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Bismuth Nitrate-Catalyzed Versatile Michael Reactions†

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Bismuth nitrate-catalyzed versatile Michael reaction was developed to reduce the complications that characterize the current standard Michael reaction and used for facile preparation of organic compounds of widely different structures. For example, several substituted amines, imidazoles, thio compounds, indoles, and carbamates were prepared at room temperature by following this method. In contrast with the existing methods using many acidic catalysts, this method is very general, simple, high-yielding, environmentally friendly, and oxygen and moisture tolerant. However, the promoting role of bismuth nitrate in this reaction is not understood at this time.

Introduction

The Michael reaction, which was discovered many years ago, is one of the most important reactions in organic chemistry. In general, this type of conjugate addition reaction of nucleophiles to unsaturated carbonyl compounds requires basic conditions[1] or acidic catalysts.[2] Some of the methods classified as Michael reactions require stoichiometric amounts of the reagents, and many side reactions can occur if the reactive partners are sensitive.[3] Recently, a number of reagents that overcome these drawbacks have been developed. The main improvement of these reagents is the ability to limit the catalysts used to catalytic amounts.[4] These methods are really very fascinating from a synthetic chemist's point of view. In addition, these processes are less expensive and environmentally friendly. Despite their tremendous success, however, the literature reveals that these catalysts are very substrate selective. For example, indium salts are very effective for Michael reactions between indoles[5] and pyrroles,[6] but they are practically ineffective in catalyzing a similar reaction with carbamates; because carbamates[7] are weakly nucleophilic, the yield of the reaction is very low. However, recent results show that platinum salts are very effective for addition reactions with carbamates.[7] Therefore, development of an alternative method, which can be applied to a number of substrates of different natures in a catalytic process, is highly desirable.

We have been studying reactions mediated by metals or their salts with the aim of developing several biologically active compounds, including anticancer agents[8] and β-lactams.[9] We have also reported the use of bismuth-derived reagents in several organic transformations.[10] For example, nitration of aromatic hydrocarbons, phenolic compounds, and β-lactams by bismuth nitrate was performed in excellent yields.[10c,d] Facile deprotection of hydrazones and oximes also worked well using bismuth

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(1) (a) Bull, S. D.; Davies, S. G.; Delgado-Ballester, S.; Fenton, G.; Kelly, P. M.; Smith, A. D. *Synlett* **2000**, 1257. (b) Davies, S. G.; McCarthy, T. D. S*ynlett* **1995**, 700.

(2) Rosenthal, D.; Braundrup, G.; Davis, K. H.; Wall, M. E. *J. Org. Chem*. **1965**, *30*, 3689.

(3) (a) Clariana, J.; Galvez, N.; Marchi, C.; Moreno-Manas, M.; Vallribera, A.; Mollins, E. *Tetrahedron* **1999**, *55*, 7331. (b) Christoffers, J. *Eur. J. Org. Chem*. **1998**, 1259. (c) Giuseppone, N.; Vander Weghe, P.; Mellah, M.; Collin, J. *Tetrahedron* **1998**, *54*, 13129.

(4) (a) Cabral, J.; Laszlo, P.; Mahe, L.; Montaufier, M.-T.; Randriamahefa, S. L. *Tetrahedron Lett*. **1989**, *30*, 3969. (b) Perez, M.; Pleixats, R. *Tetrahedron* **1995**, *51*, 8355. (c) Falborg, L.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans*. **1996**, *1*, 2823. (d) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc*. **1998**, *120*, 6615. (e) Sibi. M. P.; Liu, M. *Org. Lett*. **2000**, *2*, 3393. (f) Zhuang, W.; Hazell, R. G.; Jorgensen, K. A. *Chem. Commun*. **2001**, 1240; For a review for enantioselective conjugate addition, see: Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.

(5) (a) Bandini, M.; Cozzi, P. G.; Giacomoni, M.; Melchiorre, P.; Selva, S.; Ronchi, A. U. *J. Org. Chem*. **2002**, *67*, 3700. (b) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165.

(6) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Tetrahedron Lett*. **2001**, *42*, 8063.

(7) Kobayashi, S.; Kakumoto, K.; Sugiura. M. *Org. Lett*. **2002**, *4*, 1319.

(8) (a) Becker, F. F.; Banik, B. K. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2877. (b) Becker, F. F.; Mukhopadhyay, C., Hackfeld, L., Banik, I.; Banik, B. K. *Bioorg. Med. Chem*. **2000**, *8*, 2693. (c*)* Banik, B. K.; Becker, F. F. *Bioorg. Med. Chem*. **2001**, *9*, 593. (d) Banik, B. K.; Becker, F. F. *Cur. Med. Chem*. **2001**, *8*, 1513. Also see: (a) Becker, F. F.; Banik, B. K. U.S. Patent 6,015,811, 2000. (b) Becker, F. F.; Banik, B. K. *U.S. Patent* 6,184,224, 2001. (c) Becker, F. F.; Banik, B. K. U.S. Patent 0,-103,191, 2002, A1. (d) Becker, F. F.; Banik, B. K. U.S. Patent 6,362,-200, 2002.

(9) (a) Ghatak, A.; Becker, F. F.; Banik, B. K. *Heterocycles* **2000**, *53*, 2769. (b) Banik, B. K.; Ghatak, A.; Becker, F. F. *J. Chem. Soc., Perkin Trans 1* **2000**, 2179. (c) Banik, B. K.; Becker, F. F. *Tetrahedron Lett*. **2000**, *41*, 6551. (d) Ng, S.; Banik, I.; Okawa, A.; Becker, F. F.; Banik, B. K. *J. Chem. Res*. **2001**, *118*. (e) Dasgupta, S. K.; Banik, B. K. *Tetrahedron Lett*. **2002**, *43*, 9445. (f) Banik, I.; Becker, F. F.; Banik, B. K. *J. Med. Chem*. **2003**, in press. (g) Banik, I.; Hackfeld, L.; Banik, B. K. *Heterocycles* **2003**, in press.

(10) (a) Banik, B. K.; Mukhopadhyay, C.; Venkatraman, M. S.; Becker, F. F. *Tetrahedron Lett*. **1998**, *39*, 7243. (b) Banik, B. K.; Ghatak, A.; Mukhopadhyay, C.; Becker, F. F. *Synth. Commun*. **2000**, *30*, 108. (c) Samajdar, S.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2000**, *41*, 8017. (d) Samajdar, S.; Becker, F. F.; Banik, B. K. *Arkivoc* **2001**, TG-223. (e) Banik, B. K.; Ghatak, A.; Venkatraman, M. S.; Becker, F. F. *Synth. Commun*. **2000**, *30*, 2701. (f) Samajdar, S.; Becker, F. F.; Banik, B. K. *Synth. Commun*. **2002**, *32*, 1917.

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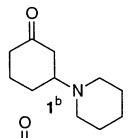
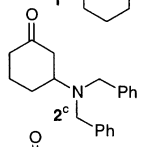
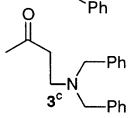
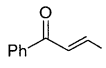
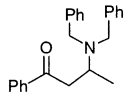
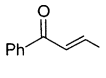
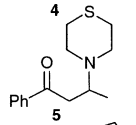
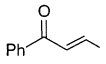
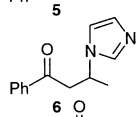
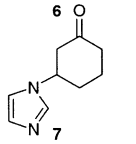
nitrate.[10f] These reactions, in principle, require the presence of acids. We hypothesized that the drawbacks of the catalysts employed in the Michael reaction may be avoided if we used bismuth nitrate as a mild reagent, as long as the acidity is controlled by using it in catalytic proportions. Our hypothesis was further strengthened by the recent discovery by Mohan and his group, who demonstrated that bismuth triflate is an efficient catalyst for the deprotection of acyclic *O*,*O*-acetals derived from ketones and conjugated aldehydes.[11] However, reactions of cyclic acetals and TBDMS ethers are not affected by this reagent. Since Michael reactions are among the most important acid-mediated reactions, development of a reaction that uses catalytic quantities of minimally toxic, readily available, economic reagent should greatly contribute to the creation of environmentally benign processes. Our results and the facts described above prompted us to investigate a bismuth nitrate-mediated Michael reaction (conjugate reaction) with a wide variety of substrates in a general reaction. This paper describes the development of a new bismuth nitrate-mediated Michael reaction of amines, carbamates, indoles, imidazoles, and thiols with unsaturated ketones for the first time. No other reports in the literature demonstrated methods that are as versatile and general.

Results and Discussion

Bismuth Nitrate-Catalyzed Addition of Amines, Imidazoles, and Thiols to Enones. β-Amino ketones are versatile intermediates for a large number of organic compounds, as exemplified in the preparation of antibiotics, natural products, γ-amino alcohols, and chiral auxiliaries.[12] In addition, they are present as a structural unit in a variety of compounds of biological interest.[13] Other applications of this type of compound are in the fine chemical and pharmaceutical fields.[14] As a result of this vast range of applications, synthesis of β-amino ketones has remained an important objective for a number of years. Acid- or base-induced conjugate addition reaction of unsaturated carbonyl groups to amines has been the method used for this purpose for many years. But because of the many side reactions that result from the presence of strong acids (polymerization of vinyl ketones) or bases in the medium, this method has not been applied in industry or resulted in any practical applications. The most common reaction for the preparation of these types of compounds is by the Mannich reaction, which has also several disadvantages.[15] Therefore, many other attractive methods have been reported. One such elegant method involves the addition of vinyl Grignard reagents.[16] To avoid many of the disadvantages of stoichiometric addition of a Lewis acid-mediated ($AlCl_3$, $SnCl_4$, or $TiCl_4$) conjugate addition reaction, two new methods have appeared in the literature. The first is Michael reaction of amines to enones in the presence of the $CeCl_3 \cdot 7H_2O-NaI$ system supported in silica gel under refluxing conditions.[17] It can produce β-amino ketones and is the most useful known reaction for this purpose. The second method is addition reaction of zinc ester enolates to sulfones.[18]

TABLE 1. Bi(NO)$_3$-Catalyzed Michael Reaction of Enones with Amines and Imidazoles[a]

Entries	Enones	Amines	Products	% yield
1			 **1**[b]	65
2			 **2**[c]	64
3			 **3**[c]	78
4			 **4**	75
5			 **5**	79
6			 **6**	69
7			 **7**	66

[a] Reaction was completed at room temperature within 12−15 h. [b] For the preparation of **1**, see: Greenhill, J. V. *J. Org. Chem.* **1971**, *14*, 971. [c] For the preparation of **2** and **3**, see ref 17.

Our method of bismuth nitrate-catalyzed Michael reaction of enones with amino compounds is very simple and efficient (Table 1, entries 1−5). The starting materials (amines and ketones) are mixed with bismuth nitrate (10 mol %) in dichloromethane, and the solvent is evaporated under reduced pressure while the residual mass is maintained at room temperature for a specified time. Unlike the processes described in previous reports,

(11) Carrigan, M. D.; Sarapa, D.; Smith, R. C.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 1027. Also see: Eash, K. J.; Paulia, M. S.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2000**, *65*, 8399.

(12) (a) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465. (b) Hashiguchi, S.; Kawada, A.; Natsugari, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2435. (c) Senanayake, C. H.; Fang, K.; Grover, P.; Bakale, R. P.; Vandenbassche, C. P.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 819. (d) Genov, M.; Dimitrov, V.; Ivanova, V. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3703. (e) Hayashi, Y.; Rode, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502. (f) Eliel, E. L.; He, X.-C. *J. Org. Chem.* **1990**, *55*, 2114.

(13) Traxler, P.; Trinks, U.; Buchdunger, E.; Mett, H.; Meyer, T.; Muller, M.; Regenass, U.; Rosel, J.; Lydon, N. *J. Med. Chem.* **1995**, *38*, 2441.

(14) (a) Bartoli, G.; Cimarelli, C.; Marcantoni E.; Palmieri, G.; Petrinim, M. *J. Org. Chem.* **1994**, *59*, 5328. (b) Devine, P. N.; Heid, R. M.; Tschaen, D. M. *Tetrahedron* **1997**, *53*, 6739. (c) Graul, A.; Castaner, J.; Castaner, J. *Drugs Future* **1997**, *22*, 956. (d) Angiolini, L.; Bizzarri, P. C.; Scapini, G.; Tramontini, M. *Tetrahedron* **1981**, *37*, 2137.

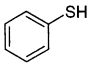
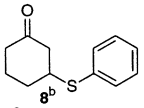
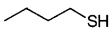
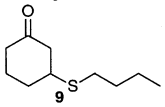
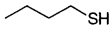
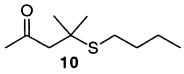
(15) Arend, M.; Westermann, B.; Risch, N. *Angew Chem., Int. Ed. Engl.* **1998**, *37*, 1044.

(16) (a) Gomtsyan, A.; Koening, R. J.; Lee, C. H. *J. Org. Chem.* **2001**, *66*, 3613. (b) Gomtsyan, A. *Org. Lett.* **2000**, *2*, 11.

(17) Bartoli, G.; Bosco M.; Marcantoni, E.; Petrinim, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052.

(18) Petrini, M.; Profeta, R.; Righi, P. *J. Org. Chem.* **2002**, *67*, 4530.

TABLE 2. $Bi(NO)_3$-Catalyzed Michael Reaction of Enones with Thiols[a]

Entries	Enones	Thiols	Products	% yield
1			 **8**[b]	65
2			 **9**	73
3			 **10**	71

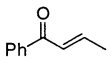
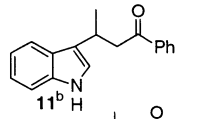
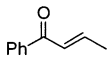
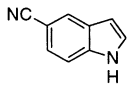
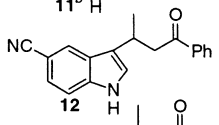
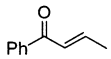
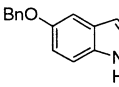
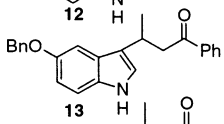
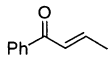
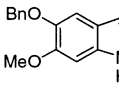
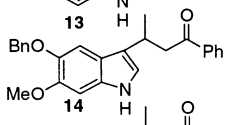
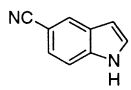
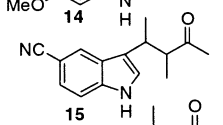
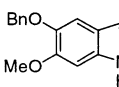
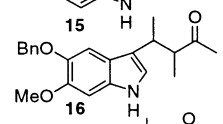
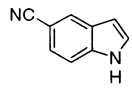
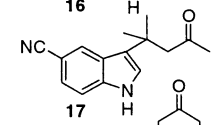
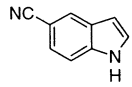
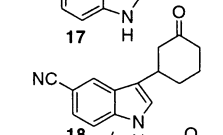
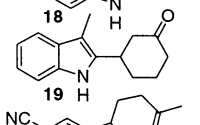
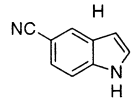
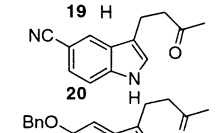
[a] Reaction was completed within 2−4 h at room temperature. [b] For the preparation of **8**, see ref 5a.

this method is totally independent of solvent choice[7] or external proton source.[5a] We have used dichloromethane, tetrahydrofuran, diethyl ether, ethyl acetate, methanol, and acetonitrile without any loss of yield. If one of the reactants is a liquid, the reaction can proceed without using solvent. However, if the reaction mixture is a very thick slurry, the addition of a small amount of any of the above listed solvents is helpful for the success of the reaction. An external proton source is not necessary to promote the reaction. Even ordinary-grade solvents and reagents that are undistilled or unpurified can be used with equal success. Additionally, it has been found that the dibenzylamine (Table 1, entries 2−4) reacts very easily with cyclic and acyclic enones and gives products in high yield. Heterocyclic bases (Table 1, entries 1 and 5) also react with enones, affording products in good yield. Care should be taken in isolating products that are heterocyclic bases from the reaction mixtures, as these products are partially soluble in water or dilute acid used for the extraction, a trend that was observed when one of the reactions was repeated using an already published method.[17] The yield of the product continually decreases with the number of washings with dilute citric acid or water.

The reaction of imidazoles with enones proceeds very nicely under these conditions (Table 1, entries 6 and 7). It is noteworthy that the Michael adducts are formed with imidazoles. Also, attack does not take place at the ring of the imidazoles. Extension of this method with aliphatic and aromatic thiols also gives Michael products in good yield (Table 2, entries 1−3). In our experience, by following our bismuth nitrate-catalyzed method, no electrophilic substitution has been observed when an aromatic thiol is used (Table 2, entry 1).

Bismuth Nitrate-Catalyzed Addition of Indoles to Enones. Our method has been tested with readily available substituted indoles. Indoles are well suited for our program, as several of their derivatives are biologically active. Moreover, indoles can undergo two types of reaction: at NH (Michael reaction) and at C_3 (Michael as well as Friedel−Crafts reactions). Several addition reactions of enones to indoles using Lewis and Bronsted acids have been published.[19] Again, acid-catalyzed reaction of indoles requires careful control of the acidity to prevent unwanted side reactions, including dimerization and polymerization.[20] Recently, in an elegant study, it was shown that indium tribromide mediates the conjugate addition of enones to indoles.[5] However, with less electron-rich indoles, the yield of the products was not satisfactory. In such cases, indium trichloride has proven to be very effective. Our bismuth nitrate-catalyzed reaction has been tested with several indoles, the results of which have been very encouraging (Table 3). Specifically, the reactions are very efficient, and the products are isolated in high yield without the formation of side products, such as dimers or trimers that are normally formed under the influence of strong acids.[5b] Many structurally diverse indoles reacted efficiently with various ketones under bismuth nitrate-catalyzed conditions

TABLE 3. $Bi(NO)_3$-Catalyzed Michael Reaction of Enones with Indoles[a]

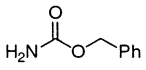
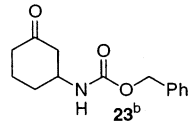
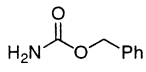
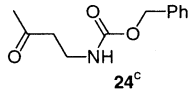
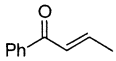
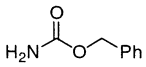
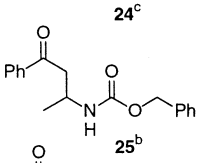
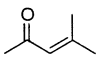
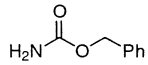
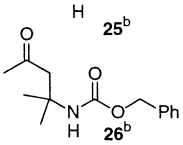
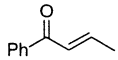
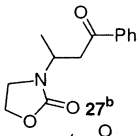
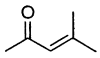
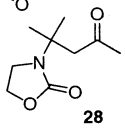
Entries	Enones	Indoles	Products	% yield
1			 **11**[b]	85
2			 **12**	78
3			 **13**	72
4			 **14**	69
5			 **15**	56
6			 **16**	73
7			 **17**	64
8			 **18**	79
9			 **19**	55
10			 **20**	76
11			**21**	71
12			**22**	45

[a] Reaction was completed within 10−15 h at room temperature. [b] For the preparation of **11**, see ref 5a.

(19) (a) Harrington, P. E.; Kerr, M. A. *Can. J. Chem.* **1998**, *76*, 1256. (b) Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047. (c) Iqbal, Z.; Jackson, A. H.; Rao, K. R. N. *Tetrahedron Lett.* **1988**, *29*, 2577. (d) Szmuszkovicz, J. *J. Am. Chem. Soc.* **1957**, *79*, 2819.

(20) (a) Houlihan, W. J. *Indoles*; John Wiley & Sons, Inc.: New York, 1972; Vol. 1, p 71. (b) Iqbal, Z.; Jackson, A. H.; Rao, K. R. *Tetrahedron Lett.* **1988**, *29*, 21.

TABLE 4. $Bi(NO)_3$-Catalyzed Michael Reaction of Enones with Carbamates[a]

Entries	Enones	Carbamates	Products	% Yield
1			 **23**[b]	72
2			 **24**[c]	76
3			 **25**[b]	80
4			 **26**[b]	65
5			 **27**[b]	67
6			 **28**	61

[a] Reaction was completed within 10−15 h. [b] For the preparation of **23**, **25**, **26** and **27**, see ref 7. [c] For the preparation of **24**, see: Wabnitz, T., C.; Spencer, J. B. *Tetrahedron Lett.* **2002**, *43*, 389.

and afford products in high yield. In general, the reactions took place at the 3-position of the indole ring when this position was unoccupied. When the 3-position was occupied by a methyl group, the reaction took place at C_2 positions (Table 3, entries 9 and 12).

Bismuth Nitrate-Catalyzed Addition of Carbamates to Enones. While amines and thiols are moderately nucleophilic, carbamates are very weakly nucleophilic. Therefore, the various acid catalysts that are successfully employed in Michael reactions with amines and thiols have failed to produce products with carbamates. Interestingly, indium chloride, which was the best catalyst for the indole addition reaction, failed to produce any desired compounds with carbamates or unsaturated ketones in a previous study.[7] Most of the conventional Lewis acids showed lower reactivity, and the isolated yield of the products was very low. The most fascinating reaction was the conjugate addition reaction of carbamates with enones, which is mediated by platinum salt.[7] The success of this method depended on the choice of solvents: less polar solvents gave inferior results, while polar solvents gave excellent results. However, the use of solvents such as DMSO, DMF, and THF did not result in a reaction. We were delighted to discover that our bismuth nitrate-catalyzed method was also applicable with carbamates as the reactive partners. Reaction of carbamates with enones proceeded under identical conditions without the bias of any solvents in high yield (Table 4, entries 1−6).

The Role of Bismuth Nitrate. The success of bismuth nitrate-mediated conjugate reactions prompted us to investigate the mechanistic process. Catalytic amounts (10 mol %) of bismuth nitrate are necessary for a complete reaction, an increase in the proportion to 25% produced comparable yields. A further increase does not improve the yield of the product; instead, additional compounds tend to be formed, as evidenced from TLC. The reaction did not proceed at all in the absence of bismuth nitrate, except for the amines (Table 1, entries 1−5), in which case a very slow reaction took place, presumably because of the stronger nucleophilicity of the substrates. But, the reaction did not proceed at all after ca. 50% conversion. Since bismuth nitrate can produce nitric acids, a reaction (Table 3, entry 5) was performed in the presence of nitric acid in various amounts. The nature of the reaction mixtures before work-up in the nitric acid-mediated reaction was clearly different from that in the bismuth nitrate-catalyzed process. However, after extraction of the reaction mixtures, it appeared that nitric acid-mediated reactions also produced products in relatively lower yields. Optimization of the concentration of nitric acid and yield of the product was attempted in various cases. But no definite conclusions or optimization could be drawn from these studies, except that the progress of the reactions with multiple components has been observed in the TLC plate under different acid concentrations. Notably, the reaction proceeds (Table 3, entry 5) with bismuth nitrate in the presence of potassium carbonate (20 mol %). With a higher proportion of potassium carbonate (50 mol %), the rate of the reaction becomes very slow, and a considerable amount of starting materials is recovered after the reaction is terminated. This suggests that there might be a complexation role for bismuth nitrate apart from its acidity, so that acidity may not be the only factor underlying the success of this reaction. To get more specific knowledge, IR and NMR studies were conducted with carbamate and phenyl propynyl ketone (Table 4, entry 3) in the presence and absence of bismuth nitrate in CD_3CN and $CDCl_3$. IR analysis of the mixture showed no changes at all. But it was reported that acetonitrile solution of this carbamate and scandium triflate produced a large shift in the frequency.[7] On the other hand, the ^{13}C and ^1H NMR study also indicated no changes of the chemical shift of the carbamate or ketone (acceptor) in the presence or absence of bismuth nitrate (10 mol %), whereas a large shift was documented when scandium triflate was the catalyst. This clearly suggested that the mode of interaction of the bismuth-mediated process is different from that using oxophilic scandium triflate or indium salts as the catalyst.

To confirm the critical role of bismuth nitrate in this reaction, other salts were tested. Ferric nitrate, zinc nitrate, copper sulfate, sodium nitrate, and ferric chloride proved to be completely ineffective, indicating the critical role of bismuth nitrate in this reaction. However, bismuth trichloride produced product in lower yield (Table 4, entry 3, 20%). The failure of these salts to promote an effective Michael reaction indicates their inability to produce sufficient amounts of acids or a precise coordinating complex (although not observed under the conditions of the experiments) that is critical for the success of this type of reaction. Therefore, we believe that bismuth nitrate has unique characteristics as a catalyst in Michael reactions.

Conclusion

In summary, Michael reactions of various organic compounds with moderate to low nucleophilicities have been successfully carried out in the presence of a catalytic amount of bismuth nitrate. In contrast to the existing methods using many acidic catalysts, this method is very general, simple, high-yielding, environmentally friendly, and oxygen and moisture tolerant. However, the promoting role of bismuth nitrate in this reaction is not understood at this time. Further exploration of the scope of addition reactions with complex structures of biological significance is in progress.

Experimental Section

General Methods. All solvents and reagents were obtained from commercial sources and used without purification. Reactions were monitored by TLC using precoated silica gel aluminum plates containing a fluorescence indicator. Chemical shifts of ^{1}H NMR spectra were given in parts per million with respect to TMS, and the coupling constant J was measured in Hz. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). ^{1}H NMR spectra were recorded in $CDCl_3$ using tetramethylsilane as an internal standard. IR spectra of neat compounds were expressed as wavenumbers (cm^{-1}).

Experimental Procedures. For a small-scale reaction, the following procedure was followed. Bismuth nitrate (100 mg, 0.2 mmol) was added to a mixture of dibenzylamine (200 mg, 1.36 mmol) and ketone (200 mg, 1.36 mmol) in dichloromethane (2 mL). Dichloromethane was then removed under reduced pressure, and the reaction mixture was kept at room temperature for the specific time as indicated in Tables 1−4. Dichloromethane (20 mL) was added to the reaction mixture, and it was filtered through filter paper to remove bismuth nitrate. The filtrate was washed with saturated $NaHCO_3$ (2 × 10 mL) and brine solution (1 × 10 mL) and dried over Na_2SO_4. The extracts were then concentrated, and the crude product was purified using flash chromatography on silica gel column eluent 30% EtOAc−70% in hexane as the eluent to give pure compound. An identical procedure was followed in other cases as described in Tables 1−4. The yield of the products was almost identical when the same amount of methanol, ethanol, diethyl ether, acetonitrile, and toluene was used as the solvent instead of dichloromethane.

For a relatively large-scale reaction (5−10 g), a different experimental procedure was adopted. If one of the reactants was liquid, the experiment was conducted without using solvent. However, if the reaction mixture was a very thick slurry, the addition of a small amount (1 g of the substrates/1 mL solvent) of any of the above solvents was necessary for the success of the reaction. However, care should be taken when mixing these reactants with solid bismuth nitrate (20 mol %) with vigorous stirring. When the reaction was over (TLC, approximately 2−24 h), during the next step it was necessary to extract the reaction mixture with dichloromethane as described above. There was no difference in yield when the reactions were performed under these experimental conditions.

3-(*N*-Dibenzylamino)-1-phenylbutan-1-one (4): yield 295 mg, 75%; IR (neat) 3364, 2800, 1673, 1624, 1597, 1579, 1524, 1494, 1448, 1363, 1330, 1291, 1218 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, J = 6 Hz, 3 H, CH_3), 2.85 (dd, J_1 = 8.3 Hz, J_2 = 14.3 Hz, 1 H, CH_2), 3.25 (dd, J_1 = 5.8 Hz, J_2 = 14.3 Hz, 1 H, CH_2), 3.43−3.54 (m, 3 H, CH and CH_2), 3.69 (d, J = 12 Hz, 2 H, CH_2), 7.19−7.29 (m, 12 H, ArH), 7.35 (m, 1 H, ArH), 7.81 (m, 2 H, ArH); ^{13}C NMR (75 MHz) δ 14.9, 43.7, 51.4, 53.4, 53.6, 54.0, 127.2, 127.4, 128.6, 128.7, 128.8, 128.9, 129.0, 133.2, 137.4, 140.3, 140.8, 199.9. Anal. Calcd for $C_{24}H_{25}NO$ (343.47): C, 83.93; H, 7.34; N, 4.08. Found: C, 83.48; H, 7.08; N, 4.02.

3-(*N*-Thiomorpholino)-1-phenylbutan-1-one (5): yield 308 mg, 79%; mp 88−90 °C; IR (neat) 2961, 2913, 2813, 1680, 1596, 1580, 1449, 1409, 1376, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, J = 6 Hz, 3 H, CH_3), 2.58 (m, 4 H, CH_2), 2.78−2.91 (m, 5 H, 2 × CH_2 and 1 H), 3.24 (dd, J_1 = 5.4 Hz, J_2 = 15.0 Hz, 1 H, CH_2), 3.29−3.34 (m, 1 H, CH_2), 7.44−7.59 (m, 3 H, ArH), 7.91−7.94 (m, 2 H, ArH); ^{13}C NMR (75 MHz) δ 15.5, 28.8, 42.6, 51.4, 58.3, 128.4, 128.9, 133.2, 137.8, 200.0. Anal. Calcd for $C_{14}H_{19}NSO$ (249.378): C, 67.43; H, 7.68; N, 5.62. Found: C, 67.07; H, 7.23; N, 5.40.

3-(*N*-Imidazolo)-1-phenylbutan-1-one (6): yield 202 mg, 69%; IR (neat) 3356, 3113, 2979, 2936, 1681, 1597, 1580, 1499, 1449, 1411, 1366, 1288 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (d, J = 6 Hz, 3 H, CH_3), 3.33 (dd, J_1 = 6.6 Hz, J_2 = 17.4 Hz, 1 H, CH_2), 3.49 (dd, J_1 = 6.6 Hz, J_2 = 17.4 Hz, 1 H, CH_2), 4.93−5.04 (m, 1 H, CH), 7.0 (d, J = 15 Hz, 2 H, ArH), 7.44−7.48 (m, 2 H, ArH), 7.59−7.61 (m, 2 H, ArH), 7.87−7.90 (m, 2 H, ArH); ^{13}C NMR (75 MHz) δ 21.8, 46.4, 49.1, 127.9, 128.7, 133.6,, 136.3, 196.3. Anal. Calcd for $C_{13}H_{14}N_2O$ (214.268): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.40; H, 6.12; N, 12.99.

3-(*N*-Imidazolo)-cyclohexan-1-one (7): yield 225 mg, 66%; IR (neat) 3383, 2955, 2127, 1704, 1659, 1501, 1415 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (m, 1 H, CH), 2.09−2.15 (m, 2 H, CH_2), 2.35−2.48 (m, 3 H, CH_2), 2.74−2.80 (m, 2 H, CH_2), 4.37−4.44 (m, 1 H, CH), 6.99 (m, 1 H, ArH), 7.09 (m, 1 H, ArH), 7.57 (brs, 1 H, ArH); ^{13}C NMR (75 MHz) δ 22.2, 32.8, 40.8, 49.1, 55.9, 117.1, 130.1, 135.5, 207.0. Anal. Calcd for $C_9H_{12}N_2O$ (164.208): C, 65.83; H, 7.37; N, 17.06. Found: C, 65.54; H, 7.23; N, 16.96.

3-(Butylthiol)cyclohexan-1-one (9): yield 282 mg, 73%; IR (neat) 2956, 2931, 2871, 1710, 1447, 1420, 1379, 1342, 1314, 1276, 1220, 1175 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3 H, CH_3), 1.42 (m, 2 H, CH_2), 1.55 (m, 2 H, CH_2), 1.72 (m, 2 H, CH_2), 2.13 (m, 2 H, CH_2), 2.35 (m, 3 H, CH_2 and CH), 2.55 (t, J = 6 Hz, 2 H, CH_2), 2.70 (m, 1 H, CH), 3.10 (m, 1 H, CH); ^{13}C NMR (75 MHz) δ 13.9, 22.4, 24.6, 30.6, 32.0, 32.1, 41.3, 43.1, 48.6, 209.2. Anal. Calcd for $C_{10}H_{18}SO$ (186.319): C, 64.46; H, 9.74. Found: C, 64.08; H, 9.65.

4-(Butylthiol)-4-methylpentan-2-one (10): yield 271 mg, 71%; IR (neat) 3417, 2930, 2873, 1709, 1464, 1378, 1355, 1196, 1174, 1122 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.92 (t, J = 7.16, 3 H, CH_3), 1.35−1.50 (m, 8 H, 2 × CH_3 and CH_2) 1.57 (q, 2 H, CH_2), 2.19 (s, 3 H, CH_3), 2.51(t, J = 7.16, 2 H, CH_2), 2.68, (s, 2 H, CH_2); ^{13}C NMR (75 MHz) δ 14.0, 22.2, 28.1, 28.8, 31.9, 32.6, 43.6, 55.0, 207.2. Anal. Calcd for $C_{10}H_{20}SO$ (188.335): C, 63.77; H, 10.70. Found: C, 63.58; H, 10.25.

3-(5-Cyano-3-indolyl)-1-phenylbutan-1-one (12): yield 307 mg, 78%; mp 136−139 °C; IR (neat) 3335, 2964, 2218, 1676, 1618, 1597, 1579, 1472, 1448, 1355, 1279 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (d, J = 6 Hz, 3 H, CH_3), 3.27 (dd, J_1 = 7.8 Hz, J_2 =16.5 Hz, 1 H, CH_2) 3.41 (dd, J_1 = 6 Hz, J_2 = 16.5 Hz, 1 H, CH_2), 3.77−3.88 (m, 1 H, CH), 7.14 (d, J = 3 Hz 1 H, ArH), 7.40−7.56 (m, 5 H, ArH), 7.91−7.94 (m, 2 H, ArH), 8.01 (s, 1 H, ArH), 8.3 (brs, 1 H, NH); ^{13}C NMR (75 MHz) δ 21.8, 27.3, 46.6, 102.7, 112.5, 121.2, 122.7, 122.8, 125.3, 126.6, 128.4, 129.0, 133.5, 137.4, 138.5, 199.5. Anal. Calcd for $C_{19}H_{16}N_2O$ (288.350): C, 79.14; H, 5.59; N, 9.71. Found: C, 78.99; H, 5.75; N, 9.50.

3-(5-Benzyloxy-3-indolyl)-1-phenylpropan-1-one (13): yield 363 mg, 72%; IR (neat) 3410, 2961, 1677, 1623, 1579, 1480, 1449, 1374, 1279 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4 1 (d, 6 Hz, 3 H, CH_3), 3.18 (dd, J_1 = 8.7 Hz, J_2 = 16.5 Hz, 1 H, CH_2) 3.39 (dd, J_1 = 5.0 Hz, J_2 = 16.5 Hz, 1 H, CH_2), 3.70−3.81 (m, 1 H, CH), 5.08 (s, 2 H, OCH_2), 6.90−6.94 (m, 2 H, ArH), 7.15−7.55 (m, 10 H, ArH), 7.90−7.93 (m, 3 H, ArH and NH); ^{13}C NMR (75 MHz) δ 20.8, 26.9, 46.3, 70.9, 102.8, 111.9, 112.7, 121.0, 121.1, 126.6, 127.6, 127.7, 128.1, 128.2, 128.4, 128.5, 131.8, 132.9, 137.2, 137.6, 152.8, 199.8. Anal. Calcd for $C_{25}H_{23}NO_2$ (369.464): C, 81.27; H, 6.27; N, 3.79. Found: C, 81.07; H, 6.33; N, 3.67.

3-(5-Benzyloxy-6-methoxy-3-indolyl)-1-phenylbutan-1-one (14): yield 377 mg, 69%; IR (neat) 3410, 1679, 1481, 1313,

1199 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J = 6 Hz, 3 H, CH_3), 3.17 (dd, J_1 = 8.8 Hz, J_2 = 16.2 Hz, 1 H, CH_2), 3.29 (dd, J_1 = 4.9 Hz, J_2 = 16.2 Hz, 1 H, CH_2), 3.66−3.72 (m, 1 H, CH), 3.87 (s, 3 H, OMe), 5.14 (s, 2 H, OCH_2), 6.84−6. 86 (m, 2 H, ArH), 7.09 (s, 1 H, ArH) 7.24−7.30 (m, 3 H, ArH), 7.42−7.49 (m, 5 H, ArH), 7.88−7.91 (m, 3 H, 2 ArH and 1 NH); ^{13}C NMR (75 MHz) δ 18.2, 27.0, 46.3, 53.4, 71.9, 72.2, 95.2, 104.9, 118.8, 119.0, 121.0, 127.5, 127.6, 127.8, 128.0, 128.3, 128.5, 128.6, 131.4, 133.1, 136.8, 137.2, 137.6, 143.4, 147.7, 199.8. Anal. Calcd for $C_{26}H_{25}NO_3$ (399.490): C, 78.17; H, 6.31; N, 3.51. Found: C, 78.01; H, 6.12; N, 3.31.

4-(5-Cyano-3-indolyl)-3-methylpentan-2-one (15): yield 274 mg, 56%; mp 128−130 °C; IR (neat) 3336, 2969, 2219, 1698, 1618, 1471, 1356, 1232, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J = 6 Hz, 3 H, CH_3), 1.32 (d, J = 6 Hz, 3 H, CH_3), 2.19 (s, 3 H, $COCH_3$), 2.90−2.95 (m, 1 H, CH), 3.27−3.32 (m, 1 H, CH), 7.13 (d, J = 2.7 Hz, 1 H, ArH), 7.43 (d, J = 1.2 Hz, 2 H, Ar H), 8.02 (brs, 1 H, ArH), 8.4 (brs, 1 H, NH); ^{13}C NMR (75 MHz) δ 16.3, 20.3, 29.0, 34.2, 52.9, 102.8, 112.6, 120.7, 123.8, 125.2, 125.4, 126.9, 138.4, 213.1. Anal. Calcd for $C_{15}H_{16}N_2O$ (240.306): C, 74.97; H, 6.71; N, 11.66. Found: C, 74.61; H, 6.52; N, 11.43.

4-(5-Benzyloxy-6-methoxy-3-indolyl)-3-methylpentan-2-one (16): yield 522 mg, 73%; IR (neat) 3374, 2963, 1700, 1632, 1547, 1480, 1313 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 6 Hz, 3 H, CH_3), 1.22 (d, J = 6 Hz, 3 H, CH_3), 2.07 (s, 3 H, $COCH_3$), 2.73−2.83 (m, 1 H, CH), 3.10−3.18 (m, 1 H, CH), 3.91 (s, 3 H, $COCH_3$), 5.18 (s, 2 H, OCH_2) 6.82 (d, J = 2.4 Hz, 1 H, ArH), 6.88 (s, 1 H, ArH), 7.27−7.48 (m, 4 H, ArH), 7.48−7.50 (m, 2 H, ArH) 7.84 (brs, 1 H, NH); ^{13}C NMR (75 MHz) δ 15.9, 19.6, 29.4, 34.1, 53.3, 56.3, 72.4, 95.0, 105.6, 119.2, 119.5, 119.7, 127.6, 127.6, 128.4, 131.3, 137.7, 143.4, 147.9, 213.5. Anal. Calcd for $C_{22}H_{25}NO_3$ (351.446): C, 75.19; H, 7.17; N, 3.98. Found: C, 74.98; H, 7.12; N, 3.85.

4-(5-Cyano-3-indolyl)-4-methylpentan-2-one (17): yield 313 mg, 64%; IR (neat) 3339, 2219, 1695, 1472, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 6 H, 2 CH_3) 1.84 (s, 3 H, $COCH_3$), 2.95 (s, 2 H, CH_2), 7.06 (d, J = 2.4 Hz, 1 H, ArH), 7.40 (d, J = 3 Hz, 2 H, ArH), 8.14 (brs, 1 H, ArH), 8.60 (brs, 1 H, NH); ^{13}C NMR (75 MHz) δ 28.9, 31.9, 34.2, 54.7, 102.3, 112.4, 120.8, 122.8, 124.6, 124.6, 125.2, 126.2, 138.8, 208.1. Anal. Calcd for $C_{15}H_{16}N_2O$ (240.306): C, 74.97; H, 6.71; N, 11.66. Found: C, 74.65; H, 6.53; N, 11.55.

3-(5-Cyano-3-indolyl)cyclohexan-1-one (18): yield 391 mg, 79%; IR (neat) 3324, 2940, 2218, 1698, 1617, 1472, 1429, 1344, 1224, 1344, 1224 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92−2.05 (m, 3 H), 2.23−2.30 (m, 1 H), 2.43−2.48 (m, 2 H, CH_2), 2.64−2.68 (m, 1 H, CH), 2.76−2.77 (m, 1 H) 3.43−3.48 (m, 1 H, CH), 7.03 (q, 1 H, ArH), 7.44 (d, 2 H, J = 1.2 Hz, ArH), 7.98 (brs, 1 H, ArH), 8.51 (brs, 1 H, NH); ^{13}C NMR (75 MHz) δ 25.0, 32.1, 35.9, 41.8, 48.1, 102.9, 112.6, 120.8, 123.1, 125.1, 125.5, 126.4, 138.5, 211.6. Anal. Calcd for $C_{15}H_{14}N_2O$ (238.290): C, 75.61; H, 5.92; N, 11.76. Found: C, 75.47; H, 5.58; N, 11.71.

3-(3-Methyl-2-indolyl)cyclohexan-1-one (19): yield 260 mg, 55%; IR (neat) 3407, 2940, 1702, 1463, 1344 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89−1.96 (m, 2 H, CH_2), 2.13−2.18 (m, 2 H, CH_2), 2.25 (s, 3 H, CH_3), 2.50−2.66 (m, 4 H, 2 x CH_2), 3.38−3.37 (m, 1 H, CH), 6.91−7.16 (m, 2 H, ArH), 7.29−7.32 (m, 1 H, ArH), 7.51 (d, J = 6 Hz, 1 H, ArH), 7.80 (brs, 1 H, NH); ^{13}C NMR (75 MHz) δ 8.8, 25.8, 31.9, 36.8, 41.7, 47.6, 107.1, 110.8, 118.7, 119.7, 121.9, 129.5, 135.5, 136.3, 210.8. Anal. Calcd for $C_{15}H_{17}NO$ (227.307): C, 79.26; H, 7.54; N, 6.16. Found: C, 79.19; H, 7.58; N, 6.01.

4-(5-Cyano-3-indolyl)butan-2-one (20): yield 467 mg, 76%; mp 108−112 °C; IR (neat) 3338, 2919, 2218, 1706, 1619, 1473, 1434, 1359, 1230 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3 H, $COCH_3$), 2.84 (t, J = 6 Hz, 2 H, CH_2), 3.02 (t, J = 6 Hz, 2 H, CH_2), 7.11−7.12 (m, 1 H, ArH), 7.41−7.42 (m, 2 H, ArH), 7.90 (brs, 1 H, ArH), 8.29 (brs, 1 H, NH); ^{13}C NMR (75 MHz) δ 102.8, 112.4, 116.6, 121.1, 124.1, 124.8, 125.3, 127.5, 127.5, 129.2, 131.3, 138.2. Anal. Calcd for $C_{13}H_{12}N_2O$ (212.252): C, 73.56; H, 5.70; N, 13.20. Found: C, 73.29; H, 5.48; N, 13.11.

4-(5-Benzyloxy-3-indolyl)butan-2-one (21): yield 603 mg, 71%; IR (neat) 3407, 3032, 2915, 1705, 1624, 1582, 1482, 1374, 1292, 1197 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (s, 3 H, CH_3), 2.78−2.83 (t, J = 9 Hz, 2 H, CH_2), 2.97−3.02 (t, J = 6 Hz, 2 H, CH_2) 5.12 (s, 2 H, OCH_2), 6.91−6.94 (m, 2 H, ArH), 7.10 (d, J = 2.4, 1 H, ArH), 7.22−7.41 (m, 6 H, ArH), 7.48 (m, 2 H, ArH), 7.80 (brs, 1 H, NH); ^{13}C NMR (75 MHz) δ 19.7, 30.4, 44.3, 71.4, 102.8, 112.2, 113.28, 115.3, 122.7, 127.9, 128.0, 128.1, 128.9, 131.2, 138.0, 153.5, 209.1. Anal. Calcd for $C_{19}H_{19}NO_2$ (293.366): C, 77.79; H, 6.53; N, 4.77. Found: C, 77.39; H, 6.34; N, 4.61.

4-(3-Methyl-2-indolyl)butan-2-one (22): yield 262 mg, 45%; IR (neat) 3407, 2400, 1714, 1605, 1455, 1360, 1166 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 2.82 (t, J = 6.6 Hz, 2 H, CH_2), 2.98 (t, J = 6.6 Hz, 2 H, CH_2), 7.05−7.11 (m, 2 H, ArH), 7.25−7.27 (m, 1 H, ArH), 7.45−7.48 (d, J = 9 Hz, 1 H, ArH), 8.29 (brs, 1 H, NH); ^{13}C NMR (75 MHz) δ 8.7, 19.7, 30.4, 44.0, 107.0, 110.7, 118.4, 119.2, 121.5, 129.3, 134.6, 135.5, 209.7. Anal. Calcd for $C_{13}H_{15}NO$ (201.269): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.39; H, 7.59; N, 6.71.

4-(*N*-Oxazolidinyl)-4-methylpentan-2-one (28): yield 230 mg, 61%; IR (neat) 3451, 2980, 2920, 1728, 1539, 1483, 1415, 1365, 1247, 1173 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 6 H, 2 x CH_3), 2.13 (s, 3 H, CH_3), 3.14 (s, 2 H, CH_2), 3.68 (m, 2 H, CH_2), 4.23 (m, 2 H, CH_2); ^{13}C NMR (75 MHz) δ 26.4, 31.3, 43.7, 50.3, 53.6, 61.4, 157.1, 207.1. Anal. Calcd for $C_9H_{15}NO_3$ (185.223): C, 58.36; H, 8.16; N, 7.56. Found: C, 58.13; H, 7.99; N, 7.09.

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