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Regioselective Reduction of 3-Substituted *N*-Acylpyrazinium Salts toward the Synthesis of 1,2-Dihydropyrazines

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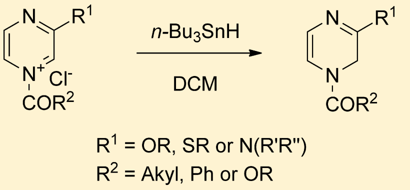
Supporting Information

ABSTRACT: The regioselective reduction of 3-substituted *N*-acylpyrazinium salts with n-Bu_3SnH has been developed for the synthesis of 3-substituted 1,2-dihydropyrazines in yields of 56−94%. Substitution of the pyrazinium salts with electron-donating groups favors the formation of the 1,2-isomers as a result of their better stability over the 1,6-isomers. Under mild acidic conditions, 3-methoxy substituted 1,2-dihydropyrazine was easily hydrolyzed in excellent yield to Δ^5-2-oxopiperazine.



The reduction of pyrazinium salts is a useful approach for synthesizing piperazines.[1] This scaffold is classified as a privileged structure and is present in a number of biologically active compounds.[2] The partial reduction of pyrazinium salts to generate dihydropyrazines,[3] on the other hand, has not received as much attention compared to reports on the reduction of pyridinium salts to synthesize dihydropyridines.[4] While it has been shown that 3-substituted pyridinium salts are selectively reduced to generate 1,2-dihydropyridines,[5] studies examining the regioselective reduction of 3-substituted pyrazinium salts to produce 1,2-dihydropyrazines are limited.[6] A report by Hirano and Tada mentioned observing the regioselective reduction of 3-cyano-5-(3,4-dimethoxyphenyl)-L-methylpyrazinium fluorosulfonate to give the dihydropyrazine 3-cyano-5-(3,4-dimethoxyphenyl)-L-methyl-l,6-dihydropyrazine using sodium borohydride or Hantzsch ester, but the authors did not provide any explanation for their observed selectivity.[6b] This lack of information on the regioselective outcome of reducing substituted activated pyrazines provides a good opportunity to explore whether this reduction mimics what was observed with substituted pyridinium salts. Also, because dihydropyrazines have been shown to behave as a NPY antagonist and possess DNA strand-breaking abilities,[7] new approaches toward their synthesis would be quite valuable. As part of our research program exploring the synthetic utility of pyrazinium salts, we wish to report our findings on the regoiselective reduction of 3-substituted *N*-acylpyrazinium salts.

We began our research effort by first examining the regiochemical outcome of reducing a pyrazinium salt substituted with a methoxy group. To carry out the reduction, we used tributyltin hydride as the reducing agent due to its reported use for reducing *N*-acylisoquinolinium salts to dihydroisoquinolines.[8,9] Starting with commercially available 2-methoxypyrazine (**1a**) in DCM, tributyltin hydride was added at 0 °C. Phenyl chloroformate was then added to generate the *N*-acyl 3-methoxypyrazinium salt, which was then readily reduced by the tributyltin hydride.[10] When the reaction was completed after 40 min, the isolated crude product was analyzed by ^1H NMR to determine the regiochemical outcome of the reaction. Our NMR analysis of the crude reaction mixture showed that the reduction produced 1-phenoxycarbonyl-3-methoxy-1,2-dihydropyrazine (**3a**) as the sole regioisomer.[11] This result was based on the NMR spectrum showing a rotameric singlet peak at 4.42 and 4.29 ppm for the methylene protons at C2 of **3a** and a pair of rotameric doublet peaks at 6.61, 6.56 ppm and 6.10, 6.06 ppm for the two vinyl protons at C5 and C6 of **3a**, respectively. Peaks corresponding to the formation of 1,6-dihydropyrazine **4a** were not observed. With the identification of the regioisomer now confirmed, purification of the crude material gave **3a** in a good yield of 90% (Table 1, entry 1).

Excited by our initial results, we went on to explore the regioselective reduction of other 3-substituted pyrazinium salts. We discovered that when substituted with a *tert*-butoxy, benzyloxy, or phenoxy group, the reactions were completed within 30 min to 3 h, and only the 1,2-dihydropyrazine regioisomer was isolated in good to excellent yields ranging from 78% to 94% (Table 1, entries 2−5). Substitution with a thio or amino group also gave 1,2-dihydroprazines as the only product but in lower yields (Table 1, entries 6−8). When the reduction was carried out with a 3-chloro substituted pyrazinium salt, Δ^5-2-oxopiperazine (**5**) was isolated instead of 1,2-dihydroprazine (**3i**) (Table 1, entry 9). It was suggested that the formation of **5** came from hydrolyzing the imidoyl chloride functionality of **3i** to an amide group during the aqueous workup of the reaction. Finally, when subjecting methyl, phenyl, and cyano substituted pyrazines to our reaction conditions, no desired products were obtained (Table 1, entry 10−12). The methyl substituted pyrazine produced only an unidentifiable solid, while substitution with both phenyl and cyano groups gave no reaction.

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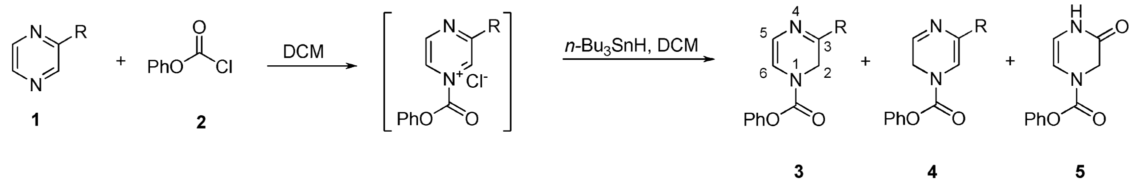
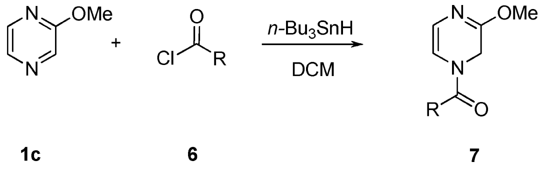
Table 1. Reduction of 3-Substituted *N*-Acylpyrazinium Salts



entry	compound	R	time (min)	temp (°C)	yield (%)^a		
					3a–l	**4a–l**	**5**
1	**1a**	OMe	40	0	90	0	0
2	**1b**	O-*t*-Bu	35	0	94	0	0
3	**1c**	OBn	50	0	81	0	0
4	**1d**	OPh	30	0	91	0	0
5	**1e**	OPh-*p*-NO_2	3 h	rt	78	0	0
6	**1f**	SCH_2CH_3	5	0	65	0	0
7	**1g**	SPh-*p*-Me	10	0	62	0	0
8	**1h**	morpholinyl	15	0	56	0	0
9	**1i**	Cl	18 h	0	0	0	46
10	**1j**	Me	30	0–rt	*b*	*b*	*b*
11	**1k**	Ph	24 h	rt	*c*	*c*	*c*
12	**1l**	CN	14 h	rt	*d*	*d*	*d*

[a] Isolated yields. [b] An unidentifiable solid product was isolated. [c] No reaction. [d] Target molecule was not obtained, and 18% of the starting material was recovered.

Table 2. Acylation Effects on Regioselective Reduction



entry	R	time (min)	temp (°C)	product	yield (%)^a
1	OMe	35	0	**7a**	91
2	OBn	45	0	**7b**	85
3	Me	5	0	**7c**	74^b
4	Ph	60	0	**7d**	89
5	cyclohexyl	15	0	**7e**	93

[a] Isolated yields. [b] Compound **7c** sublimes under high vacuum.

We next carried out the reduction with other acylating reagents and sulfonyl chlorides to determine their effect on the reactions regioselectivity. We observed that the use of methyl and benzyl chloroformates (Table 2, entry 1 and 2) along with acid chlorides (Table 2, entry 3–5) gave only the 1,2-dihydropyazine isomer in good yield. Unfortunately, when we tried to use mesyl or tosyl chloride, no reaction occurred, even after allowing the reaction to stir at rt for 24 h.

From our reaction results, we can see that *N*-acylpyrazinium salts substituted with electron-donating groups exclusively gave *N*-acyl-1,2-dihydroprazines as the only regioisomer. This outcome is similar to what was observed by Sundberg et al. when they reduced 3-substituted pyridinium salts with a variety of reducing agents.[5b] They proposed that the electronic nature of the different substituents at the 3-position influences the regiochemical outcome and that the observed regioselectivity was due to the stability of the dihydropyridine products.[5b] To study this potential effect on the reduction of 3-substituted pyrazinium salts, we calculated the energy difference between 1,2- and 1,6-dihydropyrazines using DFT calculations at the B3LYP/6-31G* level.[12] As the data in Table 3 shows, the 1,2-dihydropyazine having electron-donating groups are more stable than their 1,6-adducts. This stability is due to the 1,2-isomer having the donating substituents lone pair of electrons in conjugation with the π-system of the dihydropyrazine ring while the 1,6-isomer lone pair of electrons are in cross-conjugation with the π-system.[5b] This stabilizing effect was calculated to be highest when the dihydropyrazines are substituted with a thioethyl or morpholinyl group (Table 3, entries 6 and 8) and lowest for a *p*-toluenethiol group (Table 3, entry 7). It is interesting to note that although the stabilizing effect is highest for the thioethyl and morpholinyl group, the relative yields of reducing *N*-acylpyrazinium salts containing these two substituents are lower (Table 1). This decrease in yield is apparently due to an increase in the number of unidentifiable side products during the reaction when these two groups are present. These results support the fact that the regioselectivity, during the reduction of the 3-substituted *N*-acylpyrazinium salts with tributyltin hydride reduction, depends on the stability of the products.

With the 1,2-dihydropyrazines in hand, we envisioned that the embedded imino ether functionality of these compounds could be easily hydrolyzed to generate Δ^5-2-oxopiperazines. This hydrolysis was based on observed compound **3i** being

Table 3. Energy Difference Between 1,2- and 1,6-Dihydropyrazines[a]

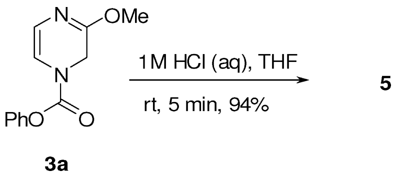
entry	isomer	R	E (kcal/mol)	ΔE (kcal/mol)	ratio (3:4)
1	**3a**	OMe	−501782.29	4.95	100:0
	4a		−501777.34		
2	**3b**	O*t*-Bu	−575794.58	4.05	100:0
	4b		−575790.52		
3	**3c**	OBn	−646769.63	4.77	100:0
	4c		−646764.86		
4	**3d**	OPh	−622102.22	6.45	100:0
	4d		−622095.76		
5	**3e**	OPh-*p*-NO_2	−750408.16	3.48	100:0
	4e		−750404.67		
6	**3f**	SCH_2CH_3	−729128.31	9.62	100:0
	4f		−729118.69		
7	**3g**	SPh-*p*-Me	−849439.81	2.30	100:0
	4g		−849437.51		
8	**3h**	morpholinyl	−609766.16	13.04	100:0
	4h		−609753.12		
9	**3i**	Cl	−718318.23	4.55	100:0
	4i		−718313.69		

[a] Total energies were obtained by DFT calculations at the B3LYP/6-31G* level.

converted to compound **5** during the aqueous workup. The Δ^5-2-oxopiperazines structure can be used as a building block for the synthesis of a number of small molecules and natural products.[13]

When we treated 1-phenoxycarbonyl-3-benzyloxy-1,2-dihydropyrazine (**3a**) with aqueous 1 M HCl, phenyl 2-oxo-1,3-dihydropyrazine-4-carboxylate (**5**) was formed very rapidly and in an excellent yield of 94% (Scheme 1). The success of our hydrolysis of **3a** prompted us to develop a one-pot approach toward synthesizing **5** (Scheme 2). As described above, we first generated 1,2-dihydropyrazine (**3a**) from 2-methoxypyrazine (**1a**) in DCM. Next, aqueous 1 M HCl was added at 0 °C, and the reaction was monitored by TLC. After 2 h, the hydrolysis of **3a** was completed to give **5** in a good yield of 84%. While examining other hydrolyzing conditions, we found that we could greatly shorten the reaction time to 5 min and increase the yield to 92% when 1 M HCl (aq) in MeOH was used. We attribute this improvement in yield and reaction time to the better solubility that 1 M HCl (aq) in MeOH has over aqueous 1 M HCl in DCM when hydrolyzing **3a**.

Scheme 1. Hydrolysis of 1-Phenoxycarbonyl-3-methoxy-1,2 Dihydropyrazine (3a)



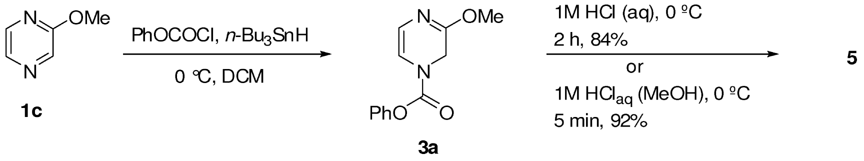
In conclusion, we have demonstrated that 3-substituted *N*-acylpyrazinium salts are regioselectively reduced by tributyltin hydride. When the substituents on these compounds are electron-donating, the 1,2-dihydropyrazine isomer is the only product produced. The observed selectivity appears to be controlled by the stability difference between the resulting possible 1,2- and 1,6-dihydropyrazine products. This reaction can be carried out with a variety of other acylating reagents giving only the 1,2-isomer. Under acidic conditions, the 3-substituted 1,2-dihydropyrazines are easily converted to Δ^5-2-oxopiperazines. Investigation into the synthetic utility of this reaction is currently underway and will be reported in due course.

■ EXPERIMENTAL SECTION

All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise stated.[14] Toluene and THF were dried using a solvent purification system. Anhydrous dichloromethane and all acylating agents were pretreated with K_2CO_3 and 4 Å molecular sieves. All reactions were performed in oven-dried glassware (either in round-bottom flasks or 25 mL vials fitted with rubber septa) under an atmosphere of nitrogen, and the reaction progress was monitored by thin-layer chromatography, GC/MS (EI) and/or LC/MS (ESI-APCI). Analytical thin-layer chromatography was performed on precoated 250 μm layer thickness silica gel 60 F_{254} plates and precoated 170−220 μm layer thickness neutral aluminum oxide Si 60 F_{254} plates. Visualization was by ultraviolet light and/or by staining with phosphomolybdic acid (PMA). Purifications were carried out on flash silica gel columns (230−400 mesh) with EtOAc/hexanes mixtures as the eluent that was basified with 0.5−1.5% triethylamine. Melting points were measured on a capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 500 MHz spectrometer. Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to it (TMS 0.0 ppm). Coupling constants (J) are reported in hertz. Multiplicities are reported using the following abbreviations: br = broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Chemical shifts (δ) for carbon are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to residual solvent peaks ($CDCl_3$ 77.0 ppm). Rotameric ratios of all compounds were determined by ^{1}H NMR. HRMS data was recorded on an LC-TOF. Elemental analyses were carried out on an elemental analyzer.

Procedures for the Synthesis of 2-Substituted Pyrazines 1e and 1g. 2-(*p*-Nitrophenoxy)pyrazine (1e). 2-Chloropyrazine (1.0 g, 8.73 mmol), *p*-nitrophenol (1.8 g, 12.94 mmol), and sodium hydride (0.7 g, 17.50 mmol) in 8 mL of DMF (anhyd) were heated to 120 °C under nitrogen for 20 h. The reaction mixture was quenched into 10 g of ice, extracted into diethyl ether (2 × 15 mL), washed with 3 M NaOH, dried over sodium sulfate, and then concentrated *in vacuo*. The crude material was purified by flash silica gel column chromatography (0−50% EtOAc/hexanes) to afford **1e** (0.616 g, 33%) as a white crystalline solid: mp 105−106 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.54 (s, 1H), 8.39 (s, 1H), 8.31 (d, J = 9.0 Hz, 2H),

Scheme 2. One-Pot Synthesis of Phenyl 2-oxo-1,3-dihydropyrazine-4-carboxylate (5)



8.15 (s, 1H), 7.34 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.9, 158.2, 144.7, 141.0, 140.0, 136.4, 125.6, 121.4; HRMS (ESI) m/z calcd for $C_{10}H_8N_3O_3$ $[M + H]^+$ 218.0562, found 218.0560.

2-(*p*-Tolylsulfanyl)pyrazine (1g). *p*-Tolylthiol (1.20 g, 9.66 mmol) was added to a slurry of sodium hydride (0.7 g, 17.50 mmol) in 5 mL of dimethoxyethane, and the mixture heated to 45−50 °C under nitrogen. A solution of 2-chloropyrazine (1.0 g, 8.73 mmol) in 3 mL of dimethoxyethane was then added over 10 min, and heating was continued for 5 h. The reaction mixture was quenched into 10 g of ice, extracted into diethyl ether (2 × 15 mL), dried over sodium sulfate, and then concentrated *in vacuo*. The crude material was purified by flash silica gel column chromatography (0−15% EtOAc/hexanes) to afford **1g** (1.71 g, 97%) as a white crystalline solid: mp 30−32 °C; ^{1}HNMR $CDCl_3$ (500 MHz) δ 8.32 (s, 1H), 8.21 (s, 1H), 8.17 (s, 1H), 7.50 (d, J = 8 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.2, 143.8, 142.6, 140.1, 139.9, 135.2, 130.7, 125.2, 21.4. HRMS (ESI) m/z calcd for $C_{11}H_{11}N_2S$ $[M + H]^+$ 203.0637, found 203.0637.

General Procedure for the Reduction of 3-Substituted *N*-Acylpyrazinium Salts To Synthesize 1,2-Dihydropyrazines (3a−3h). Representative Procedure for the Preparation of 1-Phenoxycarbonyl-3-methoxy-1,2-dihydropyrazine (3a). To a solution of 2-methoxypyrazine (**1a**) (112 mg, 1.017 mmol) in 2.5 mL of anhydrous dichloromethane was added tributyltin hydride (330 μL, 1.208 mmol), and the resulting solution was stirred under nitrogen at 0 °C. Phenyl chloroformate (190 μL, 1.510 mmol) in 0.5 mL of dichloromethane was added over 15 min, and the reaction was allowed to stir at 0 °C. The reaction was completed in 40 min, as determined by TLC (neutral alumina, EtOAc/hexanes (1/19, v/v)), and then quenched with 1.5 mL of aqueous 20% NH_4OH/NH_4Cl (1/1, w/w). The solution was extracted with dichloromethane (2 × 15 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude mixture by flash silica gel column chromatography (0−15% EtOAc/hexanes) afforded **3a** (213.5 mg, 90%) as a white crystalline solid (65:35 mixture of rotamers): mp 48−49 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (t, J = 7.5 Hz, J = 8.5 Hz, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 6.59 and 6.54 (two doublets due to rotamers, J = 6.0 Hz, J = 5.5 Hz, 1H), 6.08 and 6.03 (two doublets due to rotamers, J = 5.0 Hz, J = 5.5 Hz, 1H), 4.39 and 4.26 (two singlets due to rotamers, 2H), 3.84 and 3.83 (two singlets due to rotamers, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.4, 158.9, 151.4, 151.3, 150.8, 150.6, 129.4, 125.9, 125.9, 121.5, 121.4, 118.4, 118.3, 112.8, 112.4, 53.8, 53.7, 42.8, 42.0; HRMS (ESI) m/z calcd for $C_{12}H_{13}N_2O_3$ $[M + H]^+$ 233.0926, found 233.0921.

1-Phenoxycarbonyl-3-*tert*-butoxy-1,2-dihydropyrazine (3b). 94% yield; clear colorless oil (67:33 mixture of rotamers); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (t, J = 7.5 Hz, J = 8.0 Hz, 2H), 7.23 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 6.53 and 6.47 (two doublets due to rotamers, J = 5.0 Hz, J = 5.5 Hz, 1H), 6.05 and 6.01 (two doublets due to rotamers, J = 5.5 Hz, 1H), 4.25 and 4.12 (two singlets due to rotamers, 2H), 1.55 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.40, 156.89, 151.55, 151.37, 150.87, 150.70, 129.57, 129.42, 125.80, 121.54, 121.47, 120.91, 119.15, 111.72, 111.36, 82.01, 43.31, 42.51, 28.13; HRMS (ESI) m/z calcd for $C_{15}H_{18}NaN_2O_3$ $[M + Na]^+$ 297.1215, found 297.1225.

1-Phenoxycarbonyl-3-benzyloxy-1,2-dihydropyrazine (3c). 91% yield; white crystalline solid (64:36 mixture of rotamers); mp 76−78 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43−7.30 (m 7 H), 7.22 (t, J = 7.0 Hz, J = 7.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 2H), 6.61 and 6.56 (two doublets due to rotamers, J = 6.0 Hz, 1H), 6.10 and 6.06 (two doublets due to rotamers, J = 5.5 Hz, J = 5.0 Hz, 1H), 5.26 (s, 2H), 4.44 and 4.32 (two singlets due to rotamers, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.6, 158.2, 151.4, 151.3, 150.8, 150.6, 135.8, 129.5, 128.6, 128.6, 128.4, 128.3, 128.3, 128.2, 125.9, 121.5, 121.4, 118.4, 118.2, 113.1, 112.6, 68.4, 68.3, 42.9, 42.2. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.09; H, 5.24; N, 9.16

1-Phenoxycarbonyl-3-phenoxy-1,2-dihydropyrazine (3d). 91% yield; white crystalline solid (64:36 mixture of rotamers); mp 128−129 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45−7.35 (m, 4H), 7.29−7.12 (m, 6H), 6.63 and 6.59 (two doublets due to rotamers, J = 5.0 and 5.5 Hz, 1H), 6.01 and 5.98 (two doublets due to rotamers, J = 5.5 and 5.0 Hz, 1H), 4.66 and 4.52 (two singlets due to rotamers, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.6, 158.1, 151.8, 151.3, 150.7, 150.6, 129.5, 129.5, 126.0, 125.9, 121.7, 121.5, 121.4, 118.0, 117.9, 113.5, 113.1, 42.9, 42.1; HRMS (ESI) m/z calcd for $C_{17}H_{15}N_2O_3$ $[M + H]^+$ 295.1077, found 295.1077.

1-Phenoxycarbonyl-3-(*p*-nitrophenol)-1,2-dihydropyrazine (3e). 78% yield; white crystalline solid (62:38 mixture of rotamers); mp 157−158 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.29 (d, J = 9.0 Hz, 2H), 7.52−7.33 (m, 4 H), 7.33−723. (m, 1H), 7.23−7.08 (m, 2H), 6.70 and 6.45 (two doublets due to rotamers, J = 5.0 Hz, J = 5.0 Hz 1H,), 5.99 and 5.96 (two doublets due to rotamers, J = 5.5 Hz, J = 5.0 Hz, 1H), 4.70 and 4.56 (two singlets due to rotamers, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.2, 156.6, 151.3, 151.2, 150.6, 145.2, 129.4, 126.1, 125.3, 122.6, 122.6, 121.4, 117.1, 117.0, 114.6, 114.2, 42.8, 41.9; HRMS (ESI) m/z calcd for $C_{17}H_{14}N_3O_5$ $[M + H]^+$ 340.0928, found 340.0932.

1-Phenoxycarbonyl-3-thioethyl-1,2-dihydropyrazine (3f). 65% yield; clear light-yellow oil (64:36 mixture of rotamers); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (t, J = 7.5 Hz, 2H), 7.24 (t, 7.5 Hz, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.64 and 6.59 (two doublets due to rotamers, J = 5.5 Hz, 1H), 6.43 and 6.38 (two doublets due to rotamers, J = 5.5 Hz, 1H), 4.35 and 4.23 (two singlets due to rotamers, 2H), 3.01−3.11 (m, 2H), 1.30−1.39 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.7, 157.8, 151.5, 151.2, 150.7, 150.5, 129.5, 126.0, 125.9, 122.0, 121.5, 121.4, 114.4, 113.8, 45.7, 44.8, 23.9, 23.8, 14.0; HRMS (ESI) m/z calcd for $C_{13}H_{15}N_2O_2S$ $[M + H]^+$ 263.0849, found 263.0854.

1-Phenoxycarbonyl-3-thiotolyl-1,2-dihydropyrazine (3g). 62% yield; light-yellow semisolid (67:43 mixture of rotamers); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (d, J = 8.0 Hz, 2H), 7.38 (t, J = 8.0 Hz, J = 7.5 Hz, 3H), 7.27−7.15 (m, 3H), 7.12 (d, d, J = 8.0 Hz, 2H), 6.63 and 6.58 (two doublets J = 5.5 Hz, J = 5 Hz, 1H), 6.38 and 6.33 (two doublets J = 5.0 Hz, 1H), 4.37 and 4.23 (two singlets due to rotamers, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.2, 158.0, 151.3, 150.7, 140.2, 135.2, 135.2, 135.0, 130.7, 130.3, 129.5, 126.0, 123.6, 123.4, 122.4, 121.9, 121.4, 114.8, 114.1, 44.9, 43.9, 29.7, 21.4; HRMS (ESI) m/z calcd for $C_{18}H_{17}N_2O_2S$ $[M + H]^+$ 325.1005, found 325.1001.

1-Phenoxycarbonyl-3-morpholinyl-1,2-dihydropyrazine (3h). 56% yield; off-white semisolid (78:22 mixture of rotamers); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (t, J = 8.0 Hz, 2H), 7.24 (t, J = 7.5 Hz, 2H), 7.13 (d, J = 8 Hz, 2H), 6.45 and 6.40 (two doublets due to rotamers, J = 5.0 Hz, J = 5.5 Hz, 1H), 6.22 and 6.19 (two doublets due to rotamers, J = 5.5 Hz, J = 5.0 Hz, 1H), 4.47 and 4.33 (two singlets due to rotamers, 2H), 3.76 and 3.74 (two triplets due to rotamers, J = 7.0 Hz, J = 7.5 Hz, 4H), 3.52 (t, J = 7.0 Hz, J = 7.5 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.0, 152.5, 151.8, 151.4, 150.9, 150.6, 129.8, 129.5, 129.5, 129.4, 126.2, 126.0, 125.8, 121.7, 121.6, 121.5, 124.3, 120.1, 115.4, 109.1, 108.6, 67.4, 66.4, 66.3, 45.4, 44.9, 44.8, 40.7, 39.7; HRMS (ESI) m/z calcd for $C_{15}H_{18}N_3O_3$ $[M + H]^+$ 288.1343, found 288.1341.

Phenyl 2-oxo-1,3-dihydropyrazine-4-carboxylate (5). Subjecting 2-chloropyrazine **1i** (250 mg, 2.183 mmol) to the above procedure and purification of the crude mixture by flash silica gel column chromatography (0−75% EtOAc/hexanes) gave **5** (218.1 mg, 46%) as a white crystalline solid (56:44 mixture of rotamers): mp 170−172 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 and 7.88 (two broad singlets due to rotamers, 1H), 7.39 (t, J = 7.5 Hz, J = 8.0 Hz, 2H), 7.25 (t, J = 6.5 Hz, J = 7.5 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 6.51 and 6.47 (two doublets due to rotamers, J = 6.0 Hz, 1H), 5.72 and 5.67 (two triplets due to rotamers, J = 5.0 Hz, J = 5.5 Hz, 1H), 4.51 and 4.38 (two singlets due to rotamers, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9, 164.5, 151.5, 151.3, 150.7, 150.6, 129.5, 126.0, 121.4, 121.4, 109.1, 108.7, 108.3, 47.6, 46.9. Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.94; N, 12.84. Found: C, 60.64; H, 4.80; N, 12.54.

General Procedure for the Synthesis of *N*-Acyl-3-Methoxy-1,2-Dihydropyrazines (7a−7e). Representative Procedure for the Preparation of 1-Methoxycarbonyl-3-methoxy-1,2-dihydropyrazine 7a. To a solution of 2-methoxypyrazine (**1a**) (112 mg, 1.017 mmol) in 2.5 mL of anhydrous dichloromethane was added tributyltin hydride (330 μL, 1.208 mmol), and the resulting solution was stirred under nitrogen at 0 °C. Methyl chloroformate (125 μL, 1.569 mmol) in 0.5 mL of dichloromethane was added over 5 min, and the reaction was allowed to stir at 0 °C. The reaction was completed in 45 min, as determined by TLC (neutral alumina, EtOAc/hexanes (1/19, v/v)), and then quenched with 1.5 mL of aqueous 20% NH_4OH/NH_4Cl (1/1, w/w). The solution was extracted with dichloromethane (2 × 15 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the crude mixture by flash silica gel column chromatography (0−15% EtOAc/hexanes) afforded **7a** (158.1 mg, 91%) as a clear colorless oil (62:38 mixture of rotamers): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.50 and 6.37 (two doublets due to rotamers, *J* = 5.5 Hz, *J* = 5.0 Hz, 1H), 5.99 and 5.92 (two doublets due to rotamers, *J* = 5.0 Hz, *J* = 5.5 Hz, 1H), 5.22 (s, 2H), 4.19 and 4.17 (two singlets due to rotamers, 2H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.2, 158.7, 153.5, 153.4, 117.4, 117.4, 113.2, 112.6, 53.6, 53.4, 42.3, 41.9; HRMS (ESI) *m/z* calcd for $C_7H_{10}N_2O_3$ $[M + H]^+$ 171.0764, found 171.0766.

1-Benzyloxycarbonyl-3-methoxy-1,2-dihydropyrazine (7b). 85% yield; clear colorless oil (61:39 mixture of rotamers); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.29 (m, 5H), 6.51 and 6.41 (two doublets due to rotamers, *J* = 5.0, 1H), 5.99 and 5.91 (two doublets due to rotamers, *J* = 5.0 Hz, 1H), 5.21 (s, 2H), 4.20 (s, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.2, 158.7, 152.9, 152.7, 135.8, 135.7, 128.6, 128.5, 128.4, 128.3, 128.2, 117.5, 117.4, 113.1, 112.6, 68.0, 53.6, 42.3, 41.9; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_2O_3$ $[M + H]^+$ 247.1077, found 247.1077.

1-Acetyl-3-methoxy-1,2-dihydropyrazine (7c). 74% yield;[15] white crystalline solid (89:11 mixture of rotamers); mp 51−53 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.77 and 6.23 (two doublets due to rotamers, *J* = 5.5 Hz, 1H), 6.06 and 6.00 (two doublets due to rotamers, *J* = 6.0 Hz, *J* = 5.5 Hz, 1H), 4.25 and 4.20 (two singlets due to rotamers, 2H), 3.83 and 3.82 (two singlets due to rotamers, 3H), 2.17 and 2.13 (two singlets due to rotamers, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.2, 168.0, 160.6, 158.6, 118.7, 118.7, 113.0, 111.9, 53.8, 53.6, 44.0, 40.5, 21.6, 20.9; HRMS (ESI) *m/z* calcd for $C_7H_{10}N_2O_2$ $[M + H]^+$ 155.0815, found 155.0816.

1-Phenylcarbonyl-3-methoxy-1,2-dihydropyrazine (7d). 89% yield; off-white solid, mp 56−58 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55−7.28 (m 5H), 6.17 (s, 1H), 5.94 (s, 1H), 4.38 (s, 2H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 160.4, 133.6, 131.1, 128.7, 128.5, 118.3, 114.9, 53.8, 41.6; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}N_2O_2$ $[M + H]^+$ 217.0972, found 217.0979.

1-Cyclohexanecarbonyl-3-methoxy-1,2-dihydropyrazine (7e). 93% yield; clear colorless oil (89:11 mixture of rotamers); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.79 and 6.32 (two doublets due to rotamers, *J* = 5.5 Hz, 1H), 6.09 and 6.00 (two doublets due to rotamers, *J* = 5.0 Hz, 1H), 4.23 (s, 2H), 3.83 and 3.82 (two singlets due to rotamers, 2H), 2.57−2.46 and 2.43−2.32 (two multiplets due to rotamers, 1H), 1.86−1.66 (m, 4H), 1.58−1.46 (m, 2H), 1.35−1.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.0, 161.0, 118.8, 112.6, 53.6, 40.8, 40.7, 28.9, 25.7, 25.7; HRMS (ESI) *m/z* calcd for $C_{12}H_{19}N_2O_2$ $[M + H]^+$ 223.1441, found 223.1449.

Hydrolysis of 3a for the Synthesis of 4-Phenoxycarbonyl-1,2-dihydro-2-pyrazinone (5). To a solution of 1-phenoxycarbonyl-3-methoxy-1,2-dihydropyrazine (**3a**) (150 mg, 0.646 mmol) in 1.0 mL of anhydrous tetrahydrofuran was added 1 M HCl in methanol (1.0 mL, 1.0 mmol) over 1 min, and the resulting solution was stirred under nitrogen in an ice bath at 0 °C. The reaction was completed within 5 min, as determined by TLC (silica gel, EtOAc/hexanes (2/3, v/v)). Water (1 mL) was added, and the reaction mixture was extracted with dichloromethane (2 × 10 mL). The organic layer was washed with saturated sodium bicarbonate (1.0 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude mixture by flash silica gel column chromatography (0−75% EtOAc/hexanes) afforded **5** (132.7 mg, 94%) as a white crystalline solid.

One-Pot Synthesis of 4-Phenoxycarbonyl-1,2-dihydro-2-pyrazinone 5. To a solution of 2-methoxypyrazine (**1a**) (112 mg, 1.017 mmol,) in 2.5 mL of anhydrous dichloromethane was added tributyltin hydride (330 μL, 1.208 mmol), and the resulting solution was stirred under nitrogen at 0 °C. Phenyl chloroformate (190 μL, 1.510 mmol) in 0.5 mL of dichloromethane was added over 15 min, and the reaction was allowed to stir at 0 °C. Formation of 1,2-dihydropyrazine **3a** was completed in 25 min, as determined by TLC (neutral alumina, EtOAc/hexanes (1/19, v/v)). Next, 1 M HCl in methanol (1.5 mL, 1.5 mmol) was added at 0 °C. The hydrolysis reaction was completed in 5 min, as determined by TLC (silica gel, EtOAc/hexanes (2/3, v/v)). Water (1.0 mL) was added, and the reaction mixture was extracted with dichloromethane (2 × 10 mL). The organic layer was washed with saturated sodium bicarbonate (1.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the crude mixture by flash silica gel column chromatography (0−75% EtOAc/hexanes) afforded **5** (200.9 mg, 91%) as a white crystalline solid.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Total energies and Cartesian coordinates; copies of ^{1}H and ^{13}C NMR of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) See the NMR of crude **3a** in the Supporting Information.

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