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Cerium(IV) oxide as a neutral catalyst for aldehyde-induced decarboxylative coupling of L-proline with triethyl phosphite and nitromethane

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ABSTRACT

The application of cerium(IV) oxide (CeO_2) as a neutral and heterogeneous catalyst for aldehyde-induced decarboxylative coupling of L-proline with triethyl phosphite and nitromethane is described. In addition, a [3+2] cycloaddition reaction of the in situ generated 1,3-dipolar intermediate with benzaldehyde in the absence of a nucleophile is also reported.

L-Proline and its derivatives frequently occur in many biologically active natural products.[1] In recent years, numerous reports have appeared in the literature applying this α-amino acid as an organocatalyst[2] or substrate.[3] The merit of proline in organic synthesis is currently so vast that it is thought to be the 'simplest enzyme'.[4] Due to the important features of proline, many investigators have focused their attention and efforts to bring about the facile production of structurally diverse proline compounds bearing various functional groups.[1] Despite the attempts made in this regard, the introduction of a convenient and simple method for the preparation of proline derivatives would be of great importance and interest. Several interesting approaches for the interconversion of the carboxyl group of proline into other groups have been reported. The tandem decarboxylation-nucleophilic addition method is one of the simplest strategies for synthesizing proline derivatives. Li et al. have described the reaction of N-protected proline with terminal acetylenes using CuBr/*tert*-butyl peroxide system in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine as the ligand.[5] The same group has also reported the iron-catalyzed decarboxylative coupling of proline derivatives with naphthol and indole derivatives.[6] Li[7] and Seidel[8] independently reported the three-component coupling reaction between proline, aldehyde, and various nucleophiles (terminal acetylenes, β-naphthols, indoles, and nitro alkanes) producing the target molecules in moderate to good yields. An efficient copper-catalyzed aerobic phosphonation of sp^3 C–H adjacent to nitrogen has also been reported.[9] Following these reports, the aldehyde-induced intermolecular decarboxylative coupling of α-amino acids and phosphites or secondary phosphine oxides was developed in the presence of CuI/*N*,*N*-diisopropylethylamine (DIPEA) in toluene (20 h at 130 °C).[10] Using a similar three-component approach, the Strecker reaction has also been reported for this type of process under microwave irradiation at 200 °C.[11] Nitro-Mannich type reaction was also reported catalyzed by copper bromide in the presence of TBHP using nitromethane as a coupling partner.[12]

Attention has also been paid to the use of cerium(IV) oxide (CeO_2) as the catalyst in diesel particulate matter combustion,[13] the one-pot selective syntheses of *N*-alkyl amides from nitriles, amines, and water,[14] one-pot syntheses of organic carbamates from amines, CO_2, and alcohols,[15] the syntheses of α-aminophosphonates by ultrasonication,[16] and for Ullmann-type coupling reactions.[17]

In this report, we describe the use of CeO_2 as a useful promoter for the three-component reaction of proline, aldehyde, and a suitable nucleophile.

Initially, a survey on the reaction parameters, including the catalyst and base was conducted in air at 130 °C in *o*-xylene using triethyl phosphite (1.5 mmol), L-proline (1.2 mmol), and benzaldehyde (1 mmol) as a model reaction (Table 1). The effects of catalysts and bases were screened first. The reaction in *o*-xylene in the absence of a catalyst and base gave the desired product in only 51% yield (Table 1, entry 1). Addition of $^nPr_3N$ or NaOH to the reaction mixture gave a slightly better conversion to the desired product (Table 1, entries 2 and 3). The use of CeO_2 as the promoter enhanced

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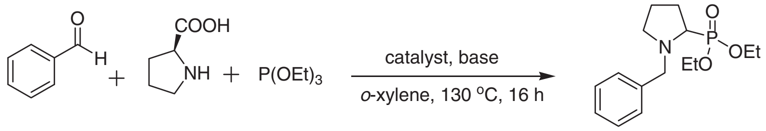
Table 1

Three-component reaction of benzaldehyde, proline, and triethyl phosphite using different catalytic systems



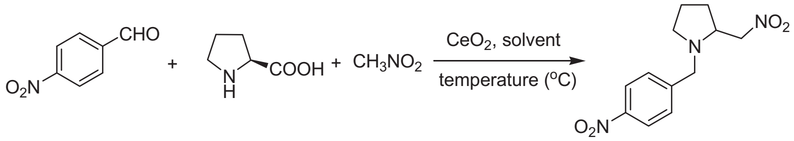
Entry	Catalyst	Base	Conversion[a] (%)
1	–	–	51
2	–	$^n\mathrm{Pr_3N}$	60
3	–	NaOH	56
4	CeO_2	–	83
5	CeO_2	$^n\mathrm{Pr_3N}$	60
6	CeO_2	NaOH	71
7[b]	CeO_2	–	100
8	$CeCl_3 \cdot 7H_2O$	–	66

[a] Conversion determined by GC.

[b] L-Proline (2 equiv) was used, reaction time: 2 h.

Table 2

Different conditions for the three-component reaction of *p*-nitrobenzaldehyde, L-proline, and nitromethane



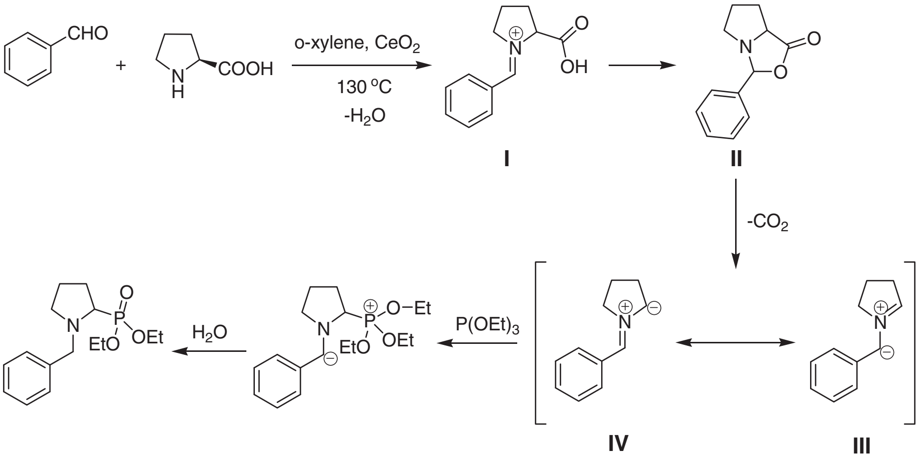
Entry	Solvent	Temp (°C)	Time (h)	Isolated yield (%)
1	Toluene	70	3	75
2	Toluene	100	1	82
3	Toluene	130	35 min	88
4	H_2O	70	12	–
5	PEG 400	70	12	Mixture

the conversion noticeably (Table 1, entry 4). Increasing the amount of L-proline (2 equiv) led the reaction to completion within 2 h in the presence of CeO_2 (Table 1, entry 7). Consequently, the optimized reaction conditions (Table 1, entry 7) were chosen for subsequent investigations. We also studied the catalytic effect of $CeCl_3.7H_2O$, however, it was not as effective as CeO_2 (Table 1, entry 8).

A proposed reaction pathway is depicted in Scheme 1. After condensation of proline with benzaldehyde, the iminium cation **I** is produced which is converted into intermediate **II**.[18] Elimination of CO_2 from **II** generates the structures **III** and **IV**. Due to the greater stability of azomethine ylide **III**,[7] it reacts with triethyl phosphite to produce the observed product.

In the presence of CeO_2, a one-pot reaction between *p*-nitrobenzaldehyde, L-proline, and nitromethane occurred. Our studies showed that toluene was the best solvent for this reaction (Table 2). The reaction in other solvents such as water and PEG 400 did not proceed. The reaction at different temperatures 70, 100, and 130 °C proceeded smoothly to give the desired product in 75%, 82%, and 88% isolated yields within 3 h, one hour, and 35 min, respectively (Table 2, entries 1–3).

Employing the optimized conditions, a range of aromatic aldehydes reacted with L-proline and triethyl phosphite (Scheme 2). However, the reactions failed using primary amino acids and ketones.



Scheme 1. Proposed pathway for the reaction of benzaldehyde with L-proline and triethyl phosphite.