Ceric ammonium nitrate impregnated on silica gel in the removal of the *tert*-butoxycarbonyl group

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Dedicated to Professor James R. Bull for his contributions to Chemistry and on his retirement from the University of Cape Town

Abstract

The *tert*-butoxycarbonyl group was efficiently (80–99% yields) removed from an amino, hydroxy, or mercapto functionality in organic compounds by use of 0.20 equiv of $Ce(NH_4)_2(NO_3)_6$ in acetonitrile at reflux. Application of the solid-supported reagent involving the use of 0.20 equiv of $Ce(NH_4)_2(NO_3)_6$ impregnated on silica gel in toluene at reflux gave the deprotected products in 90–99% yields. These reactions likely proceed through an electron transfer process.

Keywords: Ceric ammonium nitrate, silica gel, *tert*-butoxycarbonyl, deprotection, amino ester

Introduction

The *tert*-butoxycabonyl (*t*-BOC) group is often used for the protection of amino acids in peptide synthesis.[1] Reagents used to cleave the *t*-BOC group include boron trifluoride,[2] hydrogen chloride,[3] hydrogen fluoride,[4] sulfuric acid,[5] trifluoroacetic acid,[6] trimethylsilyl triflate,[7–9] trimethylsilyl perchlorate,[8] etc. Each of these methods, however, has its own limitations.[1–9] Therefore it is desirable to develop a new and efficient method for deprotection of the *t*-BOC group.

Ceric ammonium nitrate ($Ce(NH_4)_2(NO_3)_6$, CAN) can function as a one-electron transfer catalyst in various organic reactions.[10–12] Recently we have reported the use of a catalytic

amount of CAN for removal of the triphenylmethyl (Tr), monomethoxytrityl (MMTr), and *tert*-butoxycabonyl (*t*-BOC) groups from organic compounds.[11] Under the neutral conditions applied, several acid-sensitive groups survive, including isopropylidene, (dimethylamino)methylidene, *tert*-butyldimethylsilyl, and acyl functionalities.[11] Furthermore, indole, pyrimidine, and phthalimide nuclei remain intact and the undesired racemization in amino esters does not occur.[11]

Use of CAN in acetonitrile at reflux or the CAN impregnated on silica gel in boiling CH_2Cl_2 did not allow us to remove the *tert*-butyl group from 1-(*tert*-butoxy)-2-methoxyethane. We considered that an electron-withdrawing group directly connected to the *tert*-butyl functionality (e.g., RXCOO(*t*-Bu); X = NR, O, and S) would increase the potential for it to become a carbocationic species. Thus we investigated the possibility of using CAN as a catalyst for efficient removal of the *t*-BOC group from amino esters and related compounds. Herein we report our findings from a systematic study that CAN alone or, especially, CAN adsorbed on silica gel functioned as an effective reagent for removal of the *t*-BOC functionality from a variety of organic substrates.

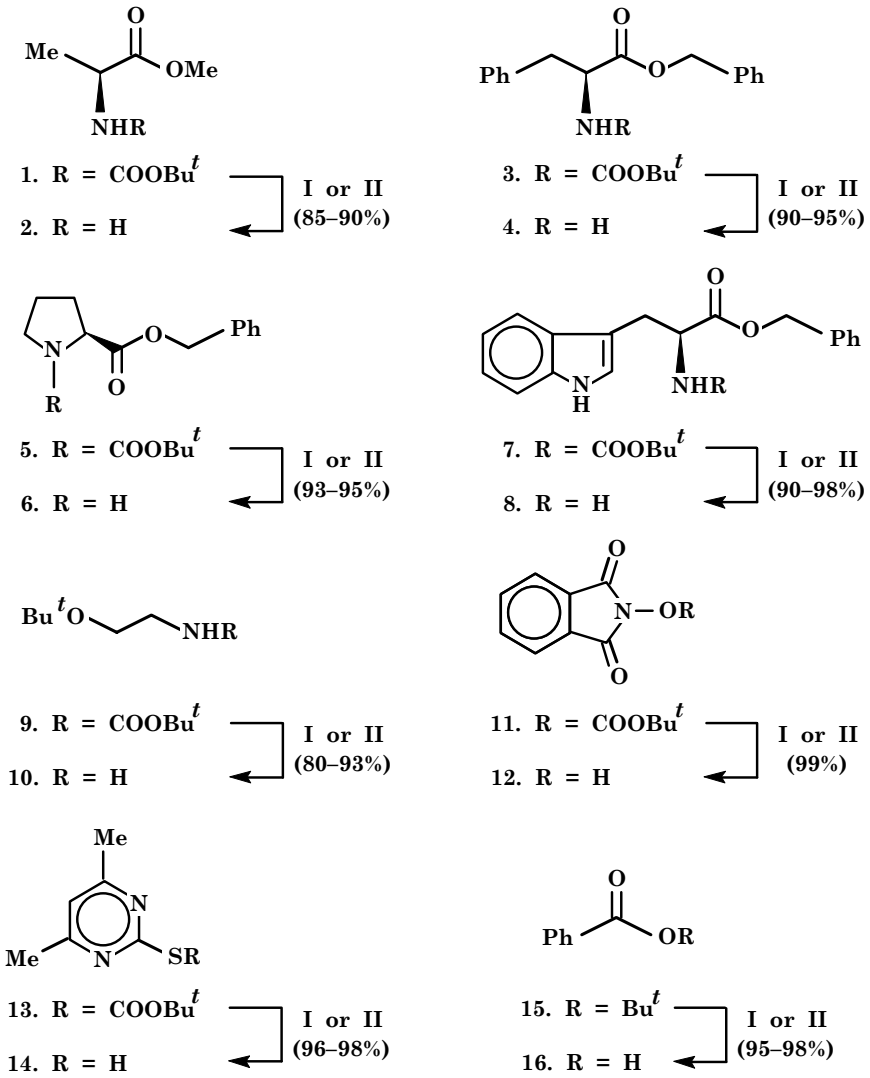
Results and Discussion

We treated several *t*-BOC-containing compounds (i.e., **1**, **3**, **5**, **7**, **9**, **11**, and **13**) in acetonitrile with CAN (0.20 equiv) to give the deprotected products (i.e., **2**, **4**, **6**, **8**, **10**, **12**, and **14**) in 80–99% yields (Scheme 1 and Table 1). Furthermore, we tested the efficiency of the CAN–silica gel reagent (containing 0.20 equiv of CAN) on debutylation. Thus treatment of this reagent with *tert*-butylbenzoate (**15**) in CH_2Cl_2 at reflux gave the corresponding benzoic acid (**16**) in 90% yield after 6.0 h. The same reaction went to completion (95% yield) in $CHCl_3$, CCl_4, or toluene at reflux after 6.5, 3.0, and 0.20 h, individually. Debutylation, however, did not proceed in the above solvents in the absence of silica gel. This is due to low solubility of CAN in those solvents. Moreover, we found that the same deprotection reaction required much longer reaction time (e.g., 30–45 h) for completion at a lower temperature (e.g., 25 °C). Our results indicate the importance on the choice of solvents as well as the reaction temperature during application of the CAN–silica gel reagent in de-*tert*-butoxycarbonylation and debutylation reactions.

Adsorption of the *t*-BOC-containing compounds to silica gel impregnated with CAN could bring the substrates and the catalyst into proximity.[13,14] This facilitates the electron transfer process between CAN and substrates; thus it may cause the deprotection reactions to proceed much faster.[15–17] Use of silica gel as support could also increase the effective surface area and constrain both the substrate and the reactant in pores for decreasing the entropy of activation for electron transfer.[13,14]

To realize generality of the CAN–silica gel reagent in de-*tert*-butoxycabonylation, we treated it with the *t*-BOC containing compounds **1**, **3**, **5**, **7**, **9**, **11**, and **13** in toluene at reflux. After ~1.0 min–3.0 h, the deprotected products (i.e., **2**, **4**, **6**, **8**, **10**, **12**, and **14**) were obtained in 90–99%

yields (see Table 1). Thus, this newly developed procedure was widely applicable to compounds bearing a *t*-BOC group attached to a nitrogen (i.e., **1**, **3**, **5**, **7**, and **9**), an oxygen (i.e., **11**), or a sulfur atom (i.e., **13**). Moreover, the *t*-BOC group can be selectively cleaved in the presence of *tert*-butyl ether as shown in the conversion of **9** to **10** (93% yield, Table 1). To the best of our knowledge, this is the first example of selective removal of the *t*-BOC group in the presence of a *tert*-butyl ether.[9]



I. CAN (0.20 equiv), MeCN, Δ
II. CAN (0.20 equiv)–silica gel, toluene, Δ

Scheme 1

This newly developed deprotection reaction could involve electron transfer processes.[10–12,18] We propose a mechanism shown in Scheme 2 for removal of the *t*-BOC group from organic

molecules **18** by using CAN–silica gel **17**. Oxidation of the carbonyl group in **19**, from adsorption of **18** to **17**, by CAN would lead to the corresponding radical cations as shown in **20**. Radical cations then undergo fragmentation to afford a *tert*-butyl cation and carboxylate radicals as shown in **21**. Deprotonation of the *tert*-butyl cation gives isobutene. In situ, Ce^{IV} is regenerated from Ce^{III} during the reduction of carboxylate radicals in **21** to carboxylate ions in **22**.[18] Consequently, the extrusion of CO_2 from carboxylate ions followed by protonation produces the free amines **23**.

Table 1. Removal of the *tert*-butoxycarbonyl group from protected compounds by use of CAN (0.20 equiv) in MeCN or silica gel-supported CAN (0.20 equiv) in toluene at reflux

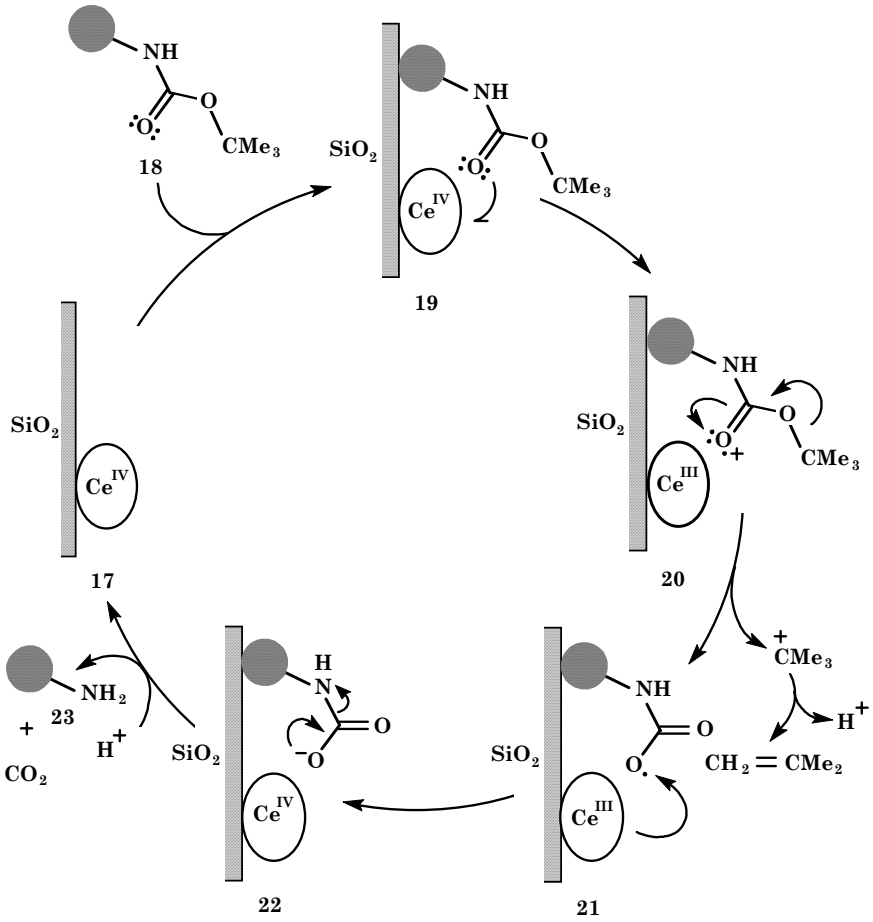
Starting		Time (h)		Yield (%) by Isolation	
Material	Product	CAN	CAN–SiO_2	CAN	CAN–SiO_2
1	2	12	2.0	85	90
3	4	10	1.5	95	90
5	6	2.0	0.50	93	95
7	8	8.0	1.0	90	98
9	10	14	3.0	80	93
11	12	1.0	0.20	99	99
13	14	0.20	0.010	96	98
15	16	5.0	0.20	98	95

In order to support our proposed mechanism, we carried out the reactions of CAN–silica gel with **9**, **11**, and **13**, individually, in the presence of 2,6-di-*tert*-butyl-4-methylphenol (0.050–0.45 equiv), which can function as a radical inhibitor.[19] We found that de-*tert*-butoxycarbonylation did not proceed and the starting materials were recovered. On the other hand, in the absence of radical inhibitors but in the presence of $NaHCO_3$ (0.45 equiv), the above reactions still produced the desired compounds **10**, **12**, and **14**, individually, in comparable yields. These results indicate that the reactions likely proceed through an electron transfer pathway rather than an acid-catalyzed cleavage.

Conclusions

Ceric ammonium nitrate adsorbed on silica gel functioned as an effective catalyst for removal of the *t*-BOC functionality from a variety of organic molecules. The undesired racemization in amino esters did not take place during cleavage of the *t*-BOC group under the applied conditions. Use of silica gel supported CAN allowed the deprotection reactions to proceed much faster and, often, to give the desired products in a higher yield. Advantages associated with this CAN–silica

gel reagent include mild reaction conditions, a relatively short reaction time, and a small amount of the reagent required.



Scheme 2

Experimental Section

General Procedures. Reagents were purchased from Aldrich or Sigma Chemical Co. Dry ether was obtained by distillation from the sodium ketyl of benzophenone under nitrogen; ethyl acetate and hexanes were distilled over CaH_2 under nitrogen. Melting points were obtained with a Büchi 510 melting point apparatus. Ultraviolet (UV) spectra were recorded on a Cary 118 spectrophotometer. Proton NMR spectra were obtained on a Varian XL-300 (300 MHz) spectrometer. Purification by gravity column chromatography was carried out by use of Merck reagent silica gel 60 (particle size 230–400 mesh). Thin-layer chromatography was carried out on glass plates (20 cm × 20 cm) coated with a 1-mm thick layer of silica gel DSF-5 (Terrochem Laboratories). Analytical TLC was performed on precoated plates purchased from Merck (Silica

Gel $60F_{254}$). Compounds were visualized by use of UV light, I_2 vapor, or 2.5% phosphomolybdic acid in ethanol with heating.

Preparation of silica gel–supported CAN. Neutral silica gel (8.02 g, Merck Kieselgel 60, particle size 0.063–0.200 mm, 70–230 mesh) was mixed with a solution of CAN (2.01 g) in water (2.0 mL). Evaporation of water under reduced pressure (0.10 torr) for 4.0 h gave a dry yellowish powder, which contained 20% (by weight) of CAN. This reagent stored in a well-capped bottle was found active for at least six months.

Standard procedure for deprotection of the *tert*-BOC group by use of ceric ammonium nitrate. Method I. A solution of the *tert*-BOC protected compound (1.0 equiv) in MeCN was treated with a catalytic amount of CAN (0.20 equiv) and then was heated at reflux until the TLC did not show any starting material. The solvent was removed under reduced pressure and the residue was purified by column chromatography to afford the desired product with purity >99.9%, as checked by GC.

Method II. A solution of the *tert*-BOC protected compound (1.0 equiv) in toluene was treated with the CAN–silica gel reagent (containing 0.20 equiv of CAN) and then was heated at reflux until the TLC did not show any starting material. The solvent was removed under reduced pressure and the residue was purified by column chromatography to afford the desired product with purity >99.9%, as checked by GC.

(*S*)-(+)-Alanine methyl ester (2). Method I. The standard procedure was followed by use of (*S*)-(+)-*N*-(*tert*-butoxycarbonyl)alanine methyl ester (**1**, 325 mg, 1.60 mmol, 1.0 equiv), CAN (175 mg, 0.319 mmol, 0.20 equiv), and MeCN (10 mL). After the reaction mixture was heated at reflux for 12 h, it was worked up and the residue was purified by column chromatography (30% EtOAc in hexanes as eluant) to afford **2** (140 mg, 1.36 mmol) in 85% yield; its hydrochloride salt: mp 109–110 °C; $[\alpha]^{25}_{D}$ +7.2° (*c* 1.76, MeOH). Its physical properties and spectroscopic characteristics are consistent with those of an authentic sample.[20]

Method II. The standard procedure was followed by use of **1** (413 mg, 2.03 mmol, 1.0 equiv), the CAN–silica gel reagent (1.13 g, containing 222 mg of CAN, 0.405 mmol, 0.20 equiv), and toluene (7.0 mL). After the reaction mixture was heated at reflux for 2.0 h, it was worked up and the residue was purified by chromatography on silica gel (30% EtOAc in hexanes as eluant) to afford **2** (189 mg, 1.83 mmol) in 90% yield.

(*S*)-(–)-Phenylalanine benzyl ester (4). Method I. The standard procedure was followed by use of (*S*)-(–)-*N*-(*tert*-butoxycarbonyl)phenylalanine benzyl ester (**3**, 382 mg, 1.07 mmol, 1.0 equiv), CAN (120 mg, 0.218 mmol, 0.20 equiv), and MeCN (10 mL). After the reaction mixture was heated at reflux for 10 h, it was worked up and the residue was purified by column chromatography (EtOAc as eluant) to afford **4** (260 mg, 1.02 mmol) in 95% yield; its *p*-toluenesulfonate salt: mp 169–171 °C; $[\alpha]^{25}_{D}$ +7.0° (*c* 1.90, MeOH). Its physical properties and spectroscopic characteristics are consistent with those of an authentic sample.[20]

Method II. The standard procedure was followed by use of **3** (290 mg, 0.816 mmol, 1.0 equiv), the CAN–silica gel reagent (450 mg, containing 90.0 mg of CAN, 0.164 mmol, 0.20 equiv), and toluene (7.0 mL). After the reaction mixture was heated at reflux for 1.5 h, it was worked up and the residue was purified by column chromatography (30% EtOAc in hexanes as eluant) to afford **4** (188 mg, 0.737 mmol) in 90% yield.

(*S*)-(–)-Proline benzyl ester (6). Method I. The standard procedure was followed by use of (*S*)-(–)-*N*-(*tert*-butoxycarbonyl)proline benzyl ester (**5**, 456 mg, 1.50 mmol, 1.0 equiv), CAN (165 mg, 0.300 mmol, 0.20 equiv), and MeCN (10 mL). After the reaction mixture was heated at reflux for 2.0 h, it was worked up and the residue was purified by column chromatography (EtOAc as eluant) to afford **6** (285 mg, 1.39 mmol) in 93% yield; its hydrochloride salt: mp 146–148 °C; $[\alpha]^{25}_{D}$ –50.1° (*c* 1.37, H_2O). Its physical properties and spectroscopic characteristics are consistent with those of an authentic sample.[20]

Method II. The standard procedure was followed by use of **5** (337 mg, 1.10 mmol, 1.0 equiv), the CAN–silica gel reagent (610 mg, containing 122 mg of CAN, 0.222 mmol, 0.20 equiv), and toluene (7.0 mL). After the reaction mixture was heated at reflux for 0.50 h, it was worked up and the residue was purified by column chromatography (EtOAc as eluant) to afford **6** (215 mg, 1.05 mmol) in 95% yield.

(*S*)-(+)-Tryptophan benzyl ester (8). Method I. The standard procedure was followed by use of (*S*)-(+)-*N*-(*tert*-butoxycarbonyl)tryptophan benzyl ester (**7**, 527 mg, 1.34 mmol, 1.0 equiv), CAN (148 mg, 0.270 mmol, 0.20 equiv) and MeCN (10 mL). After the reaction mixture was heated at reflux for 8.0 h, it was worked up and the residue was purified by column chromatography (5% MeOH in EtOAc as eluant) to afford **8** (354 mg, 1.20 mmol) in 90% yield; its hydrochloride salt: mp 220–222 °C; $[\alpha]^{25}_{D}$ +4.3° (*c* 2.16, MeOH). Its physical properties and spectroscopic characteristics are consistent with those of an authentic sample.[20]

Method II. The standard procedure was followed by use of **7** (385 mg, 0.977 mmol, 1.0 equiv), the CAN–silica gel reagent (540 mg, containing 108 mg of CAN, 0.197 mmol, 0.20 equiv), and toluene (7.0 mL). After the reaction mixture was heated at reflux for 1.0 h, it was worked up and the residue was purified by column chromatography (5% MeOH in EtOAc as eluant) to afford **8** (281 mg, 0.955 mmol) in 98% yield.

2-*O*-*tert*-Butoxyethylamine (10). Method I. The standard procedure was followed by use of *N*-(*tert*-butoxycarbonyl)-2-*O*-*tert*-butoxyethylamine (**9**, 580 mg, 2.67 mmol, 1.0 equiv), CAN (293 mg, 0.534 mmol, 0.20 equiv), and MeCN (10 mL). After the reaction mixture was heated at reflux for 14 h, it was worked up and the residue was purified by column chromatography (20% MeOH in EtOAc as eluant) to afford **10** (250 mg, 2.14 mmol) in 80% yield: R_f = 0.61 (50% MeOH in EtOAc); ^{1}H NMR (CD_3OD,) δ 1.13 (s, 9 H), 2.89 (t, *J* = 8.0 Hz, 2 H), 3.44 (t, *J* = 8.0 Hz, 2 H). Its spectroscopic characteristics are consistent with those of the same compound reported.[21]

Method II. The standard procedure was followed by use of **9** (464 mg, 2.13 mmol, 1.0 equiv), the CAN–silica gel reagent (1.17 g, containing 235 mg of CAN, 0.428 mmol, 0.20 equiv), and toluene (7.0 mL). After the reaction mixture was heated at reflux for 3.0 h, it was worked up and

the residue was purified by column chromatography (20% MeOH in EtOAc as eluant) to afford **10** (232 mg, 1.98 mmol) in 93% yield.

***N*-Hydroxyphthalimide (12). Method I.** The standard procedure was followed by use of *N*-(*tert*-butoxycarbonyloxy)phthalimide (**11**, 486 mg, 1.85 mmol, 1.0 equiv), CAN (203 mg, 0.370 mmol, 0.20 equiv), and MeCN (10 mL). After the reaction mixture was heated at reflux for 1.0 h, it was worked up and the residue was purified by column chromatography (EtOAc as eluant) to afford **12** (298 mg, 1.82 mmol) in 99% yield: mp 231–233 °C (dec.). Its physical properties and spectroscopic characteristics are consistent with those of an authentic sample.[20]

Method II. The standard procedure was followed by use of **11** (390 mg, 1.48 mmol, 1.0 equiv), the CAN–silica gel reagent (815 mg, containing 163 mg of CAN, 0.297 mmol, 0.20 equiv), and toluene (7.0 mL). After the reaction mixture was heated at reflux for 0.20 h, it was worked up and the residue was purified by column chromatography (EtOAc as eluant) to afford **12** (239 mg, 1.46 mmol) in 99% yield.

4,6-Dimethyl-2-mercaptopyrimidine (14). Method I. The standard procedure was followed by use of *tert*-butyl *S*-(4,6-dimethylpyrimidin-2-yl)thiolcarbonate (**13**, 422 mg, 1.76 mmol, 1.0 equiv), CAN (193 mg, 0.350 mmol, 0.20 equiv), and MeCN (10 mL). After the reaction mixture was heated at reflux for 0.20 h, it was worked up and the residue was purified by column chromatography (EtOAc as eluant) to afford **14** (236 mg, 1.68 mmol) in 96% yield: mp 212–214 °C (dec.). Its physical properties and spectroscopic characteristics are consistent with those of an authentic sample.[20]

Method II. The standard procedure was followed by use of **13** (350 mg, 1.46 mmol, 1.0 equiv), the CAN–silica gel reagent (802 mg, containing 160 mg of CAN, 0.290 mmol, 0.20 equiv), and toluene (7.0 mL). After the reaction mixture was heated at reflux for 0.010 h, it was worked up and the residue was purified by column chromatography (EtOAc as eluant) to afford **14** (201 mg, 1.43 mmol) in 98% yield.

Benzoic Acid (16). Method I. The standard procedure was followed by use of *tert*-butyl benzoate (**15**, 540 mg, 3.03 mmol, 1.0 equiv), CAN (332 mg, 0.605 mmol, 0.20 equiv), and MeCN (10 mL). After the reaction mixture was heated at reflux for 5.0 h, it was worked up and the residue was purified by column chromatography (Et_2O as eluant) to afford **16** (362 mg, 2.96 mmol) in 98% yield: mp 120–122 °C. Its physical properties and spectroscopic characteristics are consistent with those of an authentic sample.[20]

Method II. The standard procedure was followed by use of **15** (476 mg, 2.67 mmol, 1.0 equiv), the CAN–silica gel reagent (1.47 g, containing 294 mg of CAN, 0.536 mmol, 0.20 equiv), and toluene (7.0 mL). After the reaction mixture was heated at reflux for 0.20 h, it was worked up and the residue was purified by column chromatography (Et_2O as eluant) to afford **16** (310 mg, 2.54 mmol) in 95% yield.

Acknowledgments

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