(4i): Methyl 2(S)-(((2-bromophenyl) ((R,S) cyano) methyl)amino)-3-(1*H*-indol-3-yl)propanoate (dr 56:44). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.03-3.13 (*m*, 2H, CH_2, mixture of two diastereomers), 3.22-3.32 (*m*, 2H, CH_2, mixture of two diastereomers), 3.74 (*s*, 3H, -OMe, diastereomer A), 3.82 (*s*, 3H, -OMe, diastereomer B), 3.86 (*dd*, 1H, *J* = 8.1, 5.0 Hz, CH^{α}, diastereomer A), 4.00 (*dd*, 1H, *J* = 10.9, 4.2 Hz, CH^{α}, diastereomer B), 5.84 (*s*, 1H, C<u>H</u>CN, diastereomer A), 5.85 (*s*, 1H, C<u>H</u>CN, diastereomer B), 6.89-7.59 (*m*, 18H, H-Ar, mixture of two diastereomers), 10.36 (*s*, 1H, NH indole).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.9, 29.2 (CH_2), 52.2, 52.6 (<u>C</u>H-CN), 58.9 (-OMe), 59.3 (CH^{α}), 110.5 (Cq, indole), 111.2 (CH-Ar), 118.2, 118.6 (<u>C</u>N), 118.7, 119.6, 119.7, 122.2, 122.3, 122.9, 123.1, 127.3, 128.1, 129.2, 129.5, 130.7, 133.4, 133.5, 136.1, 136.2 (C-Ar), 173.5, 173.8 (C=O) ppm.

(4j): Methyl 2(S)-(((4-chlorophenyl) ((R,S) cyano) methyl)amino)-3-(1*H*-indol-3-yl)propanoate (dr 51:49). ^{1}H NMR (300 MHz, MeOD) δ = 3.04 (*dd*, 1H, *J* = 7.2, 2.8 Hz, CH_2, diastereomer A), 3.08 (*dd*, 1H, *J* = 7.2, 2.7 Hz, CH_2, diastereomer B), 3.12-3.21 (*m*, 2H, CH_2, mixture of two diastereomers), 3.57 (*s*, 3H, -OMe, diastereomer A), 3.62 (*s*, 3H, -OMe, diastereomer B), 3.66 (*t*, 1H, *J* = 6.6 Hz, CH^{α}, diastereomer A), 3.73 (ABq, 1H, *J* = 6.6 Hz, CH^{α}, diastereomer B), 4.83 (*s*, 1H, C<u>H</u>CN, diastereomer A), 4.95 (*s*, 1H, C<u>H</u>CN, diastereomer B), 7.02 (*s*, 1H, =CH indole, diastereomer A), 7.04 (*s*, 1H, =CH indole, diastereomer B), 7.07 (*m*, 1H, H-Ar, diastereomer A), 7.10 (*m*, 1H, H-Ar, diastereomer B), 7.24 (*d*, 1H, *J* = 8.8 Hz, H-Ar,

diastereomer A), 7.31 (*d*, 1H, *J* = 9.0 Hz, H-Ar, diastereomer B), 6.90-7.10 (*m*, 8H, H-Ar, indole, mixture of two diastereomers) ppm.

^{13}C NMR (75 MHz, MeOD) δ = 30.2, 30.4 (CH_2), 52.9, 53.0 (CH-CN), 58.0, 59.1 (-OMe), 60.5, 61.4 (CH^{α}), 110.7, 110.8 (Cq-indole), 112.1, 112.3 (CH-Ar), 118.7 (CN), 119.2, 119.3, 119.7, 119.8, 119.9, 122.4, 124.5, 124.6, 128.6, 129.7, 129.8, 129.9, 130.1, 130.2, 135.0, 135.3, 135.7, 135.8, 138.0, 138.2 (C-Ar), 175.7, 175.8 (C=O) ppm.HR-Mass (ESI) *m/z*: for $C_{20}H_{20}ClN_3O_2$ $[M+H]^+$ found: 368.11622, Calcd. 368.11617.

(4k): Methyl 2(S)-(((R,S) cyano(4-cyanophenyl) methyl)amino)-3-(1*H*-indol-3-yl) propanoate (dr 71:29). ^{1}H NMR (300 MHz, MeOD) δ = 3.12 (*dd*, 2H, *J* = 14.6, 7.0 Hz, CH_2 mixture of two diastereomers), 3.28-3.30 (*m*, 2H, CH_2 mixture of two diastereomers), 3.75 (*s*, 3H, -OMe, diastereomer A), 3.85 (*s*, 3H, -OMe, diastereomer B), 4.04-4.08 (*m*, 1H, CH^{α}, diastereomer A), 4.25-4.29 (*m*, 1H, CH^{α}, diastereomer B), 5.61 (*s*, 1H, CHCN, diastereomer A), 5.68 (*s*, 1H, CHCN, diastereomer B), 7.03 (*t*, 1H, *J* = 7.4 Hz, H-Ar, indole), 7.07-7.10 (*m*, 2H, H-Ar, indole, diastereomer A), 7.23 (*t*, *J* = 7.1 Hz, H-Ar, indole, diastereomer B), 7.44 (*s*, 1H, =CH indole, diastereomer A), 7.47 (*s*, 1H, =CH indole, diastereomer B), 7.48 (*d*, 2H, *J* = 8.1 Hz, H-Ar, diastereomer A), 7.58 (*d*, 2H, *J* = 7.8 Hz, H-Ar, diastereomer B), 7.71 (*d*, 2H, *J* = 8.0 Hz, H-Ar, diastereomer A), 7.78 (*d*, 2H, *J* = 7.8 Hz, H-Ar, diastereomer B) ppm.

^{13}C NMR (75 MHz, MeOD) δ = 30.4, 30.7 (CH_2), 53.2, 53.3 (CH-CN), 55.4, 57.7 (-OMe), 59.4 (CH^{α}), 108.5, 108.9 (Cq-indole), 112.3, 112.4 (CH-Ar), 113.6, 114.3 (C_{Ar}-**C**N), 119.3, 119.4 (CH-**C**N), 120.4, 120.6, 123.3, 123.4, 127.4, 127.5, 131.3, 131.7, 133.7, 133.9, 138.4, 138.6, 143.5, 145.3 (C-Ar), 172.0, 173.1 (C=O) ppm.

(4l): Methyl 2(S)-(((R,S) cyano(4-nitrophenyl)methyl) amino)-3-(1*H*-indol-3-yl) propanoate (dr 100:0). ^{1}H NMR (300MHz, $CDCl_3$) δ = 3.08-3.23 (*m*, 1H, CH_2), 3.48 (*t*, 1H, *J* = 5.9 Hz, CH_2), 3.80 (*s*, 3H, -OMe), 3.85 (*dd*, 1H, *J* = 11.4, 4.0 Hz, CH^{α}), 5.30 (*s*, 1H, CHCN), 7.09 (*d*, 1H, *J* = 7.9 Hz, H-Ar, indole), 7.19 (*d*, 1H, *J* = 8.2 Hz, H-Ar, indole), 7.29 (*s*, 1H, H-Ar, indole), 7.38 (*d*, 1H, *J* = 8.2 Hz, H-Ar, indole), 7.53 (*d*, 1H, *J* = 8.3 Hz, H-Ar, indole), 7.78 (*d*, 2H, *J* = 8.8 Hz, H-Ar, $CHCNO_2$), 8.21 (*d*, 2H, *J* = 8.8 Hz, H-Ar, $CHCNO_2$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 31.9 (CH_2), 47.5 (CH-CN), 53.8 (-OMe), 60.4 (CH^{α}), 109.7 (Cqindole), 111.4 (CH-Ar), 118.4 (CH-CN), 119.9, 122.5, 122.8, 123.7, 124.1, 124.4, 127.6, 128.3, 136.1, 139.3, 149.6 (C-Ar), 172.0 (C=O) ppm.

(4m): Methyl 2(S)-(((R,S)cyano(4-cyanophenyl) methyl)amino)-3-(4-hydroxyphenyl) propanoate (dr 51:49). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.80 (*dd*, 2H, *J* = 13.8, 8.3 Hz, CH_2, mixture of two diastereomers), 3.05 (*dd*, 2H, *J* = 14.1, 4.4 Hz, CH_2, mixture of two diastereomers), 3.70 (*dd*, 2H, *J* = 8.4, 4.8 Hz, CH^{α}, mixture of two diastereomers), 3.75 (*s*, 3H, -OMe, diastereomer A), 3.79 (*s*, 3H, -OMe, diastereomer B), 4.93 (*s*, 1H, CHCN, diastereomer A), 5.31 (*s*, 1H, CHCN, diastereomer B), 6.74 (*d*, 1H, *J* = 8.5 Hz, H-Ar, phenol, diastereomer A), 6.78 (*d*, 1H, *J* = 8.5 Hz, H-Ar phenol, diastereomer A), 6.98 (*d*, 1H, *J* = 8.4 Hz, H-Ar, diastereomer A), 7.05 (*d*, 1H, *J* = 8.4 Hz, H-Ar, diastereomer A), 7.50 (*d*, 1H, *J* = 5.3 Hz, H-Ar phenol, diastereomer B), 7.53 (*d*, 1H, *J* = 5.1 Hz, H-Ar phenol, diastereomer B), 7.63 (*d*, 1H, *J* = 8.7 Hz, H-Ar, diastereomer B), 7.66 (*d*, 1H, *J* = 8.3 Hz, H-Ar, diastereomer B) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.9, 29.3 (CH_2), 38.5, 38.9 (CH-CN), 52.3, 52.9 (-OMe), 59.6, 60.8 (CH^{α}), 113.1, 113.2 (Cq-CN), 115.5, 115.6 (CH-Ar), 117.3, 117.6 (CH-CN), 118.0, 118.1 (Cq-CN), 128.2, 128.3, 128.4, 128.5, 130.3, 130.5, 132.6, 132.7, 139.1, 139.2, 154.9, 155.0 (C-Ar), 173.4, 173.6 (C=O) ppm. Mass-EI (70 ev) $C_{19}H_{17}N_3O_3$ $[M]^{\cdot+}$ = 335.

(4n): Methyl 2(S)-(((R,S)cyano(4-nitrophenyl)methyl) amino)-3-(4-hydroxyphenyl) propanoate (dr 51:49). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.16 (*dd*, 2H, *J* = 13.7, 9.0 Hz, CH_2, mixture of two diastereomers), 3.47 (*dd*, 2H, *J* = 13.7, 4.3 Hz, CH_2, mixture of two diastereomers), 3.70-3.85 (*m*, 2H, CH^{α}, mixture of two diastereomers), 3.81 (*s*, 3H, -OMe, diastereomer A), 3.89 (*s*, 3H, -OMe, diastereomer B), 4.81 (*d*, 1H, *J* = 4.4 Hz, CHCN, diastereomer A), 4.84 (*d*, 1H, *J* = 4.4 Hz, CHCN, diastereomer A), 6.71 (*d*, 1H, *J* = 8.2 Hz, H-Ar tyrosine, diastereomer A), 6.87 (*d*, 1H, *J* = 8.2 Hz, H-Ar, tyrosine, diastereomer B), 6.99 (*d*, 1H, *J* = 8.1 Hz, H-Ar, tyrosine, diastereomer B), 7.03 (*d*, 1H, *J* = 8.1 Hz, H-Ar tyrosine, diastereomer B), 8.06 (*d*, 1H, *J* = 8.7 Hz, H-Ar, diastereomer A), 8.13 (*d*, 1H, *J* = 8.8 Hz, H-Ar, diastereomer B), 8.31 (*d*, 1H, *J* = 8.8 Hz, H-Ar,

diastereomer A), 8.40 (*d*, 1H, *J* = 8.7 Hz, H-Ar, diastereomer B).

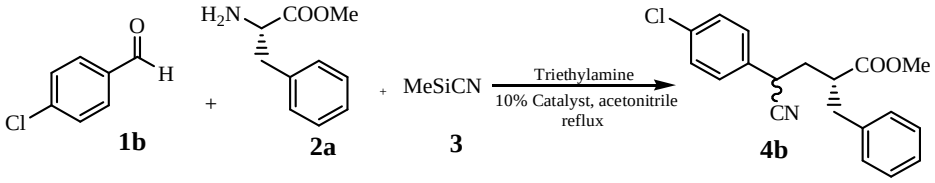
^{13}C NMR (75 MHz, $CDCl_3$) δ = 38.7, 39.2 (CH_2), 39.5, 39.6 (CH-CN), 66.3, 66.6 (-OMe), 66.7, 66.9 (CH^{α}), 115.2, 115.6 (CH-CN), 121.4, 122.6, 123.4, 123.8, 124.4, 127.6, 129.3, 129.6, 130.2, 130.4, 156.4 (C-Ar), 170.4, 170.5 (C=O) ppm. HR-Mass (ESI) *m/z*: for $C_{18}H_{18}N_3O_5$ $[M+H]^+$ found: 356.09492, Calcd.: 356.09499.

RESULTS AND DISCUSSION

Initially, methyl esters of amino acids were prepared through reaction of amino acids such as phenyl alanine, tyrosine, and valine with thionyl chloride in methanol in excellent yields. Then, the three-component reaction of phenyl alanine methyl ester, 4-chloro-benzaldehyde and trimethylsilyl cyanide was selected as a model reaction to optimize the reaction conditions.

It is noteworthy that in the absence of acidic catalyst, only a trace amount of the desired α-amino nitrile **4b** was formed even after 12 h (Table 1, Entry 4). However, when the reaction was performed in the presence of catalytic amount (10%) of phosphotungstic acid, the desired product **4b** was obtained in 85% yield and the ratio of diastereomers was 64:36 (Table 1, Entry2). In the presence of Brønsted acid ((*s*)- (+)-1,1′-binaphtyl-2-2′diyl hydrogen phosphate)

Table1. Effect of Catalyst for the Synthesis of *α*-Amino Nitrile **4b** through Three-Component Reaction Using Phenyl Alanine Methyl Ester



Entry	Catalyst	Yield (%)	Diastereomer ratio
1	-	0	-
2	$H_3[P(W_3O_{10})_4].H_2O$	85	64:36
3	(*s*)- (+)-1,1′-Binaphtyl-2-2′diyl hydrogen phosphate	39	50:50
4	*S*-Proline	78	50:50

Table 2. Synthesis of α-Amino Nitriles Using α-Amino Acids and their Diastereoselectivities Using Phosphotungstic Acid (10%)

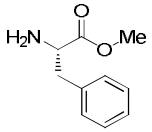
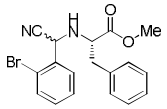
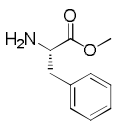
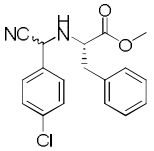
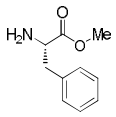
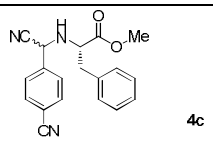
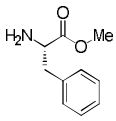
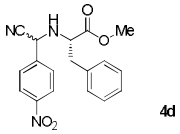
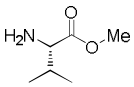
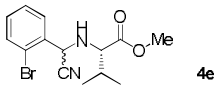
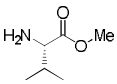
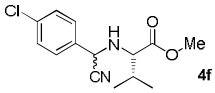
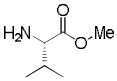
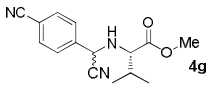
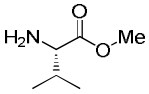
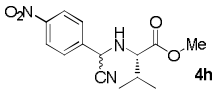
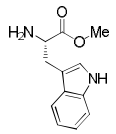
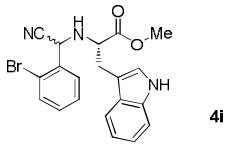
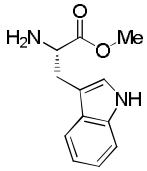
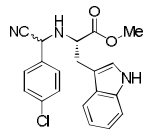
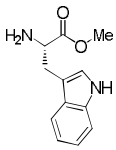
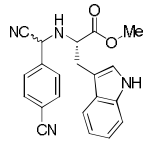
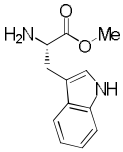
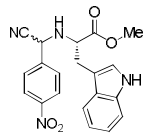
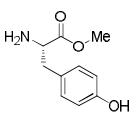
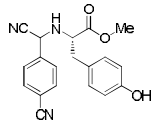
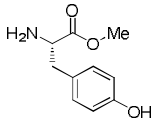
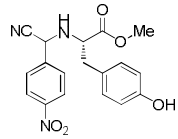
Entry	Aldehyde	Amino acid methyl ester	Product	Yield (%)	Diastereomeric ratio
1	2-Br-C_6H_4		 **4a**	58	54:46
2	4-Cl-C_6H_4		 **4b**	85	64:36

Table 2. Continued

3	4-NC-C_6H_4		 **4c**	72	59:41
4	4-O_2N-C_6H_4		 **4d**	81	52:48
5	2-Br-C_6H_4		 **4e**	48	63:37
6	4-Cl-C_6H_4		 **4f**	75	52:48
7	4-NC-C_6H_4		 **4g**	76	51:49
8	4-O_2N-C_6H_4		 **4h**	82	78:22
9	2-Br-C_6H_4		 **4i**	46	56:44
10	4-Cl-C_6H_4		 **4j**	78	51:49
11	4-NC-C_6H_4		 **4k**	71	71:29
12	4-O_2N-C_6H_4		 **4l**	80	100:0
13	4-NC-C_6H_4		 **4m**	58	51:49
14	4-O_2N-C_6H_4		 **4n**	70	51:49

*Isolated Yield

the yield was 39% and the ratio of diastereomers was 50:50.

In an effort to optimize the reaction, reaction conditions were investigated by adding 5, 10 and 20% of phosphotungstic acid as acidic catalyst. The yields of desired *α*-amino nitrile **4b** were 60, 85, 87%, respectively. Meanwhile, the model reaction was carried out in different solvents such as MeOH, CH_2Cl_2, and acetonitrile. The best yield was obtained with 10% phosphotungstic acid in acetonitrile as a solvent.

According to these results, carrying out the reaction in acetonitrile and 10% of phosphotungstic acid was determined as the best reaction conditions. To achieve more diversity, some amino acid methyl esters and also aromatic aldehydes were used. The results are summarized in Table 2.

In general, reactions were completed after 12 h. Substrates with both electron-donating and electron-withdrawing substituents on the aryl group of aromatic aldehydes underwent reaction smoothly and gave good yields. The work-up procedure is simple; catalyst was filtered off and the purification of mixture was done using prep-TLC or washing the mixture with water and extraction with EtOAc.

The percentage of each diastereomer was determined using ^{1}H NMR spectra (Table 2). Appearance of a signal in ^{1}H NMR at δ 4.80-5.20 ppm are related to the C<u>H</u>-CN and a signal at δ 59.5-60.5 ppm and also a peak at 115.0-119.0 ppm for the nitrile group in ^{13}C NMR are the best evidence for production of the corresponding *α*-amino nitriles.

Due to known activity of heteropolyacids in organic synthesis, we proposed that phosphotungstic acid plays a crucial role in fascinating this transformation through in situ generation of imine through activation of carbonyl moiety. After formation of imine, it could convert to iminium form which on subsequent nucleophilic attack of cyanide group afforded the corresponding *α*–aminonitriles in a one-pot reaction.

CONCLUSIONS

In conclusion, phosphotungstic acid was found to be an efficient, clean, green catalyst for diastereoselctive Strecker reaction of *α*-amino acid methyl esters, aromatic aldehydes and trimethylsilyl cyanide. Operational simplicity, good yields and using an environmentally friendly acid catalyst are advantages of this approach. The products have some functional group for further transformations.

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REFERENCES

[1] S.P. Pathare, K.G. Akamanchi, Tetrahedron Lett. 53 (2012) 871.

[2] S.G.K. Prakash, I. Bychinskaya, E.R. Marinez, T. Mathew, G.A. Olah, Catal. Lett. 143 (2013) 303.

[3] D. Enders, J.P. Shilvock, J. Chem. Soc. Rev. 29 (2000) 359.

[4] R. Reingruber, T. Baumann, S. Dahmen, S. Bräse, Adv. Synth. Catal. 351 (2009) 1019.

[5] M. Mantri, O. de Graaf, J. van Veldhoven, A. Goeblyoes, D.K. von Frijtag, K. Jacobien, T. Mulder-Krieger, R. Link, H. de Vries, M.W. Beukers, J. Brussee, A.P. IJzerman, J. Med. Chem. 51 (2008) 4449.

[6] R. Loeser, K. Schilling, E. Dimmig, M. Guetschow, J. Med. Chem. 48 (2005) 7688.

[7] Y.D. Ward, D.S. Thomson, L.L. Frye, C.L. Cywin, T. Morwick, M.J. Emmanuel, R. Zindell, D. McNeil, Y. Bekkali, M. Giradot, M. Hrapchak, M. DeTuri, K. Crane, D. White, S. Pav, Y. Wang, M.-H. Hao, C.A. Grygon, M.E. Labadia, D.M. Freeman, W. Davidson, L. Hopkins, M.L. Jerry Brown, D.M. Spero, J. Med. Chem. 45 (2002) 5471.

[8] R.O. Duthaler, Tetrahedron 50 (1994) 1539.

[9] J. Wang, X. Liu, X.-M. Feng, Chem. Rev. 111 (2011) 6947.

[10] H. Xie, A. Song, X. Song, X. Zhang, W. Wang, Tetrahedron Lett. 54 (2013) 1409.

[11] S.K. De, J. Mol. Catal. A: Chem. 225 (2005) 169.

[12] S. Paraskar, A. Sudalai, Tetrahedron Lett. 47 (2006) 5759.

[13] S.K. De, Synth. Commun. 35 (2005) 653.

[14] M. Narasimhulu, T.S. Reddy, K.C. Mahesh, S.M.

Reddy, A.V. Reddy, Y. Venkateswarlu, J. Mol. Catal. A: Chem. 264 (2007) 288.

[15] B.C. Banu, S.S. Dev, A. Hajri, Tetrahedron 58 (2002) 2529.

[16] S. Kobayashi, H. Ishitani, M. Ueno, Synlett (1997) 115.

[17] S.K. De, R.A. Gibbs, Synth. Commun. 35 (2005) 961

[18] S.K. De, R.A. Gibbs, Tetrahedron Lett. 45 (2004) 7407.

[19] M.A. Pasha, H.M. Nanjundaswamy, V.P. Jayashankara, Synth. Commun. 37 (2007) 4371.

[20] A. Majhi, S. Kim, S.T. Kadam, Tetrahedron 64 (2008) 5509.

[21] M.M. Heravi, M. Ebrahimzadeh, H.A. Oskooie, B. Baghernejad, Chin. J. Chem. 28 (2010) 480.

[22] J. Weitkamp, L. Puppe (Eds.), Catalysis and Zeolites: Fundamentals and Applications, Springer-Verlag, Berlin/Heidelberg, 1999.

[23] S. Kobayashi, S. Nagayama, T. Busujima, Tetrahedron Lett. 37 (1996) 9221.

[24] J.S. Yadav, B.V.S. Reddy, B. Eeshwaraiah, M. Srinivas, Tetrahedron 60 (2004) 1767.

[25] W.Y. Chen, J. Lu, Synlett 15 (2005) 2293.

[26] H. Oskooie, M.M. Heravi, A. Sadnia, F. Jannati, F.K. Behbahani, Monatsh. Chem. 139 (2008) 27.

[27] G.A. Olah, T. Mathew, C. Panja, K. Smith, G.K.S. Prakash, Catal. Lett. 114 (2007) 1.

[28] T. Ooi, ACS Symp. Ser. 1009 (2009) 177.

[29] M. Rueping, E. Sugiono, S.A. Moreth, Adv. Synth. Catal. 349 (2007) 759.

[30] R. Reingruber, T. Baumann, S. Dahmen, S. Bráse, Adv. Synth. Catal. 351 (2009) 1019.

[31] D. Enders, J.P. Shilvock, Chem. Soc. Rev. 29 (2000) 359.

[32] L. Yet, Angew. Chem. Int. Ed. 40 (2001) 875.

[33] H. Groger, Chem. Rev. 103 (2003) 2795.

[34] S. Connon, Angew. Chem. Int. Ed. 47 (2008) 1176.

[35] M. Shibasaki, M. Kanai, T. Mita, in: L.E. Overman, (Ed.), Organic Reactions, John Wiley & Sons: Hoboken, New Jersey, 2008, pp. 1-119.

[36] P. Merino, E. Marques-Lopez, T. Tejero, R.P. Herrera, Tetrahedron 65 (2009) 1219.

[37] E. Rafiee, M. Khodayari, S. Shahebrahimi, M. Joshaghani, J. Mol. Catal. A-Chem. 351 (2011) 204.

[38] H. Firouzabadi, N. Iranpoor, K. Amani, Synthesis 1 (2002) 59.

[39] D. Chaturvedi, A.K. Chaturvedi, N. Mishra, V. Mishra, Tetrahedron Lett. 53 (2012) 5398.

[40] M.M. Heravi, S. Sadjadi, J. Iran. Chem. Soc. 1 (2009) 6.

[41] S.-I. Yamada, S.-I. Hashimoto, Chem. Lett. (1976) 921.