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Sequential Addition Reactions of Two Molecules of Grignard Reagents to Thioformamides

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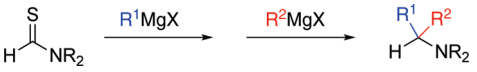


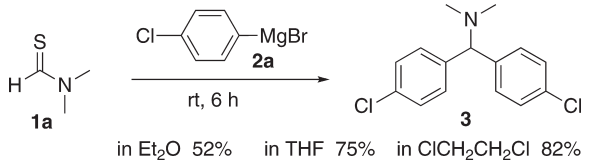
Sequential addition reactions of two molecules of Grignard reagents to thioformamides were found to yield tertiary amines in an efficient manner. The addition of two different Grignard reagents can be accomplished by using one equivalent of arylmagnesium reagent in the first step. In the second step, a variety of reagents such as alkyl, alkenyl, aryl, and alkynyl reagents were used to afford the corresponding amines in good to high yields.

The development of synthetic methods for the construction of more than two carbon−carbon bonds in a single operation, termed multiple-component coupling reactions,[1] is of great importance in the field of organic synthesis. Implementation of these processes leads to a reduction of the number of steps involved in a preparative route and, consequently, to minimization of the amounts of solvents and purification procedures employed. For the synthesis[2] of tertiary arylmethylamines[3] and tertiary propargylamines,[4] methods employing a combination of aldehydes, secondary amines, and various organometallic reagents have been explored. These processes involve addition of a single organometallic reagent to an intermediate iminium ion. In contrast, we recently described highly efficient addition reactions of organo-lithium and −magnesium reagents to thioiminium and selenoiminium salts, and thioformamides that lead to the formation of tertiary amines.[5] In these processes, two different nucleophiles are sequentially added to the electrophiles in a single operation. Similar reactions of nitriles with organocerium reagents and of thiolactams with organolithium and -cerium reagents have also been developed.[6] We envisioned that by using a combination of two different Grignard reagents,[7] as coupling partners, thioformamides would undergo transformations as part of a valuable procedure for tertiary amine synthesis since Grignard reagents are among the most readily available organometallic reagents and more readily available than organolithium reagents. However, the use of two different Grignard reagents in one vessel results in the formation of several products with no selectivity.

Below, we present the results of an investigation that has led to the development of a methodology for preparation of tertiary amines that employs the addition reaction of two of the same or different Grignard reagents to thioformamides.

In order to explore the possibility that two molecules of a Grignard reagent could be sequentially added to thioformamides, an excess of 4-chlorophenylmagnesium bromide (**2a**) was combined with *N*,*N*-dimethylthioformamide (**1a**) at room temperature (Scheme 1). The double addition of **2a** to **1a** proceeds smoothly in Et_2O or THF to form tertiary amine **3** in a moderate yield. Importantly, the efficiency of this process is enhanced by the use of dichloroethane as a solvent.

SCHEME 1. Double Addition of Grignard Reagent 2a to Thioformamide 1a



The broad scope of this methodology was demonstrated by using a range of thioformamides **1** and Grignard reagents **2** (Table 1). In these processes, *N*-thioformylmorpholine (**1b**), *N*-arylmethyl and *N*-Boc *N*-formylpiperazines **1c**−**1f**,[8] and optically active *N*-allyl-*N*-1-phenethyl thioformamide (**1 g**)[8]

(1) For reviews (a) *Multicomponent Reactions*; Zhu, J.; Bienaymé, H. Eds.; Wiley-VCH: Weinheim, 2005. (b) Ganem, B. Acc. Chem. Res. 2009, 42, 463.
(2) For a review Kouznetsov, V. V.; Méndez, L. Y. V. *Synthesis* **2008**, 491.
(3) For recent examples (a) Gall, E. L.; Troupel, M.; Nédélec, J.-Y. *Tetrahedron* **2006**, *62*, 9953. (b) Yadav, J. S.; Subba Reddy, B. V.; Lakshmi, P. N. *J. Mol. Cat. A* **2007**, *274*, 101. (c) Sengmany, S.; Gall, E. L.; Troupel, M. *Synlett* **2008**, 1031. (d) Tanaka, Y.; Hasui, T.; Suginome, M. *Synlett* **2008**, 1239. (e) Font, D.; Heras, M.; Villalgordo, J. M. *Tetrahedron* **2008**, *64*, 5226.
(4) For recent examples (a) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529. (b) Gommermann, N.; Knochel, P. *Chem.—Eur. J.* **2006**, *12*, 4380. (c) Reddy, K. M.; Babu, N. S.; Suryanarayana, I.; Prasad, P. S. S.; Lingaiah, N. *Tetrahedron Lett.* **2006**, *47*, 7563. (d) Sharifi, A.; Mirzaei, M.; Naimi-Jamal, M. R. *J. Chem. Res.* **2007**, 129. (e) Ramu, E.; Varala, R.; Sreelatha, N.; Adapa, S. R. *Tetrahedron Lett.* **2007**, *48*, 7184. (f) Kantam, M. L.; Balasubrahmanyam, V.; Kumar, K. B. S.; Venkanna, G. T. *Tetrahedron Lett.* **2007**, *48*, 7332. (g) Likhar, P. R.; Roy, S.; Roy, M.; Subhas, M. S.; Kantam, M. L.; De, R. L. *Synlett* **2007**, 2301. (h) Sreedhar, B.; Reddy, P. S.; Krishna, C. S. V.; Babu, P. V. *Tetrahedron Lett.* **2007**, *48*, 7882. (i) Gommermann, N.; Knochel, P. *Org. Synth.* **2007**, *84*, 1. (j) Maggi, R.; Bello, A.; Oro, C.; Sartori, G.; Soldi, L. *Tetrahedron* **2008**, *64*, 1435. (k) Kantam, M. L.; Laha, S.; Yadav, J.; Bhargava, S. *Tetrahedron Lett.* **2008**, *49*, 3083. (l) Zhang, X.; Corma, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4358. (m) Madhav, J. V.; Kuarm, B. S.; Someshwar, P.; Rajitha, B.; Reddy, Y. T.; Crooks, P. A. *Synth. Comun.* **2008**, *38*, 3215. (n) Omote, M.; Eto, Y.; Tarui, A.; Sato, K.; Ando, A. *Tetrahedron: Asymmetry* **2009**, *20*, 602. (o) Chen, W.-W.; Nguyen, R. V.; Li, C.-J. *Tetrahedron Lett.* **2009**, *50*, 2895.

(5) (a) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968. (b) Murai, T.; Toshio, R.; Mutoh, Y. *Tetrahedron* **2006**, *62*, 6312. (c) Murai, T.; Asai, F. *J. Am. Chem. Soc.* **2007**, *129*, 780. (d) Murai, T.; Nogawa, S.; Mutoh, Y. *Bull. Soc. Chem. Jpn.* **2007**, *80*, 2220. (e) Murai, T.; Asai, F. *J. Org. Chem.* **2008**, *73*, 9518.
(6) (a) Ciganek, E. *J. Org. Chem.* **1992**, *57*, 4521. (b) Agosti, A.; Britto, S.; Renaud, P. *Org. Lett.* **2008**, *10*, 1417.
(7) For reviews, see (a) *Main Group Metals in Organic Synthesis*; Yamamoto, H.; Oshima, K. Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1. (b) Handbook of Functionalized Organometallics; Knochel, P. Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1.
(8) New thioformamides **1d**, **1e** and **1g** were prepared by thionation of the corresponding formamides with Lawesson's reagents, see Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, 1929.

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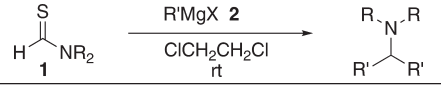
TABLE 1. Double Addition of Grignard Reagents 2 to Thioformamides 1[a]

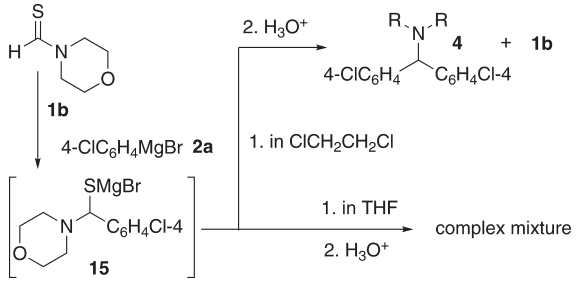


Entry	NR_2 **1**	**2**	Time	Product Yield[b]
1	**1b**	4-ClC_6H_4MgBr **2a**	1 h	**4** 75%
2	**1b**	MgBr **2b**	1 h	**5** 76%
3	**1b**	MgCl **2c**	6 h	**6** 64%
4	**1b**	Ph—≡—MgBr **2d**	1 h	**7** 99%
5	**1b**	*n*-BuMgCl **2e**	1 h	**8** 95%
6	**1b**	MgBr **2f**	1 h	**9**, 82%
7	**1c** Bn	4-$Me_2NC_6H_4MgBr$ **2g**	1 h	**10** 84%
8	**1d** $CH_2C_6H_4OMe$-4	4-FC_6H_4MgBr **2h**	1.5 h	**11** 79%
9	**1e** $CH_2C_6H_2(OMe)_3$-2,3,4	**2h**	6 h	**12** 92%
10	**1f** Boc	**2g**	1 h	**13** 63%
11	**1g**	**2b**	2 h	**14** 92%

[a] A THF solution of thioformamides **1** (1 mmol) was treated with Grignard reagents **2** (2.0−3.0 equiv) at rt in $ClCH_2CH_2Cl$.

are used along with alkyl- (**2e**), allyl- (**2b** and **2c**), alkynyl- (**2d**) and aryl- (**2a**, **2g** and **2h**) Grignard reagents. Solutions of the Grignard reagents in either Et_2O or THF are added to room temperature dichloroethane solutions of the thioformamides. The resulting mixtures are stirred at room temperature until TLC analysis shows that the reactions are complete. Sequential additions of 1-methyl-2-propenylmagnesium bromide (**2c**) to the thioformamide **1b** take place selectively at the methyl-substituted allylic carbon of **2c** to produce amine **6** as a

SCHEME 2. Reaction of 1b (1 equiv) with 2a (1 equiv)



diastereomeric mixture (entry 3). In addition, the 3-amino-1,4-diyne **7**[9] is quantitatively formed (entry 4) by using this method. No significant decrease in the efficiency of this process is observed when arylmangesium bromides **2a**, **2g**, and **2h**, containing both electron-donating and −withdrawing substituents on the aromatic rings (entries 1, 7−10) are employed. A combination of 4-FC_6H_4MgBr (**2h**) and *N*-2,3,4-trimethoxyphenylmethyl-*N*'- thioformylpiperazine (**1e**) leads to the production of lomerizine (**12**),[10] a substance known to have calcium antagonist and antimigraine properties (entry 9).[12]

Our attention next turned to addition reactions in which two different Grignard reagents are added to thioformamides. As an initial test of this process, reaction of 1 equivalent of **2a** with **1b** was carried out using $ClCH_2CH_2Cl$ as solvent (Scheme 2).

Analysis of the product mixture showed that it contained near equal amounts of tertiary amine **4** and starting thioformamide **1b.** This observation indicates that, in the initial stage of this process, reaction of the intermediate **15** with **2a** is faster than that with **1b**. Various solvents were explored in order to determine if the rate of addition of **2a** to **1b** rather than **15** could be enhanced. Importantly, reaction in THF followed by aqueous workup leads to production of a complex product mixture that does not contain tertiary amine **4**.

This result suggests that addition of **2a** to **1b** is faster than that to **15** in THF and that **15** undergoes a complex array of reactions under the aqueous workup conditions.

A variety of combinations of two different Grignard reagents were employed in reactions with thioformamide **1b** in THF (Table 2).[11] The process involving initial addition of **2a** followed by addition of allylmagnesium bromide (**2b**) leads to efficient production of the amine **16** (entry 1). Significantly, products arising by addition of two molecules of **2a** or **2b** are not formed in detectable amounts in this reaction. In contrast, addition of these Grignard reagents to **1b** in a reverse sequence (i.e., **2b** first and then **2a**) leads to generation of **16** in 11% yield along with **5** (45%) and **4** (20%) derived from addition of two molecules of **2b** and **2a**, respectively (entry 2). This finding suggests that the less reactive Grignard reagent should be added in the first step in sequential addition reactions at this stage. The generality of this process, was probed by adding a variety of

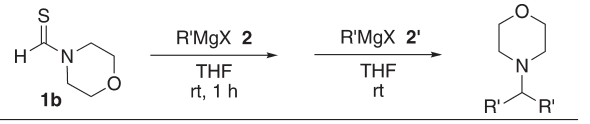
(9) Amine **7** was previously obtained in moderate yield by reacting the thioiminium salt derived from **1b** and zinc acetylide Murai, T.; Mutoh, Y.; Ohta, Y. *Tetrahedron. Lett.* **2005**, *46*, 3637.

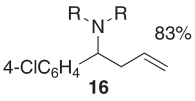
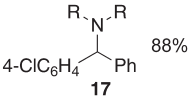
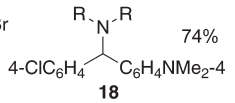
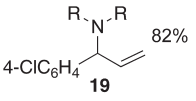
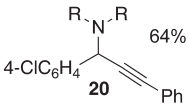
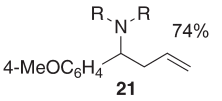
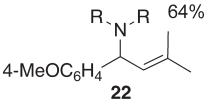
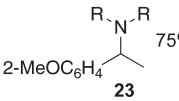
(10) Hara, H.; Toriu, N.; Shimazawa, M. *Cardiovascular Drug Rev.* **2004**, *22*, 199.

(11) Very recently, Me_3SiCl-mediated double addition of Grignard reagents to formamides in the presence of a catalytic amount of $Ti(OPr\text{-}i)_4$ has been reported. For the use of two different Grignard reagents, the corresponding amines were formed in at most 60% yield Tomashenko, O.; Sokolov, V.; Tomashevskiy, A.; Buchholz, H. A.; Welz-Biermann, U.; Chaplinski, V.; de Meijere, A. *Eur. J. Org. Chem.* **2008**, 5107.

(12) *Handbook of Grignard Reagents*; Silverman, G. S.; Rakita, P. Eds.; Dekker: New York, 1996; p. 645.

TABLE 2. Addition Reaction of Two Different Grignard Reagents 2 to Thioformamide 1b[a]



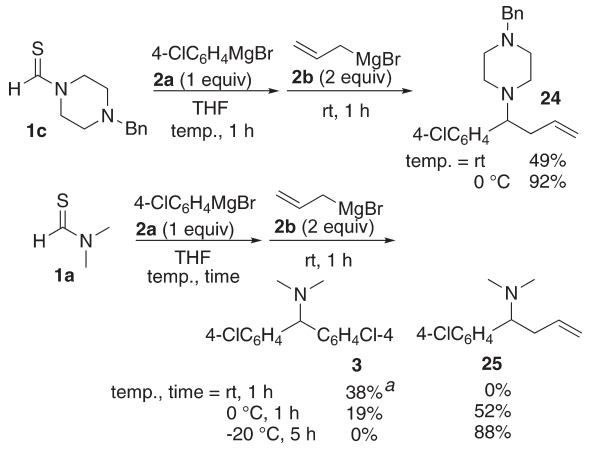
Entry	2	2'	Product[b]	Yield[c]
1	4-ClC$_6$H$_4$MgBr **2a**	MgBr **2b**	 **16**	83%
2	MgBr **2b**	4-ClC$_6$H$_4$MgBr **2a**	**16**	11%
3	4-ClC$_6$H$_4$MgBr **2a**	PhMgBr **2i**	 **17**	88%
4	4-ClC$_6$H$_4$MgBr **2a**	4-Me$_2$NC$_6$H$_4$MgBr **2g**	 **18**	74%
5	4-ClC$_6$H$_4$MgBr **2a**	MgCl **2j**	 **19**	82%
6	4-ClC$_6$H$_4$MgBr **2a**	Ph—≡—MgBr **2d**	 **20**	64%
7	Ph—≡—MgBr **2d**	4-ClC$_6$H$_4$MgBr **2a**	**20**	35%
8	4-MeOC$_6$H$_4$MgBr **2k**	MgBr **2b**	 **21**	74%
9	4-MeOC$_6$H$_4$MgBr **2k**	MgBr **2f**	 **22**	64%
10	2-MeOC$_6$H$_4$MgBr **2l**	MeMgBr **2m**	 **23**	75%

[a] A THF solution of thioformamides **1** (1 mmol) was treated with Grignard reagents **2** (1 equiv) and **2'** (2.0−3.0 equiv) at rt in THF.

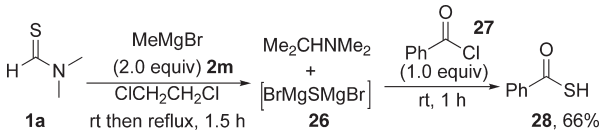
Grignard reagents to mixtures generated by the reaction of equimolar amounts of **1b** and **2a** at room temperature. Reactions, in which phenyl- (**2i**), 4-dimethylaminophenyl- (**2g**), vinyl- (**2j**), and phenylethynyl-magnesium (**2d**) were used as the second reagent, produce the corresponding amines **17**−**20** (entries 3−6). Reaction of **1b** with a combination of **2a** and **2d**, in which **2d** is added first, forms amine **20** in only a moderate yield (entry 7). The reactivity of these two reagents **2a** and **2d** toward electrophiles is not simply compared since **2d** may be less reactive than **2a** on the basis of the acidity of pK_a of the parent hydrocarbons.[12] Nevertheless, these results have suggested that the use of aromatic Grignard reagents in the first step leads to the desired products with high efficiency.

Reactions of thioamide **1b**, in which combinations of 4-methoxy- and 2-methoxy-phenylmagnesium reagents **2k** and **2 L** with allyl- (**2b**), 2-methyl-1-propenyl- (**2f**), and methyl- (**2m**) magnesium bromides are employed, lead to highly efficient formation of the corresponding amines **21**−**23** (entries 8−10).

SCHEME 3. Addition Reaction of Grignard Reagents 2a and 2b to Thioformamides 1a and 1c



SCHEME 4. Reaction of 26 with 27



In the process described above, dimagnesium sulfides that can be formulated as [XMgSMgX, X = Cl, Br] are formed as byproducts via the elimination of an SMgX group.[13] Based on the previously described reaction of [BrMgSMgBr] (**26**),[14] generated from EtMgBr and H_2S, with alkyl halides, these sulfides should be good thiolating and thionating agents. As a matter of fact, byproduct **26**, derived from reaction of **1a** with excess **2m**, reacts with benzoyl chloride (**27**) followed by aqueous workup to give thiobenzoic acid (**28**) in good yield (Scheme 4).

In summary, sequential addition reactions of two molecules of Grignard reagents with thioformamides have been investigated. The observations made in this effort show that the use of aromatic reagents in the first step[15] enables

(13) The reactions where OMgX and OLi groups formally work as a leaving group have been reported. For examples, see (a) Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2004**, *6*, 3929. (b) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Wu, Z.-Z. *Org. Lett.* **2005**, *7*, 2865. (c) Kabalka, G. W.; Yao, M.-L.; Borella, S. *Org. Lett.* **2006**, *8*, 879. (d) Kabalka, G. W.; Yao, M.-L.; Borella, S. *J. Am. Chem. Soc.* **2006**, *128*, 11320. (e) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Goins, L. K. *Organometallics* **2007**, *26*, 4112. (f) Fuchter, M. J.; Levy, J.-N. *Org. Lett.* **2008**, *10*, 4919.

(14) Nedugov, A. N.; Pavlova, N. N. *Z. Org. Khim.* **1991**, *28*, 1401.

(15) The use of alkyl and vinylic Grignard reagents as the first reagents resulted in the formation of the mixture of the desired products derived from the addition of two different Grignard reagents and the products derived from the double addition of identical Grignard reagents. The reaction at lower temperatures slightly improved the selectivity, but further optimization of the reaction is still necessary.

efficient addition of two different Grignard reagents as part of processes that produce tertiary amines bearing chiral secondary alkyl groups. The efficiencies of sequential reactions of thioformamides, in which the first Grignard reagent used displays high reactivity, can be controlled by using low reaction temperatures. Further development of this multicomponent coupling methodology, using thiocarbonyl compounds as key substrates, is underway.

Experimental Section

***N*-[1-(4-Dichlorophenyl)-2-propenyl]morpholine (16).** To a solution of thioformylmorpholine (**1b**) (0.262 g, 2.0 mmol) in THF (3.0 mL) was added slowly 0.89 M solution of 4-chlorophenylmagnesium bromide (**2a**) in Et_2O (2.25 mL, 2.0 mmol) at room temperature, and the mixture was stirred at this temperature for 1 h. To this was added 1.0 M solution of allylmagnesium bromide (**2b**) in Et_2O (4.0 mL, 4.0 mmol) at room temperature, and the mixture was stirred at this temperature for 1 h. The resulting mixture was poured into a saturated aqueous solution of NH_4Cl, and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/EtOAc/Et_3N = 5: 1: 0.01) to afford the amine **16** (0.420 g, 83%) as a yellow oil; IR (neat) 2852, 1640, 1490, 1410, 1119, 1014, 841, 541, 411 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34−2.39 (m, 4H), 2.44−2.66 (m, 2H), 3.47 (ddt, J = 17.1, 7.1, 4.9 Hz, 1H), 3.67 (t, J = 4.6 Hz, 4H), 4.91−4.95 (m, 2H), 5.50−5.60 (m, 1H), 7.18 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 37.1, 51.0, 67.2, 69.6, 117.1, 117.5, 128.4, 130.0, 135.0, 139.0; MS (EI) m/z 251 (M^+); HRMS (EI) Calcd for $C_{11}H_{13}ClNO$ ($M^+ - C_3H_5$) 210.0680. Found: 210.0660.

***N*-[1-(4-Methoxyphenyl)-3-butenyl]morpholine (21).** To a solution of thioformylmorpholine (**1b**) (0.262 g, 2.0 mmol) in THF (3.0 mL) was added slowly 0.89 M solution of 4-methoxyphenylmagnesium bromide (**2k**) in THF (4.0 mL, 2.0 mmol) at room temperature, and the mixture was stirred at this temperature for 3 h. To this was added 0.56 M solution of allylmagnesium bromide (**2b**) in Et_2O (5.4 mL, 4.0 mmol) at room temperature, and the mixture was stirred at this temperature for 1 h. The resulting mixture was poured into a saturated aqueous solution of NH_4Cl, and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/EtOAc/Et_3N = 1: 1: 0.01) to afford the amine **21** (0.364 g, 74%) as a yellow oil; IR (neat) 2908, 1607, 1512, 1347, 1030, 986, 920, 827, 641, 576 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35−2.45 (m, 4H), 2.49−2.62 (m, 2H), 3.24 (t, J = 4.9 Hz, 1H), 3.65 (t, J = 4.6 Hz, 4H), 3.78 (s, 3H), 4.88−4.95 (m, 2H), 5.58 (ddt, J = 15.1, 10.2, 6.8 Hz, 1H), 6.83 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 37.2, 51.0, 55.2, 67.2, 69.6, 113.5, 116.5, 129.7, 132.1, 135.7, 158.7; MS (EI) m/z 247 (M^+); HRMS (EI) Calcd for $C_{15}H_{21}NO_2$ (M^+) 247.1567. Found: 247.1580.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.