JOC Article

Improved Heteroatom Nucleophilic Addition to Electron-Poor Alkenes Promoted by $CeCl_3 \cdot 7H_2O$/NaI System Supported on Alumina in Solvent-Free Conditions

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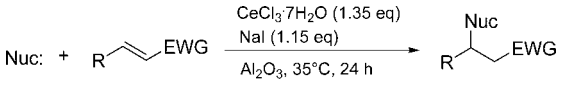
Received September 21, 2004



Conjugate addition of heteroatom nucleophiles to carbon−carbon double bonds conjugated with a strong electron-withdrawing group is one of the most important new bond-forming strategies in synthetic organic chemistry. Among the methods for these Michael additions, Lewis acids have shown the best promoter activity, and in particular, the use of reagents impregnated over inorganic supports is rapidly increased. With the increase of environmental consciousness in chemical research, the solvent-free Michael addition has attracted our attention. In continuation of our ongoing program to develop synthetic protocols utilizing cerium trichloride, we report an extension of the $CeCl_3 \cdot 7H_2O$/NaI combination supported under solvent-free conditions to promote heteroatom Michael addition. Using neutral alumina (Al_2O_3) as solid support permits us to circumvent some of the problems associated with the procedure where the inorganic support is silica gel. The $CeCl_3 \cdot 7H_2O$/NaI/Al_2O_3 system works well for hetero-Michael additions utilizing weakly nucleophiles such as imidazoles and carbamates, and also the reaction proceeds with good yields in the case of Michael acceptors different from α,β-unsaturated carbonyl compounds. An important synthetic application of this our methodology is the intramolecular aza-Michael reaction in producing 4-piperidinone derivatives, which are of interest as synthetic intermediates toward important classes of heterocycles.

Introduction

Conjugate addition (1,4-addition or Michael addition) of nucleophiles to α,β-unsaturated compounds is one of the most important new bond-forming strategies in synthetic organic chemistry.[1] The versatility of the conjugate additions is mainly due to the large variety of nucleophiles (organometallic reagents, other carbanions, heteroatom Michael donors) and acceptors (α,β-unsaturated carbonyl compounds, -nitriles, -esters, -phosphates, -sulfones, and nitroalkenes) that can be used.[2] Among this variety of synthetic transformations, the development of new methods for new and efficient conjugate addition reaction with a wide range of heteroatom nucleophiles has attracted special attention.[3] In particular, the conjugate addition of nitrogen nucleophiles to α,β-enones (aza-Michael reaction) is noteworthy as a widely used method for carbon−nitrogen bond formation. This organic transformation has been especially employed in the synthesis of products generally recognized as building blocks for the preparation of important natural and no natural target molecules.[4]

In the past years Lewis acids have been shown as the best promoters for these Michael additions, especially

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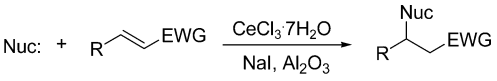
10.1021/jo048329g CCC: $30.25
Published on Web 11/20/2004

concerning the simplicity, economy, and atom efficiency aspects.[5] With the aim to improve the reaction's efficiency, several heterogeneous catalysts have been studied, and excellent results have been achieved by using palladium,[6] $InCl_3$,[7] bismuth(III) salts,[8] and copper salts.[9] Despite these results, the methods described require the use of hazardous solvents and expensive catalyst or a special treatment for its activation and are also not time efficient. These aspects are in disagreement with clean chemistry,[10] and hence the challenge for a sustainable environment calls for the use of alternative procedures avoiding the use of harmful solvents. The solvent-free approach[11] and, in particular, the use of reagents impregnated over inorganic supports[12] can offer a step forward in this direction even if, for exactness, these procedures do not meet the definition of 'no-solvent'. The solvent is only eliminated at the primary reaction stage, whereas an appreciable amount of solvent is still required for the adsorption of reactants and elution of the product at the pre- and post-reaction stages, respectively. Thus, with this increase of environmental consciousness in chemical research, the solvent-free Michael addition has attracted our attention, and in the course of our ongoing program to develop synthetic protocols using cerium trichloride,[13] we have recently reported that a $CeCl_3 \cdot 7H_2O$/NaI combination supported on silica gel is able to promote the Michael addition of indoles to electron-poor alkenes.[14]

We next attempted to extend our solventless methodology to aza-Michael additions, and in pioneering studies[15] we have reported, by addition of secondary amines to (*Z*)-α,*β*-enones, the synthesis of *β*-amino ketones, which are versatile building blocks for the preparation of many nitrogen-containing biologically important compounds.[16] Herein we report the extension of our results, and we have been able to generalize the original route and to expand its scope, thereby providing ready access to a new promoter system that allows various nucleophiles to react with carbon−carbon double bonds conjugated with a strong electron-withdrawing group (EWG). In particular we report the advantages obtained in Michael additions promoted by the $CeCl_3 \cdot 7H_2O$/NaI combination utilizing other inorganic supports than silica gel.

SCHEME 1



1 2 3

Results and Discussion

Since in our preliminary experiments aimed to obtain *β*-amino ketones via aza-Michael addition of amines to (E)-α,*β*-unsaturated ketones in the presence of $CeCl_3 \cdot 7H_2O$/NaI/SiO_2 the starting material was completely recovered, consistent with the well-documented[17] instability of *β*-amino carbonyl compounds on silica gel,[18] we thought to circumvent this problem by changing the inorganic material support. It is known, in fact, that alumina (Al_2O_3) is a particularly interesting metal oxide widely used to carry out surface organic chemistry,[19] and we tested the neutral alumina (Fluka, neutral, Brockman activity, grade 1, 150 mesh) as support of our Lewis acid promoter.Immobilization of $CeCl_3 \cdot 7H_2O$/NaI system by stirring an acetonitrile mixture of $CeCl_3 \cdot 7H_2O$/NaI with neutral Al_2O_3 at room temperature and then removing the solvent by rotary evaporation at 35 °C affords the heterogeneous Lewis acid promoter. Promoter activity of this powder is not weakened by absorption of moisture from the air, and such a system can be stored for long periods without any appreciable loss of the activity. Then, we found that with this new $CeCl_3 \cdot 7H_2O$/NaI/Al_2O_3 promoter system the Michael addition of nucleophiles **1** to electron-deficient alkenes **2** was achieved in good yields (Table 1). In the absence of alumina, the reaction gave very low yields of adducts and many side products were formed. Moreover the yields were improved when the

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(18) Treatment of *β*-amino ketone **3ab** with SiO_2 caused an elimination of 1 equiv of amine, leading to α,*β*-enone **2b**. This result is consistent with reversibility of the Michael reaction in the presence of silica gel.
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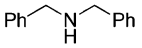
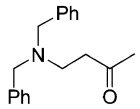
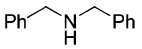
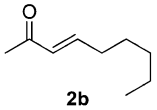
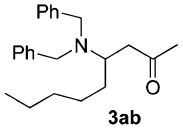
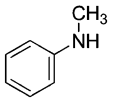
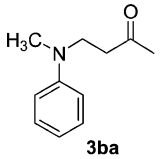
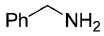
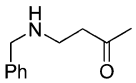
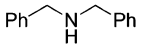
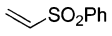
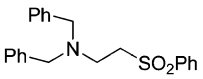
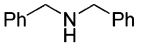
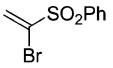
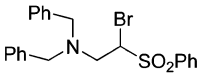
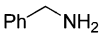
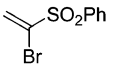
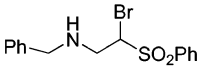
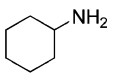
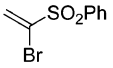
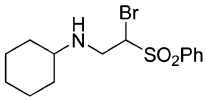
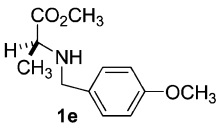
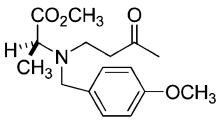
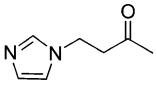
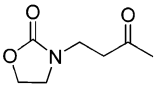
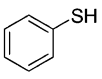
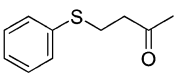
TABLE 1. Michael Addition Promoted by $CeCl_3 \cdot 7H_2O$/NaI System Supported on Al_2O_3 at 35 °C for 24 h[a]

Entry	Nucleophile	Acceptor	Product[b]	Yield (%)[c]
1	 **1a**	 **2a**	 **3aa**	95
2	 **1a**	 **2b**	 **3ab**	85
3	 **1b**	 **2a**	 **3ba**	75
4	 **1c**	 **2a**	 **3ca**	70
5	 **1a**	 **2c**	 **3ac**	88
6	 **1a**	 **2d**	 **3ad**	95
7	 **1c**	 **2d**	 **3cd**	93
8	 **1d**	 **2d**	 **3dd**	86
9	 **1e**	 **2a**	 **3ea**	85
10	 **1f**	 **2a**	 **3fa**	93
11	 **1g**	 **2a**	 **3ga**	91
12	 **1h**	 **2a**	 **3ha**	98

[a] Reactions performed in the presence of 1.35 equiv of $CeCl_3 \cdot 7H_2O$ and 1.15 equiv of NaI supported on neutral alumina (1.00 g/mmol amines **1**). The rate and yields of this reaction improved when it was warmed to 35 °C. [b] All products were identified by their IR, NMR, and GC−MS. [c] Yields of products isolated by column chromatography over neutral alumina.

reaction mixture was mechanically stirred at an external temperature of 35 °C for 24 h. The first clear point coming out is that the Michael addition of amines as nitrogen nucleophiles proceeds well, giving the corresponding β-amino ketones, but the most important feature of the present method seems to be the possibility of using a Michael acceptor such as (*E*)-α,β-unsaturated carbonyl compounds (Table 1, entry 2). Furthermore, although the nucleophilic addition of primary and secondary arylamines generally proceeds sluggishly, owing to their reduced nucleophilicity,[20] with our protocol of Michael addition, their addition is accomplished with good yields (Table 1, entry 3).

Encouraged by our recent discovery, we examined the hetero-Michael addition of a class of less nucleophilic nitrogen compounds. Because carbamates and imidazoles are weak nucleophiles,[21] the development of more efficient promoter systems for addition reactions with these nucleophiles is highly desirable.[22] For this, our attention has been focused on similar Michael donors, and we found that our reaction constitutes a new synthetic procedure for the preparation of N-substituted oxazolidin-2-ones and 1-alkylimidazoles[23] (Table 1, entries 10 and 11) with good yields and under mild reaction conditions. It is also noteworthy that the *N*-(*p*-methoxybenzyl) protecting group of amino acids can be utilized as nitrogen nucleophile, and the corresponding β-amino ketone **3ea** has been obtained without racemization as confirmed by the optical rotation of the product (Table 1, entry 9).

In continuing our quest to exploit the usefulness of the $CeCl_3 \cdot 7H_2O/NaI/Al_2O_3$ system, we were interested to find whether thiols could undergo 1,4-addition to suitable Michael acceptors in the presence of our promoter system. In a typical experiment thiophenol (**1h**) was treated with methyl vinyl ketone (**2a**) in the presence of the $CeCl_3 \cdot 7H_2O/NaI$ combination supported on neutral alumina, and the corresponding β-phenylthio ketone **3ha**[24] was isolated in near quantitative yield.[25] Certainly, the fact that the reaction can be accomplished without solvent allowed us to adopt the best experimental conditions to reduce the large amounts of organic solvents.[26] In general, the use of neutral alumina support makes the workup of the reaction mixture easy and improves the rate and yield of products, even though the reaction occurred even in its absence. Presumably, Al_2O_3 acts as a carrier to increase the surface area in our heterogeneous reaction, and it is very probable that cerium salt interacts with oxide groups at the surface of the support, forming new active sites on the alumina local structure.

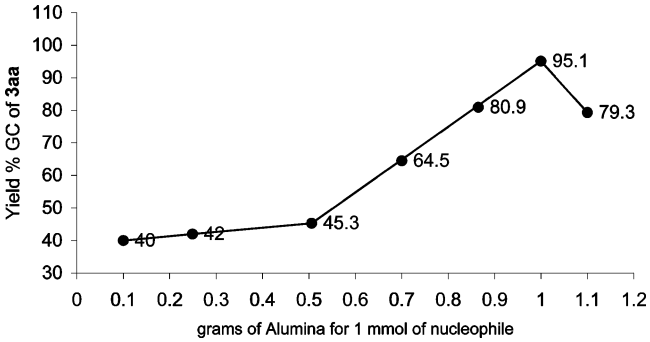


FIGURE 1. The amount of alumina influences the efficiency of the reaction.

However, the fact that our methodology is clean and the adducts have been obtained in high yields without any side reactions such as polymerization and bis-addition, normally observed under the influence of strong acids, excludes the existence in the solid of a distribution of sites that may contain simultaneously Brönsted and Lewis sites.[14b] Furthermore, the $CeCl_3 \cdot 7H_2O/NaI/Al_2O_3$ system has been used for addition of thiophenol (**1h**) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine,[27] and as expected our Lewis acid promoter has afforded adduct **3ha** in high yield and with absolutely purity. In fact, a strongly hindered base, namely, 2,6-di-*tert*-butyl-4-methylpyridine, has been added to neutralize traces of HX, which might contaminate the reaction mixture, without deactivating the $CeCl_3 \cdot 7H_2O/NaI/Al_2O_3$ system because side reaction polymerization of the reagents is promoted by residual HX. Also, the amounts of $CeCl_3 \cdot 7H_2O$ and NaI used in the reaction were tested and optimized. Neither $CeCl_3$ nor NaI alone could accomplish the Michael reaction even after 1 week, and the optimal molar ratio of nucleophile, Michael acceptor, $CeCl_3 \cdot 7H_2O$, and NaI was found to be 1:1.25:1.35:1.15. Anyway, it was found that the amount of Al_2O_3 was decisive for completion of this type of Michael addition (Figure 1). The results indicate that 1.00 g over mmol of Michael donor is the most appropriate ratio, and the use of an excessive amount of alumina (more than 1.00 g/mmol) caused a significantly lower yield of Michael adduct **3aa**. Analogously, a decrease in the amount of alumina led to the partial recovery of the starting material even when the reaction time was prolonged. It is plain, thus, the minor activity of the $CeCl_3 \cdot 7H_2O/NaI/Al_2O_3$ system with regard to the $CeCl_3 \cdot 7H_2O/NaI/SiO_2$ system as previously reported,[14] and this can be due to the chemical properties of alumina.[28] The undercoordinate Al sites are thought to generate sp^2 hybridized aluminum atoms capable of strong Lewis acidic behavior.[29] Hydrolysis reaction of these sites for the presence of water in the reaction mixture produces stable hydrates, and undercoordinate Lewis acid sites can be reformed by dehydration from

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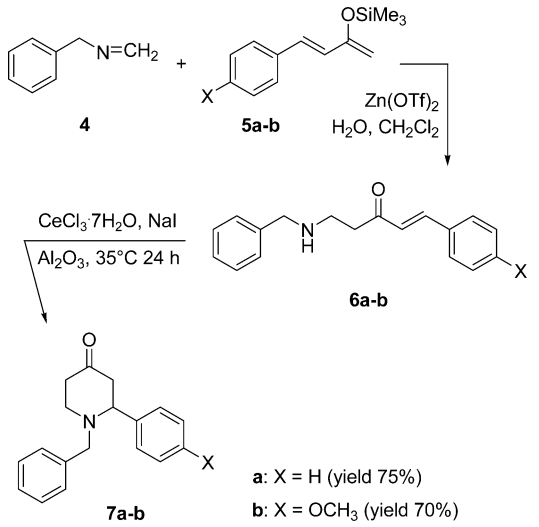
adjacent OH groups.[30] However, this minor activity of Al_2O_3 with respect to SiO_2 as solid support was exploited to improve productivity in many critical aspects of the generation of new chemical entities, first of all, the possibility to accomplish the aza-Michael addition of primary amines to an electron-deficient alkene, without the problem of double-conjugate addition[15] (Table 1, entries 4, 7 and 8).

With regard to Michael acceptors, β-disubstituted electron-poor alkenes are less reactive than their mono- and nonsubstituted homologues as a result of increased steric interaction with the Lewis acid promoter; for example, with mesityl oxide the Michael adduct was obtained in very modest yield even after extended reaction time. Our procedure, on the contrary, works well for α,β-unsaturated sulfones (Table 1, entries 5−8), given their known ability to undergo efficient conjugate addition reactions with a wide range of nucleophiles.[31] The use of a Lewis acid to activate alkenyl sulfone as a Michael acceptor has been reported in the literature,[32] and as shown in Table 1, our system promotes this aza-Michael addition. The resulting β-amino sulfone derivatives are versatile synthons for the synthesis of alkaloids,[33] β-lactams,[34] and nitrogen heterocycles.[35] We then tried to extend this aza-Michael reaction finding to see if with phenyl-α-bromovinyl sulfone **2d** our conditions promoted the cyclization into aziridines.[36] These are attractive targets as a result of their occurrence in biologically active compounds, synthetic intermediates, or chiral auxiliaries.[37] Nevertheless, by utilizing benzylamine (**1c**) and cyclohexylamine (**1d**) as primary amine nucleophiles, the corresponding α-bromo-β-amino sulfones **3cd** and **3dd** were isolated in good yield, and no aziridine was detected under these conditions. It should be noted that in the case of heteroatom nucleophilic addition to α-nitroalkenes our procedure gives, contrary to the results of the solvent-free aza-Michael addition proposed by Pellacani et al.,[38] very low yield of adduct, and many side products are formed.

An important extension of the outlined protocol is the intramolecular aza-Michael reaction to generate substituted six-member nitrogen-heterocycles, which are key intermediates particularly useful in the synthesis of alkaloids and pharmacological active compounds.[39] We focused our attention on the development of a very convenient route (Scheme 2) to the selectively substituted piperidin-4-ones, which are ubiquitous scaffolds in medicinal chemistry.[40] The earlier organic transformation involves the reaction of aldimine **4** with 4-aryl-2-trimethylsilyloxy-1,3-butadiene (1.2 equiv to aldimine) in the presence of a Lewis acid in dichloromethane. Then, the intramolecular aza-Michael reaction for β-amino ketones **6a** and **6b** using our combination system of $CeCl_3{\cdot}7H_2O/NaI/Al_2O_3$ afforded the corresponding N-substituted 2-arylpiperidin-4-one **7a** and **7b**, respectively.[41]

SCHEME 2



The availability of precursors β-amino ketones **6a,b** having a terminal olefin[42] substantiates the scope of our procedure.

In conclusion, we have shown that improved Michael addition of heteroatom nucleophiles to carbon−carbon double bonds conjugated with a strong electron-withdrawing group has been obtained exchanging the amorphous silica gel with neutral alumina as an inorganic solid support. In our procedure cerium(III) salt acts as Lewis acid promoter of Michael additions, and this establish another motif of interest for this lanthanide compound, as a result of its low toxicity, ease of handling, low cost, and stability in the presence of moisture.[43] Furthermore, the combination of these advantages with the use of an organic solvent-free approach by using an inorganic oxide support makes our procedure a more

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efficient method for the preparation of compounds that are of profound importance in organic chemistry. Undoubtedly the presence of NaI is essential for the Michael reaction too. In considering the mechanistic role of NaI, this is intriguing and complex because the exact nature of the intermediate obtained by the reaction of reagents with the $CeCl_3 \cdot 7H_2O$/NaI system on Al_2O_3 is not yet known. The characterization then of all components generated during the treatment of $CeCl_3 \cdot 7H_2O$, NaI, and Al_2O_3 is being carried out in our laboratories. The development of this new protocol also prompts us to investigate further applications of our reagent system in new schemes of synthesis, and the preparation of biologically important substances is in progress in our laboratories.

Experimental Section

NMR spectra were recorded in a $CDCl_3$ solution at 300 MHz (^1H) and 75.5 MHz (^{13}C). Mass spectra were determined by means of the EI technique (70 eV) or by means of a source API-electronspray. IR absorption spectra were recorded with thin films on NaCl plates, and only noteworthy absorptions (cm^{-1}) are listed. All solvents were dried and distilled according to standard procedures.[44]

***(E)*-5-(Benzylamino)-1-(4-methoxyphenyl)-1-penten-3-one (6b).** To a stirred solution of zinc triflate (2.71 g, 4.53 mmol) and water (0.136 mL, 1.53 mmol) in dichloromethane (25 mL) were added Mannich reagent **4**[45] (0.45 g, 3.77 mmol) and 4-methoxyphenyl-2-trimethylsilyloxy-1,3-butadiene[46] (1.12 g, 4.53 mmol) at room temperature. The reaction mixture was stirred at room temperature for 5 h, quenched with aqueous saturated $NaHCO_3$, and extracted with dichloromethane. The organic layers were dried over $MgSO_4$, the solvent was evaporated, and the resulting oil residue of **6b** (0.87 g, 78% yield) was sufficiently spectroscopic pure for further use:[47] IR (neat, cm^{-1}) 3301, 1675, 1620, 1588; ^1H NMR δ 2.26 (s, 3H), 3.01−3.08 (m, 1H), 3.09−3.16 (m, 2H), 3.64 (d, 1H, J = 13.62 Hz), 3.61 (d, 1H, J = 13.45 Hz), 4.43 (dd, 2H, J = 8.96 and 4.30 Hz), 6.70 (d, 1H, J = 15.96 Hz), 7.17−7.26 (m, 3H), 7.30−7.48 (m, 7H); ^{13}C NMR δ 39.6, 52.7, 56.4, 60.3, 114.8, 126.3, 127.6, 128.3, 128.6, 129.0, 136.4, 153.2, 160.4, 196.6; HR-MS (ESI) *m/z* 296 [M + H], 318 [M + Na], 334 [M + K]. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.27; H, 7.17; N, 4.74. Found: C, 77.10; H, 7.12; N, 4.59.

***N*-Benzyl-2-(4-methoxyphenyl)-4-pipiridinone (7b).** Aluminum oxide (Fluka, neutral, Brockman activity, grade 1, 150 mesh, 1.35 g) was added to a mixture of $CeCl_3 \cdot 7H_2O$ (0.68 g, 1.82 mmol) and NaI (0.23 g, 1.55 mmol) in acetonitrile (10 mL), and the mixture was stirred overnight at room temperature. The acetonitrile was removed by rotary evaporation, and to the resulting powder reagent was added Mannich base **6b** (0.4 g, 1.35 mmol). Then, the mixture was mechanically stirred for 24 h at an external temperature of 35 °C. The intramolecular Michael adduct was extracted from the solid mass by filtration chromatography over a short plug of neutral alumina using diethyl ether as solvent. The filtrate was washed with aqueous saturated $NaHCO_3$ solution and with saturated NaCl solution and finally dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure furnished the crude product, which was further purified by column chromatography over neutral alumina to give 0.28 g (70% yield) of the corresponding 4-piperidinone **7b** as oil: IR (neat, cm^{-1}) 3028, 1723, 1645; ^1H NMR δ 2.29−2.39 (m, 2H), 2.52−2.78 (m, 3H), 2.92 (s, 3H), 3.03 (d, 1H, J = 14.12 Hz), 3.19−3.32 (m, 1H), 3.64 (dd, 1H, J = 11.30 and 5.70 Hz), 3.83 (d, 1H, J = 14.00 Hz), 7.21−7.27 (m, 3H), 7.45−7.71 (m, 6H); ^{13}C NMR δ 40.6, 46.7, 53.2, 56.0, 59.3, 70.2, 114.7, 126.5, 128.0, 129.3, 136.5, 138.3, 165.0, 207.3; EI-MS *m/z* 295 [M^+], 294, 237, 207, 131, 91 (100), 104, 77, 65. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.27; H, 7.17; N, 4.74. Found: C, 77.08; H, 7.12; N, 4.68.

Acknowledgment. The authors are grateful to Dr. Massimo Ricciutelli performing mass spectral analyses. This work was carried out under the framework of the National Project 'Stereoselezione in Sintesi Organica. Metodologie ad Applicazioni' supported by MIUR, Rome, and by the University of Camerino. M.B. gratefully acknowledges the Pharmacia Gruppo Pfizer Inc. Ascoli Piceno Plant for post-graduate fellowship.

Supporting Information Available: Detailed description of experimental procedures, NMR spectra, MS spectra, and other characterization data for new compounds, not reported previously, designated by their entries in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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