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Intramolecular Aldol Reaction of N-Acylated (2-Aminophenyl)-α-oxoacetic Acids: Rapid Access to Tri- and Tetracyclic 1,2-Dihydroquinolin-2(1*H*)-ones

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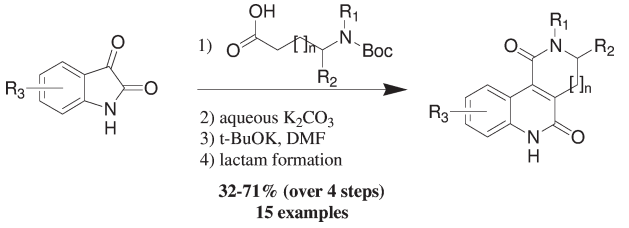

A four-step synthesis of tri- and tetracyclic 1,2-dihydroquinolin-2(1*H*)-ones via acylation of various substituted isatins with readily available *N*-Boc-protected amino-acids followed by an intramolecular aldol reaction and cyclization has been developed. The final products were obtained in moderate to excellent overall yields.

Heterocycles are among the most prevalent lead molecules for the discovery of novel therapeutics. For example, 4-carboxyl substituted quinolines are present in an array of biologically active compounds and have been explored for potential pharmaceutical applications.[1] Many of these compounds have been shown to inhibit therapeutically relevant enzymes as well as to modulate the activity of various cellular receptors. For example, substituted 4-carboxyl-quinolines were reported as potent antagonists of tachykinin NK_2 and NK_3 receptors, thus potentially being useful as analgesic or antiarthritic agents.[2] This class of molecules has also displayed

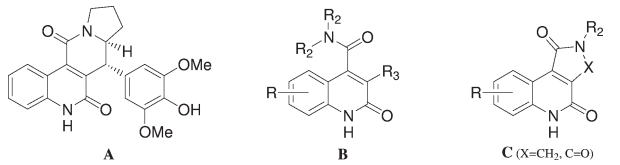

FIGURE 1. Biologically active 4-carboxylquinoline derivatives.

neuroprotective, antistroke, and anticancer activities.[3] Quinoline-4-carboxamides were also described as serotonin 5-HT_3 antagonists, as inhibitors of caspase-3 and AChE, and as antimalarial agents.[4] Tri- and tetracyclic quinolines that display antiproliferative activities, caspase-3 inhibition, or 5-HT_3 affinity have also been reported.[3a,4] In addition, isaindigotidione, **A** (Figure 1), is a recently identified tetracyclic 1,2-dihydroquinolin-2(1*H*)-one natural product isolated from the herbaceous plant *Isatis indigotica* indigenous to China's Changjiang river valley.[5]

The synthesis of indolizino[7,6-*c*]quinoline derivates, such as **A**, using an intramolecular aldol reaction of glyoxylamides has been reported.[6] Several synthetic strategies for the preparation of substituted 2-oxo-1,2-dihydroquinoline-4-carboxamides **B** have also been described. However, the synthesis of tricyclic derivatives **C** has remained less explored.[4a,c] Unfortunately, many of the reported methods for the synthesis of **C** suffer from several disadvantages, including requiring large excess of reagents, and are only applicable to generating fused five-membered rings. Herein is reported a versatile method for the synthesis of tri- and tetracyclic 1, 2-dihydroquinolin-2(1*H*)-ones.

A retrosynthetic analysis for **1** is outlined in Scheme 1, where **1** is obtained from **2** via cyclization. In turn, **2** can be prepared by intramolecular aldolisation of N-acylated (2-aminophenyl)-α-oxoacetic acids **3**, which are obtained from isatins and N-protected aminoacids **4**. *tert*-Butylcarbamate protection of the aminoacids was chosen because it could be readily removed during lactam formation under acidic condition.

In order to avoid using an excess of acid to affect isatin acylation,[7] the reaction was initially attempted with a mixed anhydride. However, the desired acylation was followed by nucleophilic attack of the isobutyl carbonate byproduct to give **5** in 71% yield (Scheme 2). Presumably this reaction resulted from the nucleophilic nature of carbonates[8] and

(1) (a) Giardina, G. A.; Raveglia, L. F.; Grugni, M.; Sarau, H. M.; Farina, C.; Medhurst, A. D.; Graziani, D.; Schmidt, D. B.; Rigolio, R.; Luttmann, M.; Cavagnera, S.; Foley, J. J.; Vecchietti, V.; Hay, D. W. *J. Med. Chem.* **1999**, *42*, 1053. (b) Suzuki, F.; Nakasato, Y.; Tsumuki, H.; Ohmori, K.; Nakajima, H.; Tamura, T.; Sato, S. U.S. Patent 5371225, 1993; *Chem. Abstr.* **1994**, *120*, 217318. (c) Deady, L. W.; Desneves, J.; Kaye, A. J.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. *Bioorg. Med. Chem.* **2000**, *8*, 977. (d) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627.

(2) (a) Yan, H.; Kerns, J. K.; Jin, Q.; Zhu, C.; Barnette, M. S.; Callahan, J. F.; Hay, D. W. P.; Jolivette, L. J. *Synth. Commun.* **2005**, *35*, 3105. (b) Farina, C.; Gagliardi, S.; Giardina, G.; Grugni, M.; Martinelli, M.; Nadler, G. WO 0238547, 2002; *Der. Abst. C* **2002**, 454769.

(3) (a) Tseng, C. H.; Chen, Y. L.; Lu, P. J.; Yang, C. N.; Tzeng, C. C. *Bioorg. Med. Chem.* **2008**, *16*, 3153. (b) Ivachtchenko, A. V.; Kobak, V. V.; Ilyn, A. P.; Khvat, A. V.; Kysil, V. M.; Williams, C. T.; Kuzovkova, J. A.; Kravchenko, D. V. *J. Comb. Chem.* **2005**, *7*, 227.

(4) (a) Capelli, A.; Anzini, M.; Vomero, S.; Mennuni, L.; Makovec, F.; Doucet, E.; Hamon, M.; Menziani, C. M.; De Benedetti, P. G.; Giorgi, G.; Ghelardini, C.; Collina, S. *Bioorg. Med. Chem.* **2002**, *10*, 779. (b) Hayashi, H.; Miwa, Y.; Miki, I.; Ichikawa, S.; Yoda, N.; Ishii, A.; Kono, M.; Suzuki, F. *J. Med. Chem.* **1992**, *35*, 4893. (c) Kravchenko, D. V.; Kuzovkova, Y. A.; Kysil, V. M.; Tkachenko, S. E.; Maliarchouk, S.; Okun, I. M.; Balakin, K. V.; Ivachtchenko, A. V. *J. Med. Chem.* **2005**, *48*, 3680. (d) Cappelli, A.; Gallelli, A.; Manini, M.; Anzini, M.; Mennuni, L.; Makovec, F.; Menziani, M. C.; Alcaro, S.; Ortuso, F.; Vomero, S. *J. Med. Chem.* **2005**, *48*, 3564. (e) Xiao, Z.; Waters, N. C.; Woodard, C. L.; Li, Z.; Li, P. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2875.

(5) Wu, X.; Qin, G.; Cheung, K. K.; Cheng, K. F. *Tetrahedron* **1997**, *53*, 13323.

(6) Poon, C. Y.; Chiu, P. *Tetrahedron Lett.* **2004**, *45*, 2985.

(7) (a) Bursavich, M. G.; Lombardi, S.; Gilbert, A. M. PCT Int. Appl. WO 2007146138, **2007**. (b) Rajamanickam, P.; Shanmugam, P. *Synthesis* **1985**, *5*, 541.

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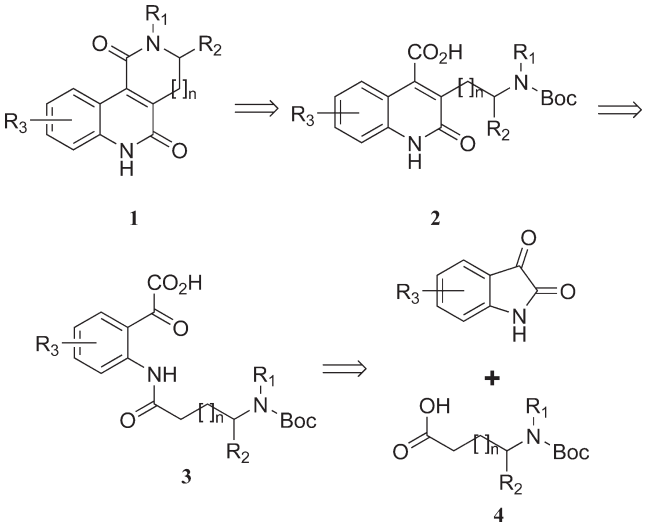
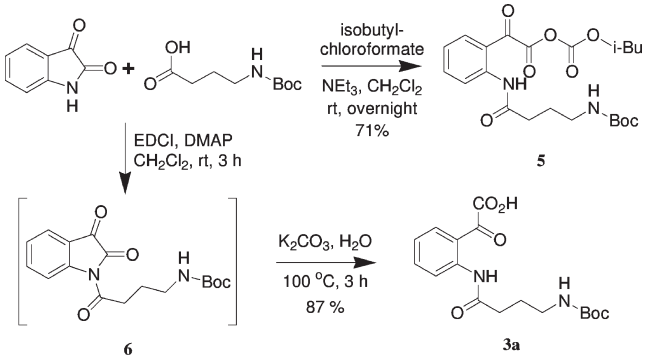
SCHEME 1. Retrosynthetic Analysis of Tri- or Tetracyclic 1,2-Dihydroquinolin-2(1*H*)-ones 1



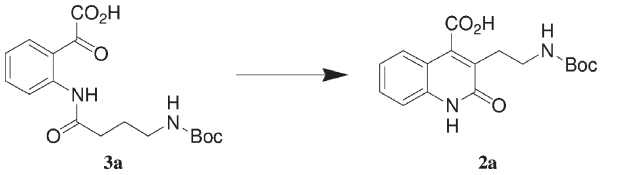
SCHEME 2



N-acylated isatin's susceptibility to nucleophilic attack.[9] Several other acylation strategies were explored, including use of the corresponding acid chloride or pentafluorophenol ester,[10] or using various coupling agents (i.e., HBTU, HATU, and BOP), but all failed to give the desired product **6**.[11] Finally, successful acylation was accomplished with EDCI. However, the N-acylated isatin **6** was difficult to purify and therefore was treated with aqueous potassium carbonate at 100 °C for 1 h, generating **3a** in excellent yield (87%).

Next, the aldol cyclization of **3a** to give **2a** was studied by examining various reaction parameters, including the nature and quantity of base, solvent, and temperature. Utilizing conditions described in the literature for the synthesis of 3-alkyl-4-carboxyquinolinones (NaOH, H_2O, 100 °C, 5 h)[12,4b] gave only trace amounts of **2a** (Table 1, entry 1). No cyclized product was obtained with organic bases such as NEt_3 or DBU (entries 2 and 3). Likewise, stronger bases such as NaH or *t*-BuOK in THF were not effective (entries 4 and 5). However, when these bases were used in DMF or DMA, **2a** was obtained (entries 6, 7, and 10). However, in solvents such as 1,4-dioxane or CH_3CN, yields generally were lower (entries 8 and 9).

TABLE 1. Optimization of the Aldol Reaction



entry	base	equiv of base	solvent	temp (°C), time (h)	yield[a] (%)
1	NaOH	2	H_2O	100, 12	trace
2	NEt_3	2	DMF	80, 4	0
3	DBU	2	DMF	80, 4	0
4	NaH	2	THF	60, 2	0
5	*t*-BuOK	2	THF	60, 2	0
6	NaH	2	DMF	80, 4	49[b]
7	*t*-BuOK	2	DMA	80, 4	67
8	*t*-BuOK	2	CH_3CN	80, 4	53[b]
9	*t*-BuOK	2	dioxane	80, 4	33[b]
10	*t*-BuOK	2	DMF	80, 4	77
11	*t*-BuOK	1	DMF	80, 4	0
12	*t*-BuOK	3	DMF	80, 4	88
13	*t*-BuOK	4	DMF	80, 4	53
14	*t*-BuOK	3	DMF	rt, 72	24
15	*t*-BuOK	3	DMF	60, 4	70
16	*t*-BuOK	3	DMF	100, 4	81

[a]Isolated yield. [b]Conversions determined by HPLC.

Next, the quantity of base required for cyclization was examined. No reaction was observed with 1 equiv of *t*-BuOK (entry 11). The highest yield was obtained with 3 equiv of *t*-BuOK (entry 12), whereas further increasing the quantity of base did not improve the yield (entry 13). Finally, the reaction temperature was also determined to be important with 80 °C being best (entries 12, 14−16). In summary, the aldol reaction of **3a** to give **2a** was optimal with *t*-BuOK (3 equiv) in DMF for 4 h at 80 °C.

With the optimized conditions identified, the scope of the reaction with respect to the aminoacid substrate was examined. Acylation and aldol reaction of the corresponding N-acylated isatins showed remarkable tolerance to a range of aminoacids with markedly different steric and electronic properties (Table 2, entries 1−13). For example, using various β-, γ-, δ-, or ε-*N*-Boc-protected aminoacids resulted in the generation of **2** in moderate to high yields. With some *N*-Boc-protected secondary aminoacids or an anilino acid, slightly lower yields were obtained (entries 6, 8, 10−12). Aminoacids containing substituents on the β- or γ-position of the aliphatic chain were also tolerated in the aldol reaction (entries 9−12).

The last step for the synthesis of tri- or tetracyclic 1,2-dihydroquinolin-2(1*H*)-ones was lactam formation. Three different methods were used, depending on the substrate. The first method required an initial deprotection of the N-protected carbamate with TFA followed by EDCI-mediated cyclization (Table 2, method A). The other two methods involved direct one-pot processes. For example, method

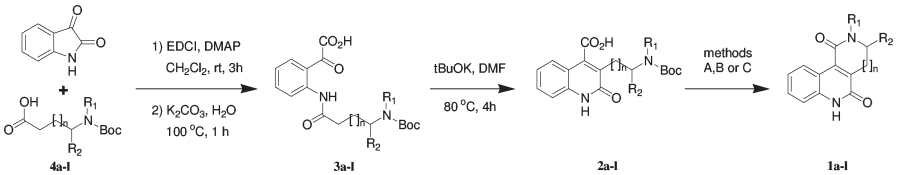
(9) (a) Bergman, J.; Engqvist, R.; Stalhandske, C.; Wallberg, H. *Tetrahedron* **2003**, *59*, 1033. (b) Cheah, W. C.; Black, D. StC.; Goh, W. K.; Kumar, N. *Tetrahedron Lett*. **2008**, *49*, 2965.

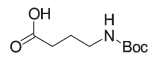
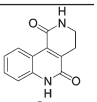
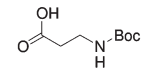
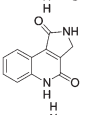
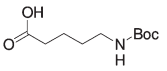
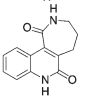
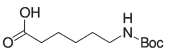
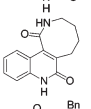
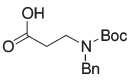
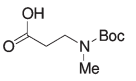
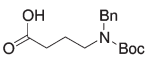
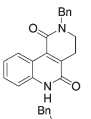
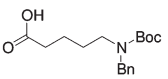
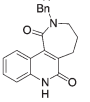
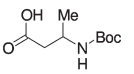
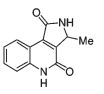
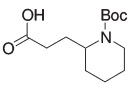
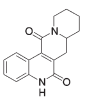
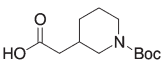
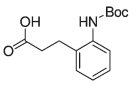
(10) (a) Luppi, G.; Galeazzi, R.; Garavelli, M.; Formaggio, F.; Tomasini, C. *Org. Biomol. Chem*. **2004**, *2*, 2181. (b) Ramesh, R.; Rajasekaran, S.; Gupta, R.; Chandrasekaran, S. *Org. Lett*. **2006**, *8*, 1933. (c) Gopinath, K. W.; Govindachari, T. R.; Rajappa, S. *Tetrahedron* **1960**, *8*, 291.

(11) For acid chlorides or pentafluorophenol esters only the corresponding hydrolyzed acids were recovered. For the other coupling reagents the HOBt byproduct formed during acid activation appeared to be more nucleophilic than isatins leading to acylated HOBt products.

(12) Lyle, R. E.; Portlock, D. E.; Kane, M. J.; Bristol, J. A. *J. Org. Chem*. **1972**, *37*, 3967.

TABLE 2. Substrate Scope of Aminoacids 4a−l



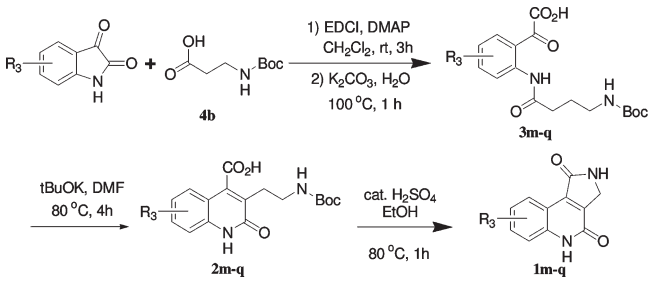
entry		Aminoacid (4a-l)	Yield[a] (%) 3a-l	2a-l	1a-l	Method[b]		Final Product
1	**4a**		87	88	57 0 0	A B C	**1a**	
2	**4b**		91	89	32 80 0	A B C	**1b**	
3	**4c**		83	68	0	A, B, C	**1c**	
4	**4d**		81	63	0	A, B, C	**1d**	
5	**4e**		92	87	89	C	**1e**	
6	**4f**		91	66	38 83 0	A B C	**1f**	
7	**4g**		89	76	80 0 92	A B C	**1g**	
8	**4h**		83	53	73	C	**1h**	
9	**4i**		81	63	78	B	**1i**	
10	**4j**		83	67	86	C	**1j**	
11	**4k**		75	56	75	C	**1k**	
12	**4l**		73	67	71	C	**1l**	

B simply involved refluxing the substrate in ethanol in the presence of a catalytic amount of sulfuric acid. In method C the substrate was heated at 80 °C in neat sulfonyl chloride.

γ-Lactams **1b**, **1f** and **1i** were obtained in good yields using method B (entries 2, 6, and 9). In contrast, **1b** was obtained in only 32% yield using method A, and no cyclization was observed with method C. Surprisingly, when the terminal nitrogen was substituted with a benzyl group, **1e** was obtained in 89% yield using method C (entry 5). Concerning δ-lactam synthesis, **1a** and **1g** were obtained using method A in 57% and 80% yields, respectively (entries 1 and 7). However, method C was more efficient for **1g** (entry 7). The syntheses of seven- or eight-membered ring lactams starting from primary amines were unsuccessful (entries 3 and 4). Nevertheless, when the terminal nitrogen was substituted with a benzyl group, lactam formation was performed using method C generating **1h** in 73% yield (entry 8). Method C was also useful to synthesize tetracyclic quinolinones **1j**, **1k**, and **1l** in good yields (entries 10−12).

To further study the scope of this overall process, the effect of substituents on the aromatic ring of the isatin was briefly examined. Both electron-withdrawing and electron-donating

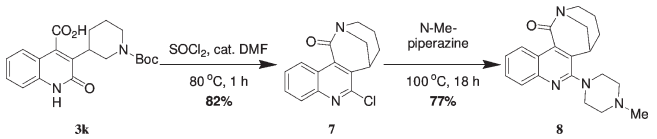
TABLE 3. Substrate Scope of Isatins



			yield[a] (%)		
entry	R_3		**3**	**2**	**1**
1	4-Cl	**m**	91	62	0
2	5-Cl	**n**	94	73	80
3	6-Cl	**o**	90	74	78
4	7-Cl	**p**	0		
5	5-OMe	**q**	88	58	81

[a]Isolated yield.

SCHEME 3



substituents in either the 5- or 6-positions of the isatin were tolerated (Table 3, entries 2, 3, and 5). However, introduction of a chlorine in the 4-position of the isatin prevented cyclization to the corresponding γ-lactam (entry 1), whereas introduction of the chlorine at the 7-position of the isatin did not permit the initial N-acylation (entry 4). Presumably steric hindrance was responsible for both of these effects.

Interestingly, addition of a catalytic amount of DMF to the reaction solution during lactamization using method C gave the expected lactam but also resulted in the concomitant conversion of the 2-quinolone to the corresponding 2-chloroquinoline. For example, treatment of **3k** utilizing these alternate conditions gave **7** in 82% yield (Scheme 3). This material upon treatment with *N*-methylpiperazine underwent a nucleophilic aromatic substitution to generate **8** in 77% yield.

In summary, an efficient approach to the synthesis of tri- and tetracyclic quinolin-2(1*H*)-ones has been developed by exploiting an intramolecular aldol reaction of N-acylated (2-aminophenyl)-α-oxoacetic acids followed by lactam formation. Substrates for this sequence of reactions are readily available or can be easily prepared. This methodology provided access to various substituted tri- and tetracyclic quinolin-2(1*H*)-ones, including a bicyclic analogue. These compounds can be used for various applications, including screening for biological activities. The utilization of this methodology for the synthesis of additional tri- and tetracyclic quinolin-2(1*H*)-ones, including **A**, are currently under development.

Experimental Section

General Procedure for the Synthesis of 3a−q. Under argon, isatin (1 equiv) was added to **4a-l** (1.2 equiv) in CH_2Cl_2 (6 mL/mmol of isatin) at 0 °C, followed by EDCI (1.2 equiv) and DMAP (0.1 equiv). The reaction was maintained at room temperature for 3 h. The solvent was removed in vacuo, and then the mixture was diluted in EtOAc (20 mL/mmol) and washed with HCl (1 N, 5 mL), satd $NaHCO_3$ (2 × 5 mL), and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered, evaporated, and concentrated. To this material was added water (10 mL/mmol) following by K_2CO_3 (2 equiv), and the mixture was heated at 100 °C for 1 h. After cooling to 0 °C, the reaction was acidified with HCl (1 N). The aqueous solution was extracted with EtOAc (2 × 20 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by chromatography on silica gel (3 to 20% MeOH in CH_2Cl_2) to yield a yellow solid.

General Procedure for the Synthesis of 2a−q. To a solution under argon of **3a−q** (1 equiv) in DMF (10 mL/mmol) was added *t*-BuOK (3 equiv). The mixture was heated to 80 °C for 4 h. After cooling to 0 °C, HCl (1 N) was added until pH 3. The solution was extracted with EtOAc (2 × 20 mL). The organic layers were combined, washed twice with 10% aqueous LiCl (5 mL) and brine, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by chromatography on silica gel (5−20% MeOH in CH_2Cl_2 + AcOH 0.5%) to yield a yellow solid.

2,3,4,6-Tetrahydro-benzo[*c*][2,6]naphthyridine-1,5-dione (1a). A solution of **2a** (0.5 mmol) in CH_2Cl_2/TFA (1:1 v/v) was stirred at room temperature for 30 min. The solvent was removed. Then the crude product was dissolved in DMF (5 mL/mmol), and EDCI (1.2 equiv) was added, following by NEt_3 (2 equiv). The reaction was stirred at room temperature for 24 h. The solvent was removed, and the crude product was dissolved in MeOH. SiO_2 (5 g) was added, and then the mixture was evaporated to dryness before purification by silica gel chromatography (2−5% MeOH in CH_2Cl_2 + AcOH 1%) to yield a white powder (61 mg, 57%). ^{1}H NMR (DMSO-d_6) δ: 12.06 (s, 1H), 8.82 (d, J = 8.0 Hz, 1H), 8.33 (s, 1H), 7.47 (t, J = 8.5 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 3.23 (t, J = 7.5 Hz, 2H), 2.75 (t, J = 7.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ: 163.7, 160.5, 137.9, 134.5, 133.1, 129.4, 127.0, 121.8, 116.5, 115.3, 37.7, 22.5; HRMS (MALDI-TOF) calcd for $C_{12}H_{11}N_2O_2$ $[M + H]^+$: 215.0815. Found: 215.0820.

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Supporting Information Available: Compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.