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Nucleophilic Addition onto Methyl-4*H*-1,4-oxazine-3-carboxylate Moiety: Short Access to 1,4-Diazine Privileged Substructures

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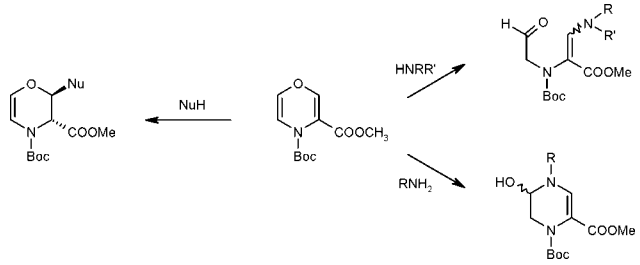
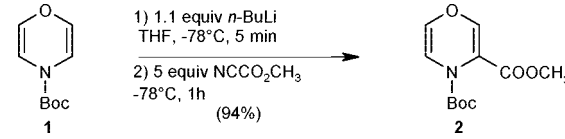
Received February 10, 2009



To determine the synthetic potential of the original 1,4-oxazine ring, which appears as a valuable building block for the synthesis of more complex derivatives, Michael-type nucleophilic additions were studied. According to the nature of the nucleophile, either acyclic or cyclic derivatives were isolated. In the presence of primary amines, a short and efficient access to diazinic hemiaminals was described.

Heterocycles display an intrinsic reactivity that enables rich, versatile, and productive transformations. Taking into account their ubiquitous presence in natural products and drugs, the development of new, fast, and efficient preparative protocols for these structures remains a fundamental task in organic synthesis. As part of our interest in using readily available enol phosphates for the synthesis of new heterocyclic compounds,[1,2] we have recently described an original and efficient access to 1,4-oxazine and substituted 1,4-oxazine derivatives.[1c] Specifically, starting from 1,4-oxazine **1**, we outlined the preparation under anionic conditions of α,β-unsaturated methyl ester **2** (Scheme 1).

SCHEME 1. Preparation of Unsaturated Methyl Ester 2



The regioselectivity of this functionalization α to the ring nitrogen was verified by NMR spectra and also by crystal X-ray analysis. The ORTEP drawing of **2** confirms the flat boat conformation of this original antiaromatic system (see Supporting Information).[3]

To determine the synthetic potential of the 1,4-oxazine ring, which appears as a valuable building block for the synthesis of more complex derivatives, we engaged in a study of its chemical properties. We first examined the behavior of α,β-unsaturated methyl ester **2**, an unusual Michael acceptor, in the presence of a range of nucleophiles. Thus compound **2** was treated, in a basic medium (K_2CO_3 6 equiv, CH_3CN, rt) with the following nucleophiles: 1,2,4-triazole, 4-methoxyphenol, and thiophenol.[4] The requisite adducts **3a**−**c**, resulting from a classical Michael-type addition reaction, were thus isolated in fair to good yields as a single diastereomer (Table 1). The expected 2,3-*trans* stereochemistry of **3** was confirmed by the small coupling constant observed between the H-2 and H-3 protons ($^3J_{2-3}$ = 1,6 Hz).[5] It is worth pointing out that, in these cases, the Michael-type addition reactions allowed an easy access to 2,3-disubstituted oxazinic systems; moreover, the presence of the remaining double bond must also be noted, as the use of its reactivity might lead to many substituted morpholine derivatives.[6]

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(1) (a) Mousset, D.; Gillaizeau, I.; Sabatié, A.; Bouyssou, P.; Coudert, G. *J. Org. Chem.* **2006**, *71*, 5993. (b) Mousset, D.; Gillaizeau, I.; Hassan, J.; Lepifre, F.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett.* **2005**, *46*, 3703. (c) Claveau, E.; Gillaizeau, I.; Blu, J.; Bruel, A.; Coudert, G. *J. Org. Chem.* **2007**, *72*, 4832. (d) Cottineau, B.; Gillaizeau, I.; Farard, J.; Auclair, M.-L.; Coudert, G. *Synlett* **2007**, 1925. (e) Chaignaud, M.; Gillaizeau, I.; Ouhamou, N.; Coudert, G. *Tetrahedron* **2008**, *64*, 8059.

(2) (a) Nicolaou, K. C.; Shi, G. Q.; Namoto, K.; Bernal, F. *Chem. Commun.* **1998**, 1757. (b) Nicolaou, K. C.; Shi, G. Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467. (c) Huffman, M. A.; Yasuda, N. *Synlett* **1999**, 471. (d) Jiang, J. L.; Devita, R. J.; Doss, G. A.; Goulet, M. T.; Wyvratt, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 593. (e) Moraes, D. N.; Barrientos-Astigarraga, R. E.; Castelani, P.; Comasseto, J. V. *Tetrahedron* **2000**, *56*, 3327. (f) Coe, J. W. *Org. Lett.* **2000**, *2*, 4205. (g) Wu, J.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 7875. (h) Takakura, H.; Sasaki, M.; Honda, S.; Tachibana, K. *Org. Lett.* **2002**, 2771. (i) Lo Galbo, F.; Occhiato, E. G.; Guarna, A.; Faggi, C. *J. Org. Chem.* **2003**, *68*, 6360. (j) Campbell, I. B.; Guo, J.; Jones, E.; Steel, P. G. *Org. Biomol. Chem.* **2004**, *2*, 2725. (k) Larsen, U. S.; Martiny, L.; Begtrup, M. *Tetrahedron Lett.* **2005**, *46*, 4261. (l) Occhiato, E. G.; Lo Galbo, F.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 7324. (m) Tsukano, C.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4326. (n) Fuwa, H.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 9648. (o) Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989. (p) Ebine, M.; Fuwa, H.; Sasaki, M. *Org. Lett.* **2008**, *10*, 2275. (q) Fuwa, H.; Sasaki, M. *J. Org. Chem.* **2009**, *74*, 212. (r) Ebran, J.-P.; Hansen, A. L.; Gøgsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931. (s) Hansen, A. L.; Ebran, J.-P.; Gøgsig, T. M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464. (t) Lindhart, A. T.; Skrydstrup, T. *Chem. Eur. J.* **2008**, *14*, 8756.

(3) (a) Borbulevych, O. Y.; Shishkin, O. V. *J. Mol. Struct.* **1998**, *446*, 11. (b) Trinajstic, N. *J. Mol. Struct.* **1971**, *8*, 236.

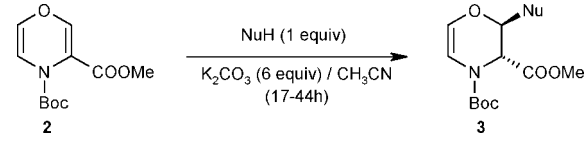
(4) For 1,4-dihydropyrazine derivatives, see: Rodrigues, A.; Ferreira, P. M.; Monteiro, L. S. *Tetrahedron* **2004**, *60*, 8489.

(5) Two NMR signals were observed for each oxazinic protons that corresponded to the two conformers (transdiaxial and transdiequatorial structures) of **3**. This was confirmed by performing NMR studies in DMSO-d_6 at 80°C; splitting of the signals was not observed anymore.

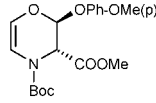
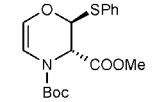
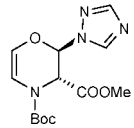
(6) Reviews: (a) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E; van Delft, F. L; Blaauw, R. H; Rutjes, F. P. J. T. *Synthesis* **2004**, 641. (b) Sladojevich, F.; Trabocchi, A.; Guarna, A. *Org. Biomol. Chem.* **2008**, *6*, 3328.

10.1021/jo900291f CCC: $40.75 © 2009 American Chemical Society
Published on Web 03/11/2009

TABLE 1. Michael Addition Reaction onto α,β-Unsaturated Methyl Ester 2

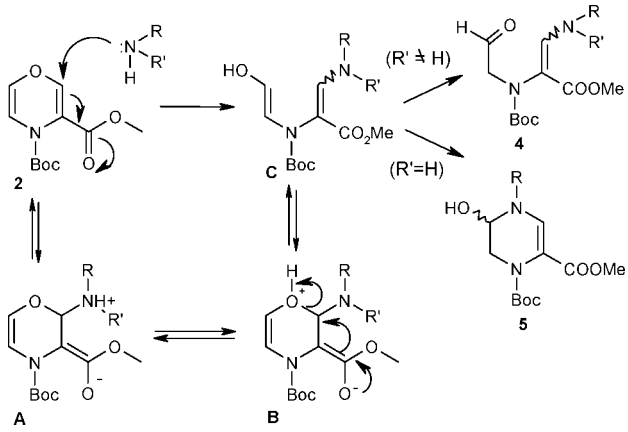


2 3

Entry	NuH	Time	Adducts **3** (yield %)[b]
1	(p)MeO-PhOH	44h	 **3a** (70%)
2	PhSH	17h	 **3b** (80%)
3[a]		24h	 **3c** (48%)

[a] Three equivalents of 1,2,4-triazole used in this case. [b] Isolated yield.

SCHEME 2. Mechanism Hypothesis for the Reaction of α,β-Unsaturated Methyl Ester 2 with Secondary or Primary Amines

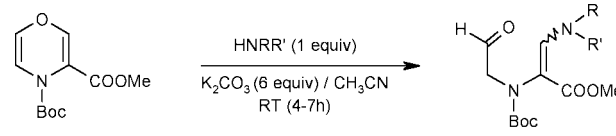


We next examined the protocol using primary or secondary amines as nucleophiles (Scheme 2). Nucleophilic addition of secondary amines (diethylamine or morpholine) onto α,β-unsaturated methyl ester **2** involved the opening of the heterocyclic system via an addition−elimination process. Stable acyclic enamines **4a** and **4b** were thus isolated in good yields as a mixture of *Z* and *E* isomers (Table 2).

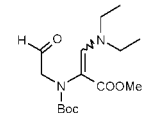
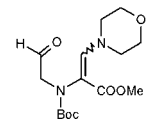
It is noteworthy that in the previous case (Table 1), given the nature of the base (K_2CO_3) and of the nucleophiles, a Michael-type addition was observed to give adducts **3**; no elimination process could occur. In the second case, in the presence of secondary amines as nucleophiles (Table 2), the resulting adduct **A** (Scheme 2) is envisioned to undergo a hydrogen transfer to form the oxonium intermediate **B**. The latter ultimately goes on to the final acyclic enamine **4** via an elimination process.

These first results incited us to turn this addition−elimination process to account by using primary amines instead of secondary ones. By doing so, we expected the formation of a new heterocyclic diazinic system **5**[1e] via the intramolecular nucleophilic attack of the intermediate secondary amine (Scheme 2)

TABLE 2. Nucleophilic Addition of Secondary Amines onto α,β-Unsaturated Methyl Ester 2



2 4

Entry	HNRR'	Time	Adducts **4** (yield %)[b]
1		7h	 **4a**[a] (75%)
2		4h	 **4b**[a] (64%)

[a] *Z*/*E* ratio of 66:33 as determined by ^{1}H NMR. [b] Isolated yield.

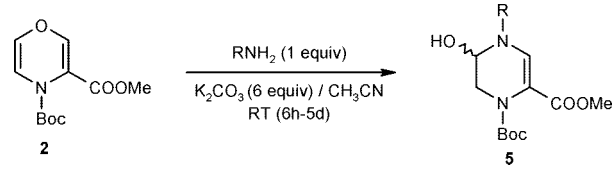
onto the carbonyl group. In fact, we were pleased to observe that treatment of α,β-unsaturated methyl ester **2** with 1 equiv of benzylamine in acetonitrile at room temperature for 22 h afforded the original tetrahydropyrazinol **5a** in a one-pot process and in quantitative yield. The structure of **5a** was unambiguously confirmed by crystal X-ray analysis (see Supporting Information). This original result paralleled those described by Yao for the synthesis of a spirocyclic chromophore of chlorofusin.[7] Table 3 summarizes the scope of this reaction. A range of primary amines was allowed to react with α,β-unsaturated methyl ester **2** and afforded the desired tetrahydropyrazinols **5a**−**h** in good yields after somewhat prolonged reaction times. In the presence of 0.5 equiv of 1,4-diaminobutane (Table 3, entry 3), a double nucleophilic addition was observed to give the original bis-tetrahydropyrazinol **5c** in 87% yield. In the case of propargylamine (Table 3, entry 7), the tetrahydropyrazinol **5g** was isolated in only 26% yield together with 16% of the parent α,β-unsaturated methyl ester **2**. No improvement of the yield was observed by warming the reaction. The use of chiral (*S*)-(−)-α-methylbenzylamine (Table 3, entry 8) afforded the corresponding tetrahydropyrazinol **5h** in 82% yield and as a 47:53 diastereomeric mixture.

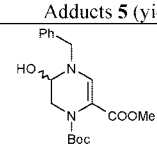
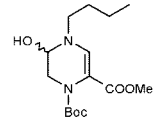
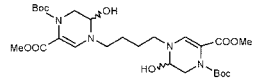
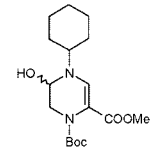
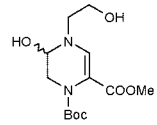
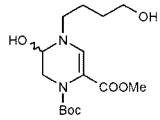
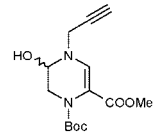
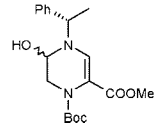
With a facile access to benzylic hemiaminal **5a** in hand, we next examined the reactivity of the potential iminium ion intermediate toward nucleophiles.[8] In the presence of $BF_3 \cdot Et_2O$ in dichloromethane at room temperature and by using TMSCN as a nucleophile, the attempted addition quickly occurred. However, in this case, simultaneous removal of the Boc group was also observed to give the unprotected unstable aminonitrile **6**, which was quantitatively isolated. It is noteworthy that by applying the aminonitrile chemistry this versatile intermediate might afford a broad range of synthetic applications (i.e., alkaloids analogues).[9]

In summary, from 1,4-oxazine moiety, we have developed a short and efficient method that allowed an easy access to either morpholine derivatives or diazinic hemiaminals. Ongoing studies are aimed at expanding the scope of this reaction, in particular by taking advantage of the reactivity of the potential iminium

(7) (a) Wei, W.-G.; Yao, Z.-J. *J. Org. Chem.* **2005**, *70*, 4585. (b) Wei, W.-G.; Qian, W.-J.; Zhang, Y.-X.; Yao, Z.-J. *Tetrahedron Lett.* **2006**, *47*, 4171.
(8) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311.
(9) Enders, D.; Shilvock, J. P. *Chem. Rev.* **2000**, *29*, 359.

TABLE 3. Nucleophilic Addition of Primary Amines onto α,β-Unsaturated Methyl Ester 2



Entry	RNH_2	Time	Adducts **5** (yield %)[c]
1	$PhCH_2NH_2$	22h	 **5a** (100%)
2	n-$C_4H_9NH_2$	15h	 **5b** (100%)
3[a]	$NH_2C_4H_8NH_2$	20h	 **5c** (87%)
4		15h	 **5d** (90%)
5	$HO(CH_2)_2NH_2$	6h	 **5e** (79%)
6	$HO(CH_2)_4NH_2$	40h	 **5f** (70%)
7[b]		68h	 **5g** (26%)
8		5d	 **5h** (82%)

[a] One-half equivalent of 1,4-diaminobutane used in this case. [b] Starting material was recovered in 16% yield. [c] Isolated yield.

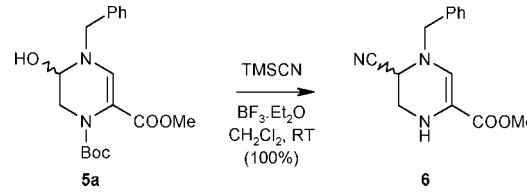
ion. This method might constitute a useful tool to easily prepare a range of direct precursors of natural products and offers the potential advantage of directly introducing molecular diversity onto the molecules as a result of the original choice of the starting nucleophile.

Experimental Section

Only representative procedures and characterizations of the products are described here. Full details can be found in Supporting Information.

***tert*-Butyl Methyl 4*H*-1,4-Oxazine-3,4-dicarboxylate (2).** A solution of *tert*-butyl 4*H*-1,4-oxazine-4-carboxylate **1**[1c] (0.300 g, 1.64 mmol, 1 equiv) in THF (15 mL) was cooled to −78 °C under argon. Subsequently, *n*-butyllithium (1.13 mL, 1.6 M in hexane, 1.80 mmol, 1.1 equiv) was added dropwise. After 5 min of stirring at −78 °C, a solution of methyl cyanoformate (0.650 mL, 8.19 mmol, 5 equiv) in THF (1 mL), previously dried over molecular sieves (4 Å), was added dropwise. After 1 h at −78 °C, the reaction was quenched by slow addition of water. The aqueous phase was then extracted with EtOAc and the organic phase was washed with brine. The organic phase was dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography (petroleum ether/EtOAc, 9:1) afforded **2** (0.370 g, 94%) as a yellow solid: mp 57−58 °C; IR (KBr) 2977, 1729, 1705, 1626, 1353, 1136 cm^{-1}; ^1H NMR 250 MHz ($CDCl_3$) δ 6.81 (s, 1 H), 6.13 (d, J = 3.9 Hz, 1 H), 5.97 (d, J = 3.9 Hz, 1 H), 3.78 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR 62.5 MHz ($CDCl_3$) δ 163.4 (*s*), 150.3 (*s*), 143.9 (*d*), 133.1 (*d*), 116.6 (*s*), 112.7 (*d*), 82.3 (*s*), 52.0 (*q*), 28.1 (*q*); HRMS (EI) *m*/*z* $[M]^{+\bullet}$ calcd for $C_{11}H_{15}NO_5$ 241.09502, found 241.0954. X-ray crystal data: $C_{11}H_{15}NO_5$, transparent, white color crystal, M = 241.25; triclinic, space group $P\bar{1}$, a = 6.2233(2) Å, b = 7.3164(2) Å, c = 13.5519(4) Å, α = 77.0301(11)°, β = 76.9064(10)°, γ = 81.5540(13)°, V = 582.67(3) $Å^3$, Z = 2, D_{calc} = 1.375 g cm^{-3}; R(int) = 0.021 and $R1$ = 0.043 for reflections with $F^2 > 2\sigma(F^2)$. A crystal of 0.25 × 0.22 × 0.14 mm was used.

SCHEME 3. Access to 1,4-Diazinic Aminonitrile 6



General Procedure for Preparation of Compounds 3. 4-*tert*-Butyl 3-Methyl 2-(4-Methoxyphenoxy)-2,3-dihydro-1,4-oxazine-3,4-dicarboxylate (3a). To a solution of *tert*-butyl methyl 4*H*-1,4-oxazine-3,4-dicarboxylate **2** (0.050 g, 0.21 mmol, 1 equiv) in MeCN (2 mL) was added K_2CO_3 (0.172 g, 1.24 mmol, 6 equiv), followed by 4-methoxyphenol (0.026 g, 0.21 mmol, 1 equiv), with fast stirring at room temperature. The reaction was monitored by TLC (petroleum ether/EtOAc, 8:2), and when no starting material was detected (44 h), the reaction mixture was filtered through Celite. The solution was washed with water, the aqueous phase was extracted with EtOAc, and the organic phases were then washed with brine. They were dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography (petroleum ether/EtOAc/toluene, 7:2:1) afforded **3a** (0.053 g, 70%) as a colorless oil, as an enantiomeric mixture of the *trans* diastereomer: IR (NaCl) 2818, 1697, 1436, 1236, 1050 cm^{-1}; ^1H NMR 400 MHz ($CDCl_3$) (2 conformers) δ 7.00−7.03 (m, 3.2 H), 6.81−6.84 (m, 3.2 H), 6.56 (dd, J = 5.2 Hz and J = 1.6 Hz, 0.6 H), 6.41 (dd, J = 5.2 Hz and J = 1.6 Hz, 1 H), 6.06 (d, J = 1.6 Hz, 1 H), 6.01 (d, J = 1.6 Hz, 0.6 H), 5.84 (d, J = 5.2 Hz, 0.6 Hz), 5.74 (d, J = 5.2 Hz, 1 H), 5.17 (s, 1 H), 4.99 (s, 0.6 H), 3.80 (s, 1.8 H), 3.78 (s, 3 H), 3.77 (s, 1.8 H), 3.76 (s, 3 H), 1.55 (s, 9 H), 1.50 (s, 5.4 H); ^{13}C NMR 100 MHz ($CDCl_3$) δ 167.6 (*s*), 167.3 (*s*), 155.7 (*s*), 155.6 (*s*), 151.9 (*s*), 151.4 (*s*), 150.1 (*s*), 149.7 (*s*), 124.5 (*d*), 123.4 (*d*), 119.0 (*d*), 118.9 (*d*), 114.7 (*d*), 114.6 (*d*), 107.5 (*d*), 107.1 (*d*), 93.7 (*d*), 93.1 (*d*), 82.3 (*s*), 82.1 (*s*), 57.8 (*d*), 56.4 (*d*), 55.7 (*q*), 53.0 (*q*), 52.9 (*q*), 28.3 (*q*), 28.2 (*q*); HRMS (EI) *m*/*z* $[M]^{+\bullet}$ calcd for $C_{18}H_{23}NO_7$ 365.14745, found 365.1504.

General Procedure for Preparation of Compounds 4. Methyl 2-(*tert*-Butoxycarbonyl(2-oxoethyl)amino-3-(diethylamino)acrylate (4a). To a solution of *tert*-butyl methyl 4*H*-1,4-oxazine-3,4-dicarboxylate **2** (0.050 g, 0.21 mmol, 1 equiv) in MeCN (2 mL) was added K_2CO_3 (0.172 g, 1.24 mmol, 6 equiv), followed by diethylamine (0.021 mL, 0.21 mmol, 1 equiv), with fast stirring at room temperature. The reaction was monitored by TLC (petroleum ether/EtOAc, 6:4), and when no starting material was detected (7 h), the reaction mixture was filtered through Celite. The solution was washed with water, the aqueous phase was extracted with

EtOAc, and the organic phases were then washed with brine. They were dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography (petroleum ether/EtOAc, 6:4) afforded **4a** (0.049 g, 75%) as a colorless oil, as a mixture of *Z* and *E* isomers: IR (NaCl) 2971, 1730, 1653, 1627, 1425, 1165 cm^{-1}; ^1H NMR 250 MHz ($CDCl_3$) δ 9.78−9.83 (m, 1.5 H), 7.30 (s, 0.5 H), 7.17 (s, 1 H), 3.65 (s, 3 H), 3.64 (s, 1.5 H), 3.52−3.60 and 3.92−4.06 (m, 3 H), 3.21−3.38 (m, 6 H), 1.43 (s, 4.5 H), 1.40 (s, 9 H), 1.17 (t, $J = 7.3$ Hz, 3 H), 1.16 (t, $J = 7.3$ Hz, 6 H); ^{13}C NMR 62.5 MHz ($CDCl_3$) δ 201.2 (*d*), 201.0 (*d*), 168.2 (*s*), 168.1 (*s*), 156.8 (*s*), 155.0 (*s*), 144.6 (*d*), 143.6 (*d*), 101.2 (*s*), 100.7 (*s*), 81.6 (*s*), 80.9 (*s*), 61.4 (*t*), 60.7 (*t*), 51.3 (*q*), 46.8 (*t*), 28.3 (*q*), 14.3 (*q*); HRMS (EI) *m*/*z* $[M]^{+\bullet}$ calcd for $C_{15}H_{26}N_2O_5$ 314.18417, found 314.1860.

General Procedure for Preparation of Tetrahydropyrazinols 5. 1-*tert*-Butyl 2-Methyl 4-Benzyl-5,6-dihydro-5-hydroxypyrazine-1,2(4*H*)-dicarboxylate (5a). To a solution of *tert*-butyl methyl 4*H*-1,4-oxazine-3,4-dicarboxylate **2** (0.295 g, 1.22 mmol, 1 equiv) in MeCN (12 mL) was added K_2CO_3 (1.014 g, 7.34 mmol, 6 equiv), followed by benzylamine (0.134 mL, 1.22 mmol, 1 equiv), with fast stirring at room temperature. The reaction was monitored by TLC (DCM/MeOH, 98:2), and when no starting material was detected (22 h), the reaction mixture was filtered through Celite. The solution was washed with water, the aqueous phase was extracted with EtOAc, and the organic phases were then washed with brine and dried over anhydrous $MgSO_4$. Removal of the solvent afforded **5a** (0.426 g, 100%) as a white solid: mp 164−165 °C; IR (KBr) 3471, 3065, 2975, 2951, 1716, 1683, 1602, 1438, 1169 cm^{-1}; ^1H NMR 250 MHz ($CDCl_3$) δ 7.21−7.39 (m, 5 H), 7.04 (s, 1 H), 4.86 (br s, 1 H), 4.44 (AB syst.: 2 × d, 2 H, 4.35 ppm and 4.54 ppm, $J = 15.0$ Hz), 3.49 (s, 3 H), 3.53 (AB syst.: 2 × dd, 2 H, 2.75 ppm and 4.30 ppm, $J = 13.3$ Hz and $J = 1.5$ Hz and $J = 2.0$ Hz), 3.49 (br s, 1 H), 1.43 (s, 9 H); ^{13}C NMR 62.5 MHz ($CDCl_3$) δ 165.1 (*s*), 154.9 (*s*), 136.6 (*s*), 134.2 (*d*), 129.0 (*d*), 128.1 (*d*), 127.9 (*d*), 105.0 (*s*), 81.1 (*s*), 77.3 (*d*), 56.3 (*t*), 51.3 (*q*), 46.8 (*t*), 28.1 (*q*); HRMS (EI) *m*/*z* $[M - H_2O]^{+\bullet}$ calcd for $C_{18}H_{24}N_2O_5$ 330.15796, found 330.1591. X-ray crystal data: $C_{18}H_{24}N_2O_5\ H_2O$, transparent, white color crystal, $M = 348.40$; monoclinic, space group $P2_1/c$, $a = 14.2955(4)$ Å, $b = 8.3964(2)$ Å, $c = 16.8240(5)$ Å, $\beta = 105.4699(12)°$, $V = 1946.24(9)$ $Å^3$, $Z = 4$, $D_{calc} = 1.25$ g cm^{-3}; R(int) = 0.036 and $R1 = 0.064$ for reflections with $F^2 > 2\sigma(F^2)$. A crystal of 0.35 × 0.25 × 0.10 mm was used.

Methyl 4-Benzyl-5-cyano-1,4,5,6-tetrahydropyrazine-2-carboxylate (6). To a solution of hemiaminal **5a** (70 mg, 0.20 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was added trimethylsilyl cyanide (38 μL, 0.30 mmol, 1.5 equiv), followed by $BF_3 \cdot OEt_2$ (37 μL, 0.30 mmol, 1.5 equiv). The mixture was stirred at room temperature for 30 min. The reaction was then hydrolyzed by addition of water. The aqueous phase was extracted with CH_2Cl_2. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. Removal of the solvent afforded **6** (52 mg, 100%) as a yellow oil: IR (NaCl) 3367, 2952, 2922, 2850, 2234, 1692, 1639, 1455, 1299, 1157 cm^{-1}; ^1H NMR 250 MHz ($CDCl_3$) δ 7.29−7.39 (m, 5 H), 6.75 (s, 1 H), 4.30 (s, 2 H), 4.00 (t, 1 H, $J = 2.3$ Hz), 3.76 (s, 3 H), 3.42 (AB syst.: 2 × dd, 2 H, 3.24 ppm and 3.60 ppm, $J = 12.5$ Hz and $J = 2.8$ Hz and $J = 2.5$ Hz); ^{13}C NMR 62.5 MHz ($CDCl_3$) δ 165.1 (*s*), 134.9 (*s*), 129.2 (*d*), 128.7 (*d*), 128.5 (*d*), 125.7 (*d*), 116.4 (*s*), 112.5 (*s*), 57.9 (*t*), 51.6 (*q*), 45.6 (*d*), 44.4 (*t*); MS (IS) *m*/*z* = 258.0 $[M + H]^+$. Slow decomposition of **6** over several hours precluded satisfactory HRMS analysis.

Acknowledgment. We are grateful to the CNRS and the Region Centre for financial support.

Supporting Information Available: Detailed experimental procedures, full characterization for all new compounds synthesized, ^1H and ^{13}C NMR Spectra for compounds **2**−**6**, X-ray structures and CIF files of compounds **2** and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900291F