

Cerium Ammonium Nitrate-Catalyzed Multicomponent Reaction for Efficient Synthesis of Functionalized Tetrahydropyridines

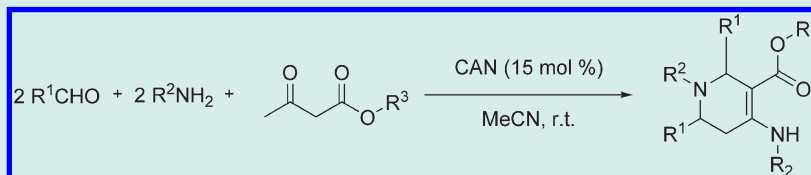
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S Supporting Information

ABSTRACT: A highly atom-economic one-pot synthesis of functionalized tetrahydropyridines by a multicomponent condensation reaction of β -keto ester, two equivalents of aromatic aldehyde, and two equivalents of amine in the presence of a catalytic amount of cerium ammonium nitrate (CAN) is reported. In this way, a series of pharmacologically interesting substituted piperidine derivatives were obtained in moderate to good yields at room temperature.

KEYWORDS: multicomponent reaction, one-pot, cerium ammonium nitrate, tetrahydropyridines, heterocycles



INTRODUCTION

Multicomponent coupling reactions (MCRs) represent a highly valuable synthetic tool for the construction of novel and complex molecular structures with a minimum number of synthetic steps. These types of reactions have some advantages over conventional linear syntheses, including lower costs, shorter reaction times, high degrees of atom economy, the possibility for combinatorial surveying of structural variations, and environmental friendliness. Among notable recent efforts to develop new MCRs,¹ Bonfield et al. recently reported an efficient method for the preparation of the isoindoline framework via a six-component, tandem double A3-coupling and [2+2+2]-cycloaddition reaction.² Brauch et al. have extended MCRs to seven components by taking advantage of the different chemoselectivities of the Ugi–Mumm and the Ugi–Smiles reaction.³ Recently, the Orru group developed a one-pot reaction of up to eight components that involves nine new bond formations and eleven points of diversity.⁴ In this content, MCRs that involve 1,3-dicarbonyl compounds, aldehydes, and nucleophilic compounds have received much attention in recent years because the formation of different condensation products can be expected depending on the specific conditions and structures of the building blocks.

The tetrahydropyridine ring is an essential building block for numerous natural products, synthetic pharmaceuticals, and a wide variety of biologically active compounds.⁵ (See Supporting Information for a list of activities and references.) As a consequence, the development of general methods for the synthesis of tetrahydropyridine derivatives has been the subject of considerable synthetic efforts and still requires attention. Most current procedures either require advanced starting materials or involve multistep and low-yielding reaction sequences. Among the more successful are a proline-mediated cascade Mannich-type/intramolecular cyclizations,⁶ a palladium-catalyzed alkynyl and

allenyl iminium ion cyclizations,⁷ phosphine-promoted [3+3]-annulations of aziridines with allenates,⁸ and radical cyclization of *N*-allylamino-substituted Baylis–Hillman adducts.⁹

One-pot, multicomponent reactions offer potential advantages.¹⁰ Of the many approaches to the synthesis of tetrahydropyridines, the atom and step economic (PASE)¹¹ synthesis of functionalized tetrahydropyridines from relatively simple starting materials is especially attractive. Recently, one-pot syntheses of these heterocyclic compounds by condensation reactions employing InCl_3 ,¹² *L*-proline/TFA,¹³ bromodimethylsulfonium bromide,¹⁴ and tetrabutylammonium tribromide (TBATB)¹⁵ have been reported. However, in these limited cases high loadings (up to 33 mol %)¹² of expensive catalysts¹³ were necessary to achieve reasonably high yields. The development of simple and environmentally benign synthetic methods for efficient preparation of functionalized tetrahydropyridines is therefore a significant challenge.

In recent years, cerium ammonium nitrate (CAN) has been employed as a multipurpose promotor of a wide range of synthetically useful reactions.¹⁶ However, most examples require stoichiometric quantities of CAN. We report herein a highly atom-economic synthesis of functionalized tetrahydropyridines by a one-pot, three (in situ five)-component reaction requiring CAN in only 15 mol % (Scheme 1).

RESULTS AND DISCUSSION

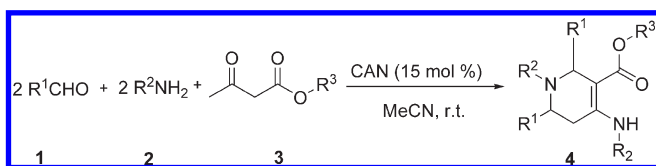
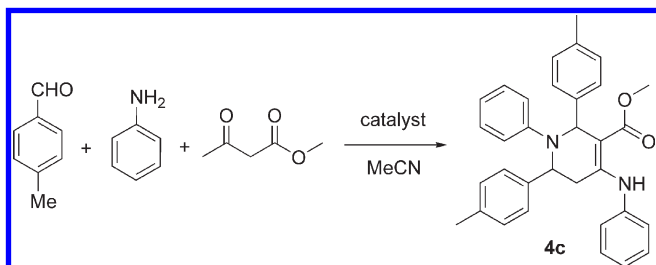
Various potential catalysts were tested for the direct synthesis of **4c** by the model reaction of 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate (1 mmol) in acetonitrile at room temperature, with results listed in Table 1. CAN

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Scheme 1. CAN Catalyzed Synthesis of Tetrahydropyridines

Table 1. Effect of Different Catalysts on the Model Reaction of 4-Methylbenzaldehyde, Aniline, and Methyl Acetoacetate^a

entry	catalyst	reaction time (h)	yield (%) ^b
1	none	30	trace
2	HClO ₄ /SiO ₂	50	60
3	<i>p</i> -toluenesulfonic acid	50	58
4	phosphotungstic acid	50	65
5	(NH ₄) ₃ PMo ₁₂ O ₄₀ ·6H ₂ O	50	41
6	Mg(ClO ₄) ₂	50	40
7	LiClO ₄ ·3H ₂ O	50	35
8	ZrOCl ₂ ·8H ₂ O	50	45
9	ZrO(NO ₃) ₂	50	72
10	Co(NO ₃) ₃ ·6H ₂ O	50	68
11	(NH ₄) ₄ Ce(SO ₄) ₄ ·2H ₂ O	50	42
12	CAN	22	85

^a Experimental conditions: 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol), and catalyst (0.15 mmol) in 5 mL of MeCN at room temperature. ^b Isolated yields.

proved to be superior, producing the best yield of **4c**, only trace amounts of which were formed in the absence of catalyst (Table 1, entry 1).

A survey of solvents revealed acetonitrile to be the best choice, used directly without rigorous drying. Low yields were obtained when EtOAc or water was employed as the solvent. Some dependence was also observed on the amount of CAN used. A satisfactory result was obtained in the presence of 15 mol % CAN (Table 2, entry 6), with no improvement upon increasing the catalyst loading to 20 mol %.

The scope and limitations of this five-component reaction under optimized conditions were explored using a variety of aldehydes, amines, and β -keto esters, as summarized in Table 3. In general, aromatic aldehydes bearing electron-donating or electron-withdrawing functional groups at different positions reacted with methyl acetoacetate smoothly in the presence of aniline to generate the corresponding products in good to excellent yields. In contrast, aliphatic aldehydes such as *n*-hexanal

Table 2. Investigation of the Amounts of Catalyst and Solvent Effects on the Model Reaction of Table 1^a

entry	catalyst loading (mol %)	solvent	time (h)	yield (%) ^b
1	15	EtOAc	46	50
2	15	EtOH	40	75
3	15	THF	47	70
4	15	H ₂ O	50	28
5	10	MeCN	35	70
6	15	MeCN	22	85
7	20	MeCN	22	86

^a Experimental conditions: 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol), and CAN in 5 mL of solvent at room temperature. ^b Isolated yields.

and cyclohexanecarboxaldehyde did not provide the desired products. Aromatic amines were found to be effective substrates and afforded the corresponding tetrahydropyridine derivatives in high yields. Aliphatic amines gave moderate yields (Table 3, entries 44–47), presumably due to the higher basicity of aliphatic amines compared to anilines. Lastly, other β -keto esters such as ethyl acetoacetate, *iso*-butyl acetoacetate, *tert*-butyl acetoacetate, allyl acetoacetate, and 2-methoxyethyl acetoacetate were examined. The alkoxy (–OR³) moiety present had little influence on the reaction, and generally good yields were obtained. Benzoyl acetone (**5**) also proved to be an excellent substrate, giving good yields of the corresponding products (Scheme 2).

The products were characterized by IR, ¹H NMR, and ¹³C NMR spectra and by elemental analysis. The stereochemistry of the products **4** with 2- and 6-substituents on the six-membered ring of tetrahydropyridine was determined as *trans* by single-crystal X-ray analysis (see the Supporting Information, Figure 1).

A proposed reaction mechanism for this five-component reaction is outlined in Scheme 3. CAN can serve as a Lewis acidic catalyst for the reaction of aniline and methyl acetoacetate or 4-chlorobenzaldehyde to give the β -enaminone¹⁷ or imine,^{16a} respectively. The intermolecular Mannich addition of the β -enaminone (**7**) to the imine (**8**) affords the intermediate **9**. Subsequently, the reaction of activated aldehyde with the intermediate **9** proceeds to afford the intermediate **10** by the elimination of H₂O. Intermediate **10** should tautomerize to provide **11**, stabilized by intramolecular hydrogen bonding. Intramolecular Mannich addition gives intermediate **12**, which finally transforms to the expected piperidine tautomer **4c**. CAN may enhance the rates of several of these transformations. This scheme is supported by two principal experimental observations: (1) the reaction intermediates **7** and **8** could be isolated in the course of reaction, and (2) the reaction of **7**, **8**, and 4-methylbenzaldehyde gave the same product as the reaction of methyl acetoacetate, 4-methylbenzaldehyde, and aniline.

In conclusion, we have developed an efficient synthesis of functionalized tetrahydropyridines suitable for combinatorial synthesis through a one-pot, five-component reaction using a catalytic amount of CAN at room temperature. The attractive features of this procedure are the mild reaction conditions, high atom efficiency, clean reaction profiles, inexpensive starting materials, and an environmentally friendly catalyst.

Table 3. CAN-Catalyzed Synthesis of Functionalized Tetrahydropyridines

entry	R ¹	R ²	R ³	products	time (h)	yield (%) ^a	mp (°C)	
							found	reported
1	Ph	Ph	Me	4a	20	82	194–195	194 ¹³
2	3-CH ₃ C ₆ H ₄	Ph	Me	4b	23	84	131–134	89.3–90.2 ¹²
3	4-CH ₃ C ₆ H ₄	Ph	Me	4c	22	85	215–216	212–214 ¹⁴
4	2-OCH ₃ C ₆ H ₄	Ph	Me	4d	30	80	248–251	
5	4-OCH ₃ C ₆ H ₅	Ph	Me	4e	16	83	182–183	180 ¹³
6	3,4,5-(OMe) ₃ C ₆ H ₂	Ph	Me	4f	30	73	156–158	153–156 ¹⁴
7	4-FC ₆ H ₄	Ph	Me	4g	20	81	161–162	160 ¹³
8	3-ClC ₆ H ₄	Ph	Me	4h	24	75	220–221	220 ¹³
9	4-ClC ₆ H ₄	Ph	Me	4i	15	86	225–226	225–227 ¹⁸
10	4-BrC ₆ H ₄	Ph	Me	4j	16	84	245–246	245–247 ¹³
11	2-NO ₂ C ₆ H ₄	Ph	Me	4k	20	75	232–234	217–219 ¹⁴
12	3-NO ₂ C ₆ H ₄	Ph	Me	4l	19	80	181–182	180 ¹³
13	4-NO ₂ C ₆ H ₄	Ph	Me	4m	18	78	240–241	239–241 ¹⁴
14	3-CF ₃ C ₆ H ₄	Ph	Me	4n	45	80	140–142	
15	Ph	4-OCH ₃ C ₆ H ₄	Me	4o	20	82	224–225	223.5–224.1 ¹²
16	3-CH ₃ C ₆ H ₄	4-OCH ₃ C ₆ H ₄	Me	4p	18	81	193–194	193.5–194.5 ¹²
17	4-CH ₃ C ₆ H ₄	4-OCH ₃ C ₆ H ₄	Me	4q	17	75	226–227	225–226 ¹⁴
18	4-FC ₆ H ₄	4-OCH ₃ C ₆ H ₄	Me	4r	17	82	204–205	205 ¹³
19	3-ClC ₆ H ₄	4-OCH ₃ C ₆ H ₄	Me	4s	17	80	162–163	160 ¹³
20	4-ClC ₆ H ₄	4-OCH ₃ C ₆ H ₄	Me	4t	17	75	214	
21	4-BrC ₆ H ₄	4-OCH ₃ C ₆ H ₄	Me	4u	16	83	179–180	179 ¹³
22	3-CF ₃ C ₆ H ₄	4-OCH ₃ C ₆ H ₄	Me	4v	22	80	157–158	156.2–157.2 ¹²
23	3-CH ₃ C ₆ H ₄	Ph	ⁱ Bu	4w	23	62	140–142	
24	3-CH ₃ C ₆ H ₄	Ph	^t Bu	4x	23	81	154–155	
25	3-CH ₃ C ₆ H ₄	Ph	CH ₂ CH=CH ₂	4y	24	56	157–159	
26	3-CH ₃ C ₆ H ₄	Ph	CH ₂ CH ₂ OMe	4z	23	85	140–142	
27	Ph	Ph	Et	4aa	23	80	175–176	174–175 ¹⁴
28	Ph	Ph	^t Bu	4ab	23	78	162–163	162–163 ¹⁴
29	Ph	Ph	CH ₂ CH=CH ₂	4ac	24	60	150–151	149–150 ¹⁴
30	Ph	4-OCH ₃ C ₆ H ₄	Et	4ad	20	82	172–173	173 ¹³
31	Ph	4-ClC ₆ H ₄	Et	4ae	35	68	201–202	202 ¹³
32	4-CH ₃ C ₆ H ₄	Ph	Et	4af	23	78	230–231	227–230 ¹⁴
33	4-CH ₃ C ₆ H ₄	Ph	^t Bu	4ag	23	81	170–171	171–173 ¹⁸
34	4-CH ₃ C ₆ H ₄	Ph	CH ₂ CH=CH ₂	4ah	24	66	175–176	172–174 ¹⁴
35	4-NO ₂ C ₆ H ₄	Ph	Et	4ai	20	75	247–250	
36	4-CH ₃ C ₆ H ₄	4-BrC ₆ H ₄	Me	4aj	28	67	253–254	253–254 ¹⁴
37	4-BrC ₆ H ₄	4-ClC ₆ H ₄	Me	4ak	28	69	159–160	160–163 ¹³
38	4-OCH ₃ C ₆ H ₄	4-ClC ₆ H ₄	Me	4al	21	65	194–195	195 ¹³
39	4-OCH ₃ C ₆ H ₄	4-BrC ₆ H ₄	Me	4am	21	68	177–178	178 ¹³
40	4-FC ₆ H ₄	4-ClC ₆ H ₄	Me	4an	22	75	175–176	176 ¹³
41	4-CH ₃ C ₆ H ₄	4-OCH ₃ C ₆ H ₄	Et	4ao	22	81	221–224	
42	3-ClC ₆ H ₄	4-OCH ₃ C ₆ H ₄	Et	4ap	20	83	168–169	167–170 ¹³
43	3-ClC ₆ H ₄	4-ClC ₆ H ₄	Et	4aq	25	82	189–190	190 ¹³
44	4-CH ₃ C ₆ H ₄	PhCH ₂	Me	4ar	40	52	172–173	172–173 ¹⁴
45	4-CH ₃ C ₆ H ₄	CH ₃ (CH ₂) ₃	Me	4as	40	51	155–156	153–154 ¹⁴
46	3-CH ₃ C ₆ H ₄	CH ₃ (CH ₂) ₂	Me	4at	40	53	151–153	
47	3-CH ₃ C ₆ H ₄	CH ₃ (CH ₂) ₃	Me	4au	40	55	144–146	

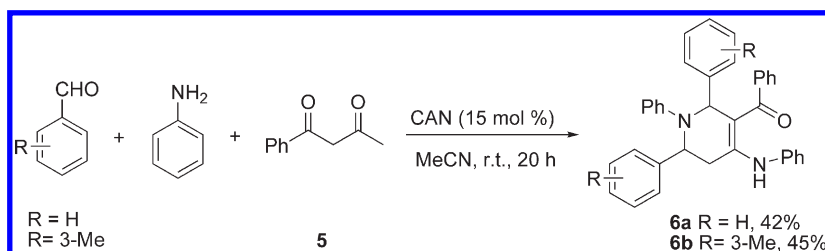
^a Isolated yields.

EXPERIMENTAL PROCEDURES

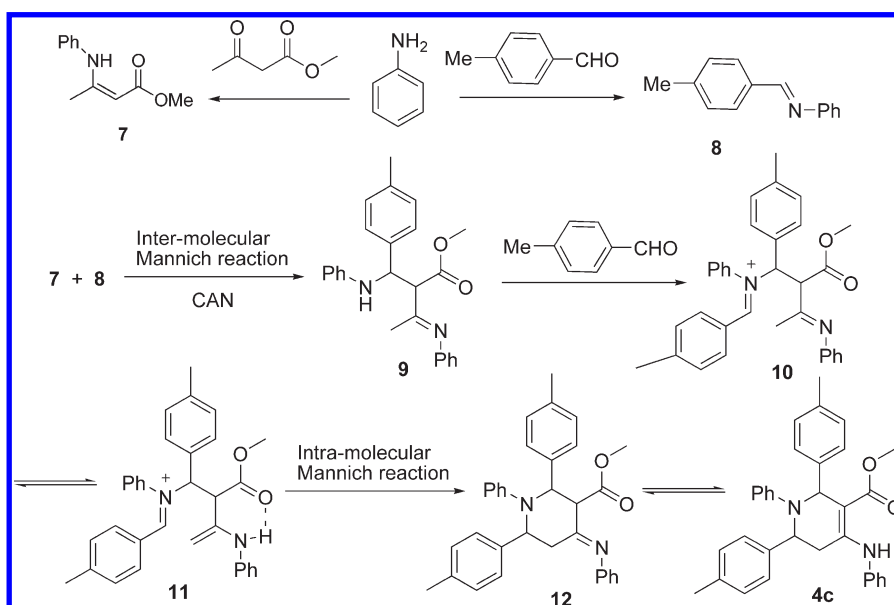
General Procedure for the Preparation of Functionalized Tetrahydropyridines (4). A mixture of β -keto ester (1.0 mmol),

aldehyde (2.0 mmol), amine (2 mmol), and CAN (0.15 mmol) in 5 mL of acetonitrile was stirred at room temperature for an appropriate time (Table 3). After completion of the reaction, as indicated by TLC,

Scheme 2. Reaction of Aldehyde, Aniline, and Benzoyl Acetone Catalyzed by CAN



Scheme 3. Proposed Mechanistic Steps for the Multicomponent Synthesis of Tetrahydropyridines



the mixture was diluted with ethyl acetate (20 mL), washed with water and then brine, and dried with anhydrous Na_2SO_4 . The filtrate was concentrated and purified by silica gel column chromatography.

■ ASSOCIATED CONTENT

S Supporting Information. Experimental procedure, spectroscopic characterization for compound 4, and the X-ray crystallographic information for compound 4i. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Structure 7 of Scheme 3 was modified in the version of this paper published December 16, 2010. The correct version published January 7, 2011.