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Microwave-Assisted Synthesis of New Polysubstituted Dienaminoesters and Their Cyclization to 3-Bromo-2(1*H*)-Pyridinones

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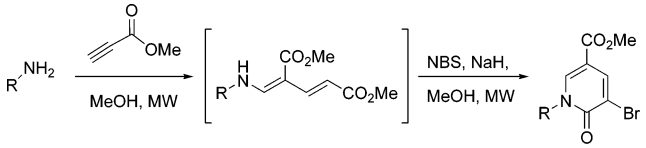

1 2 3

A microwave-assisted, telescoped synthesis, involving a Michael-type addition followed by intramolecular cyclization, provides an effective entry to the polysubstituted 3-bromo-2(1*H*)-pyridinone core.

With increasing frequency, molecules possessing a 3-bromo-2(1*H*)-pyridinone ring system, such as that represented by **3**, are being evaluated as useful platforms in natural product synthesis[1] and are of particular interest as potential therapeutics.[2] Furthermore, the 3-bromo-2(1*H*)-pyridinone core is a common template utilized for the synthesis of a wide variety of nitrogen heterocycles such as pyridine, piperidine, quinolizidine, and indolizidine alkaloids.[3]

Several methods have been developed for the synthesis of these compounds which include, among others,[4−6] oxidation of pyridinium salts to produce the corresponding 2-pyridinones,[4a] cycloaddition of 2(1*H*)-pyrizinones with (m)ethyl propynoate to give amino-substituted pyridinone derivatives,[5] and intramolecular vinylketene cyclizations onto the C=N bond of nitrogen heteroaromatics to provide access to ring-fused pyrid-5-ones.[6a] Although useful, most of these methods have limited substrate scope, require harsh reaction conditions, and often require several steps. The most general approach for accessing substituted 2-pyridinones is from acyclic starting materials which often incorporate a Michael addition as the key synthetic step.[7] However, these methods are not general for the preparation of halogenated or N-substituted 2(1*H*)-pyridinones which are essential for further elaboration of the 2(1*H*)-pyridinone core.[8]

To the best of our knowledge, only one method has been reported in the literature describing the synthesis of halogenated N-substituted 2(1*H*)-pyridinones starting from acyclic substrates. Dechoux and co-workers recently reported a synthetic route to this class of compounds which centered on a Michael-type addition between an amine and a methyl propiolate followed by bromocyclization of the ensuing *δ*-dienaminoester (Scheme 1).[9] This method was demonstrated with benzyl amine substrates and required long reaction times (ca. 48 h). As such, an extension of this methodology for the preparation of polysubstituted 3-bromo-2(1*H*)-pyridinones that facilitates functional group variation on the pyridone nucleus, as well as reduced reaction times, is highly desirable.

Herein, we report that a variety of *δ*-dienaminoesters were prepared via microwave-assisted Michael-type additions employing methyl propiolate and a variety of amines. In addition to providing access to diene derivatives, the products can be easily telescoped and transformed into polysubstituted 3-bromo-2(1*H*)-pyridinones **3** via microwave-assisted bromocyclization (Scheme 2).[10]

The effect of microwave heating on the aforementioned Michael-type addition was hoped to show a reduction in reaction times from the previously reported 2 days to minutes. Table 1 shows the variation in time (min), temperature (°C), and equivalents of methyl propiolate (**5**) tested to find the optimum conditions for the microwave-assisted reaction. The initial conditions (entry 1) did not fully convert all of the starting materials to *δ*-dienaminoester, and instead, they resulted in a mixture of *δ*-dienaminoester (**6**)/enaminoester (**7**) addition products in a ratio of 1:2.[11] Prolonged reaction times (entries 2 and 3) resulted in a modest improvement of the ratio to 2:1. The use of 2.5 equiv of methyl propiolate and systematically increasing the reaction temperature from 80 to 110 °C resulted in higher ratios of *δ*-dienaminoester formation (entries 4−7).

(1) (a) Wagenaar, M. M.; Gibson, D. M.; Clardy, J. *Org. Lett.* **2002**, *4*, 671. (b) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691.

(2) Pierce, J. B.; Ariyan, Z. S.; Ovenden, G. S. *J. Med. Chem.* **1982**, *25*, 131.

(3) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. In *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1996; Vol. 5.

(4) (a) Decker, H. *Chem Ber.* **1892**, *25*, 443 (b) Sieburth, S. M.; Hiel, G.; Lin, C. H.; Kuan, D. P. *J. Org. Chem.* **1994**, *59*, 80. (c) Comins, D. L.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 2819. (d) Schmidhauser, J. C.; Khouri, F. F. *Tetrahedron Lett.* **1993**, *34*, 6685. (e) Sieburth, S. M.; Chen, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 8163.

(5) (a) Tutonda, M. G.; Vandenberghe, S. M.; Van Aken, K. J.; Hoornaert, G. J. *J. Org. Chem.* **1992**, *57*, 2935. (b) Padwa, A.; Sheehan, S. M.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 8648.

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(7) (a) Aggarwal, V.; Singh, G.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 214. (b) Datta, A.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1990**, *55*, 5589. (c) Chuit, C.; Corriu, R. J. P.; Perz, R.; Reye, C. *Tetrahedron* **1986**, *42*, 2293. (d) Cainelli, G.; Panunzio, M.; Giacomini, D.; Di Simone, B.; Camerini, R. *Synthesis* **1994**, 805. (e) Marcoux, J. F.; Marcotte, F. A.; Wu, J.; Dormer, P. G.; Davies, I. W.; Hughes, D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 4194.

(8) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, *508.* (b) Choi, W. B.; Houpis, I. N.; Churchill, H.; Molina, O.; Lynch, J. E.; Volante, R. P.; Reider, P. J.; King, A. O. *Tetrahedron Lett.* **1995**, *36*, 4571. (c) Houpis, I. N.; Choi, W. B.; Reider, P. J.; Molina, O.; Churchill, H.; Lynch, J. E.; Volante, R. P. *Tetrahedron Lett.* **1994**, *35*, 9355. (d) Domagala, J. M. *J. Heterocycl. Chem.* **1984**, *21*, 1705.

(9) Agami, C.; Dechoux, L.; Hebbe, D.; Moulinas, J. *Synthesis* **2002**, *1*, 79.

(10) For cyclizations of dehalogenated *δ*-dienaminoesters, see: (a) Cocco, M. T.; Congiu, C.; Maccioni, A.; Onnis, V. *Synthesis* **1992**, 371. (b) Palacios, F.; Garcia, J.; Ochoa de Retana, A.; Oyarzabal, J. *Heterocycles* **1995**, *41*, 1915.

(11) Dienaminoesters of type **6** were first reported by Bottomley who observed that an excess of methyl propiolate reacted with primary amines at 100 °C to give diadducts by a two-stage mechanism proceeding via an enaminoester (**7**). See: (a) Bottomley, W. *Tetrahedron Lett.* **1967**, *21*, 1997. (b) Bottomley, W.; Phillips, J. N.; Wilson, J. G. *Tetrahedron Lett.* **1967**, *31*, 2957.

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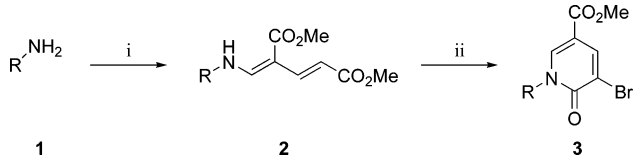
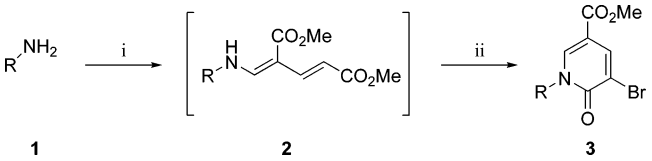
SCHEME 1. Preparation of 3-Bromo-2(1*H*)-pyridinones[a]



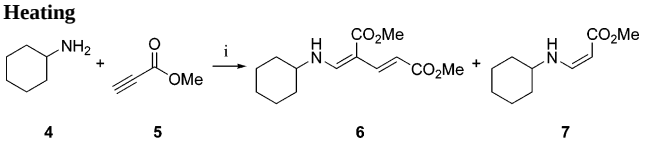
[a] Reagents and conditions: (i) methyl propiolate, MeOH, 60 °C, 2 days; (ii) NaOMe, NBS, MeOH, 60 °C, 1 h.

SCHEME 2. Microwave-Assisted Preparation of 3-Bromo-2(1*H*)-pyridinones[a]



[a] Reagents and conditions: (i) methyl propiolate, MeOH, 120 °C, 30 min; (ii) NaH, NBS, MeOH, 120 °C, 30 min.

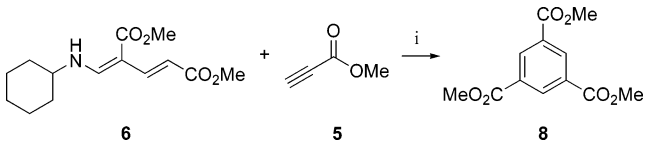
TABLE 1. Optimization of Diene Formation with Microwave Heating



entry	time (min)[a]	temp (°C)	equiv of **5**	ratio[b] **6**[c]:**7**[d]
1	13	110	2	1:2
2	20	110	2	2:1
3	30	110	2	6:1
4	30	80	2.5	1:1
5	30	90	2.5	3:1
6	30	100	2.5	5:1
7	30	110	2.5	8:1
8	30	120	2.5	10:1

[a] Includes 2 min ramp time. [b] Conversion observed by NMR. [c] It should be noted that all these reactions showed essentially complete regioselectivity to give **6** with the *Z*-configuration about the double bond α to the nitrogen and the *E*-configuration of the α,*β*-unsaturated double bond. [d] Monoaddition products could be easily removed using acidic extraction or chromatography after bromocyclization.

SCHEME 3. Formation of a Trimethyl 1,3,5-Benzenetricarboxylate Byproduct (8)[a]

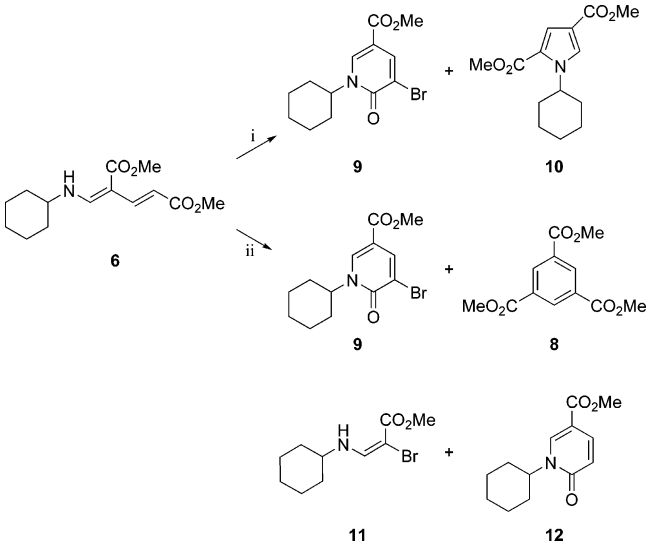


[a] Reagents and conditions: (i) MeOH, MW, 120 °C, 30 min.

Increasing the reaction temperature to 120 °C, in combination with using 2.5 equiv of **5**, resulted in a dramatic improvement in selectivity for compound **6** with an observed ratio of 10:1 (**6**/**7**) (entry 8).

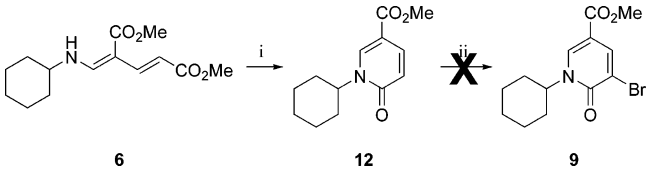
An interesting and unexpected byproduct of the reaction was isolated and identified as trimethyl 1,3,5-benzenetricarboxylate (**8**). Formation of this byproduct is believed to arise as a result of *δ*-dienaminoester (**6**) reacting with excess methyl propiolate (**5**) (Scheme 3). Indeed, when *δ*-dienaminoester (**6**) and an excess of methyl propiolate (**5**) were microwave heated at 120 °C for 30 min, a second crop of **8** was obtained. To the best of our knowledge, this is the first example of a benzene nucleus being formed via reaction of a nontertiary dienaminoester and methyl propiolate.[12]

SCHEME 4. Bromocyclization of *δ*-Dienaminoester (6)[a]



[a] Reagents and conditions: (i) NaOMe, NBS, methanol, MW, 120 °C, 30 min; (ii) NaH, NBS, MeOH, MW, 120 °C, 30 min.

SCHEME 5. Attempted Bromination of Pyridone (12)[a]



[a] Reagents and conditions: (i) NaH, MeOH, MW, 120 °C, 30 min; (ii) NBS, MeOH, MW, 120 °C, 30 min.

Next, we examined the bromocyclization of *δ*-dienaminoester (**6**) using the procedure of Dechoux et al.,[5,13] and consistent with their observations, we obtained a mixture of pyridone/pyrrole (**9**/**10**) in a ratio of 95:5 (Scheme 4). When we switched from NaOMe to NaH, we observed exclusive formation of pyridinone (**9**) in 70% yield. Other byproducts isolated from the reaction mixture include the brominated monoaddition product (**11**) carried over from the first step as well as desbromo pyridinone (**12**).

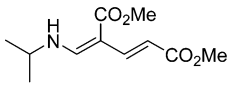
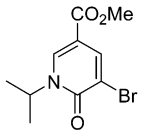
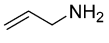
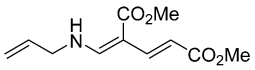
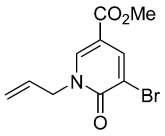
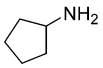
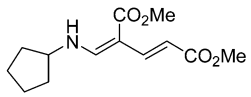
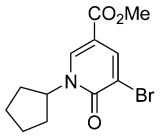
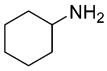
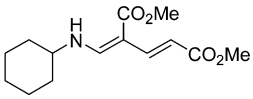
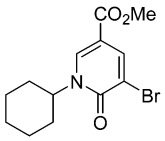
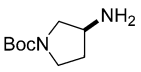
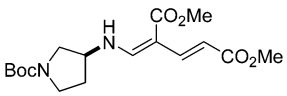
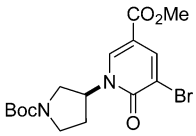
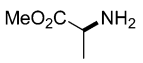
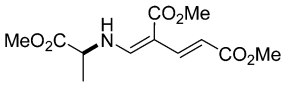
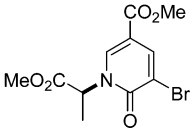
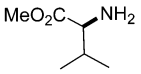
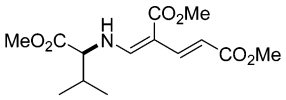
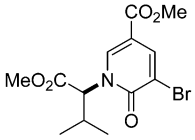
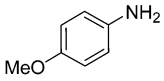
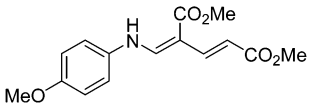
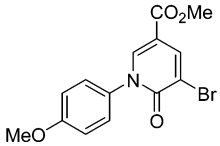
To ascertain whether bromination precludes cyclization, we performed additional experiments, the results of which strongly support that bromination occurs before cyclization. *δ*-Dienaminoester (**6**) was first treated with NaH in MeOH and heated in the microwave at 120 °C for 30 min facilitating the formation of **12** (Scheme 5). When **12** was then treated with NBS and microwave irradiated at 120 °C for 30 min, only starting material was recovered.

With optimum conditions for both the Michael-type addition and bromocyclization in hand, our attention was directed toward a telescoped synthesis. The generality and scope of the aforementioned tandem reaction sequence were examined using several different classes of amines. This work was initiated with considerable success, as demonstrated in Table 2. Step one

(12) For examples of tertiary dienaminoesters reacting in this fashion, see: Anghelide, N.; Draghici, C.; Raileanu, D. *Tetrahedron* **1974**, *30*, 623.

(13) (a) Agami, C.; Dechoux, L.; Hamon, L.; Severine, H. *Synthesis* **2003**, *6*, 859. (b) Agami, C.; Dechoux, L.; Hebbe, S. *Synlett* **2001**, *9*, 1440.

TABLE 2. Microwave-Assisted Pyridinone Formation with Various Amines

Entry	Amine + 5	Diene	Pyridinone	Yield[a]
1				44%
	13	**20**	**27**	
2				45%
	14	**21**	**28**	
3				53%
	15	**22**	**29**	
4				51%
	4	**6**	**9**	
5				29%
	16	**23**	**30**	
6				36%
	17	**24**	**31**	
7				33%
	18	**25**	**32**	
8				29%
	19	**26**	**33**	

[a] Isolated yield of chromatographed product.

proceeded well with isopropylamine (entry 1), allylamine (entry 2), five- and six-membered cyclic amines (entries 3 and 4), chiral heterocyclic amines (entry 5), α-amino acids[14] (entries 6 and 7), and aryl amines (entry 8) to give polysubstituted dienaminoesters. Subjection of compounds **6** and **20**−**26**, involving treatment with NBS and NaH in methanol at 120 °C for 30 min, resulted in the smooth formation of **9** and **27**−**33** incorporating the halogenated pyridinone framework. Significantly, this process was successful with amines **16**−**18** allowing for the introduction of chirality while providing access to pyridones bearing functionalized N-substituents which are of greater synthetic value.

In summary, a highly efficient microwave-assisted, telescoped synthesis of polysubstituted 3-bromo-2(1*H*)-pyridinone cores has been described. The methodology presented herein represents

(14) Khan, M. A.; Adams, H. *Tetrahedron Lett.* **1999**, *40*, 5389.

a convenient entry into multifunctionalized building blocks, starting from comparatively simple and readily available starting materials. Its scope incorporates branched and linear alkyl amines, cyclic amines, chiral heterocyclic amines, aryl amines, and α-amino acids. Further work is underway to study the effect of solvent, bases, and Lewis acid activation for synthesis of the 3-bromo-2(1*H*)-pyridinone core.

Experimental Section

General Procedure for the Synthesis of δ-Dienaminoesters: (2*E*,4*E*)-Dimethyl 4-δ-Dienaminoesters (6).[7a] A microwave process vial was charged with cyclohexyl amine (**4**) (5 mmol) followed by methanol (5 mL) and methyl propiolate (**5**) (12.5 mmol). The resulting mixture was sealed appropriately, placed into the microwave cavity, and microwave irradiated at 120 °C for 30 min. The reaction mixture could be purified at this stage [solvent reduced in vacuo (silica gel chromatography)] or telescoped into the next step: white crystalline solid, mp 99−101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.00 (br s, 1H), 7.40 (d, J = 15.65 Hz, 1H), 7.30 (d, J = 13.89 Hz, 1H), 6.01 (d, J = 15.65 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.20 (br s, 1H), 1.95 (m, 2H), 1.80 (m, 2H), 1.65 (m, 1H), 1.37 (m, 4H), 1.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6, 169.3, 155.4, 143.6, 107.0, 94.1, 57.7, 51.0, 50.8, 33.8, 25.1, 24.4.

General Procedure for the Bromocyclization: 3-Bromo-2(1*H*)-pyridinone (9). A microwave process vial was charged with δ-dienaminoester (**6**) (5 mmol) followed by methanol (15 mL) and the portionwise addition of NaH (5 mmol). The reaction mixture was cooled to 0 °C after which time NBS (6 mmol) was added in small portions. The resulting mixture was sealed appropriately, placed into the microwave cavity, and microwave irradiated at 120 °C for 30 min. The solvent was reduced in vacuo, and the residue was quenched with aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, washed with brine (10 mL), and reduced in vacuo to give a dark yellow oil. The oil was chromatographed on silica gel (EtOAc/hexanes, gradient 0 to 30% EtOAc) to furnish **9** (790 mg, 51% over two steps): white crystalline solid, mp 149−151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (s, 1H), 8.20 (s, 1H), 4.87 (m, 1H), 3.88 (s, 3H), 1.97 (m, 4H), 1.77 (m, 1H), 1.57−1.49 (m, 5H), 1.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.9, 158.6, 139.5, 138.2, 115.5, 109.8, 56.8, 52.3, 32.6, 25.6, 25.2; HRMS Calcd for $C_{13}H_{16}BrNO_3$ [M + H] m/z 314.0391, found 314.0394.

3-Bromo-2(1*H*)-pyridinone (27). A microwave process vial was charged with δ-dienaminoester (**20**) (5 mmol) followed by methanol (15 mL) and the portionwise addition of NaH (5 mmol). The reaction mixture was cooled to 0 °C after which time NBS (6 mmol) was added in small portions. The resulting mixture was sealed appropriately, placed into the microwave cavity, and microwave irradiated at 120 °C for 30 min. The solvent was reduced in vacuo, and the residue was quenched with aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, washed with brine (10 mL), and reduced in vacuo to give a dark yellow oil. The oil was chromatographed on silica gel (EtOAc/hexanes, gradient 0 to 30% EtOAc) to furnish **27** (600 mg, 44% over two steps): white crystalline solid, mp 98−100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, J = 2.15 Hz, 1 H), 8.21 (d, J = 2.15 Hz, 1H), 5.26 (septet, J = 6.85 Hz, 1H), 3.88 (s, 3H), 1.42 (d, J = 6.85 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.9, 158.5, 139.5, 137.6, 115.6, 110.0, 52.3, 49.5, 21.9; HRMS Calcd for $C_{10}H_{12}BrNO_3$ [M + H] m/z 274.0078, found 274.0078.

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Supporting Information Available: General experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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