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10-ARYL-7,7-DIMETHYL-5,6,7,8,9,10-HEXAHYDRO-11H-PYRIDO[3,2-*b*][1,4]BENZODIAZEPIN-9-ONES

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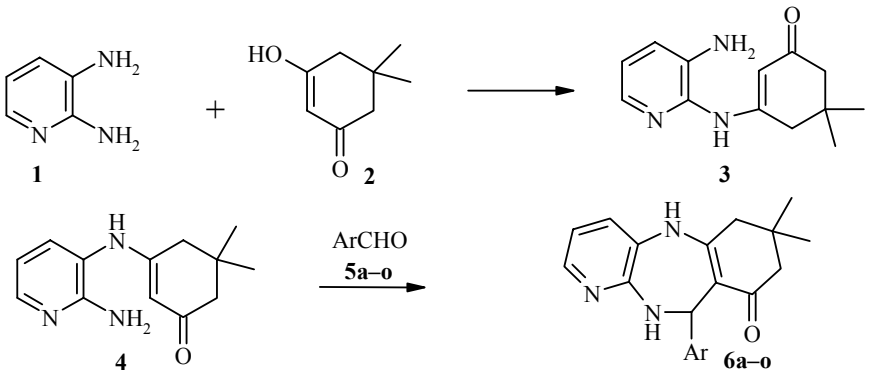
In reactions of 3-(2-amino-3-pyridyl)amino-5,5-dimethylcyclohex-2-en-1-one with aromatic aldehydes (2- and 4-hydroxy-, 2-hydroxy-3-methoxy-, 4-dimethylamino-, 4-methoxy-, 2,4- and 3,4-dimethoxy-, 3,4-methylenedioxy-, 4-bromo-, 4-fluoro-, 4-chloro-, 2-nitro- and 3-nitrobenzaldehydes, furfural, and 2-thiophenecarbaldehyde), we have obtained the corresponding 10-aryl-7,7-dimethyl-5,6,7,8,9,10-hexahydro-11H-pyrido[3,2-b][1,4]benzodiazepin-9-ones.

Keywords: aromatic aldehydes, 2,3-diaminopyridine, dimedone, pyrido[3,2-*b*][1,4]benzodiazepine derivatives.

Our attempts to synthesize derivatives of hydrogenated pyrido[3,2-*b*][1,4]- or pyrido[2,3-*b*]-[1,4]benzodiazepines by reactions of 2,3-diaminopyridine (**1**) with 2-formyldimedone [1] and 2-carbamidodimedone [2] did not lead to the indicated type of compounds.

In this paper, we describe the reactions of 3-(2-amino-3-pyridyl)amino-5,5-dimethylcyclohex-2-en-1-one with aromatic aldehydes, which lead to synthesis of 10-aryl-7,7-dimethyl-5,6,7,8,9,10-hexahydro-11H-pyrido[3,2-*b*][1,4]benzodiazepin-9-ones. Such a general scheme (reaction of enamines, obtained from 1,3-cyclohexanediones, and aromatic *o*-diamines with aldehydes) has been widely used for synthesis of derivatives of dibenzodiazepine [3-7] and also pyridobenzodiazepine [8], among which the pyrido[2,3-*b*]-[1,4]benzodiazepine derivatives have the most valuable pharmacological properties [9-11].



5, **6 a Ar** = 2-HOC_6H_4; **b** Ar = 4-HOC_6H_4; **c** Ar = 2-HO-3-$MeOC_6H_3$; **d** Ar = 4-$Me_2NC_6H_4$; **e** Ar = 4-$MeOC_6H_4$; **f** Ar = 2,4-$(MeO)_2C_6H_3$; **g** Ar = 3,4-$(MeO)_2C_6H_3$; **h** Ar = 3,4-$CH_2O_2C_6H_3$; **i** Ar = 4-BrC_6H_4; **j** Ar = 4-ClC_6H_4; **k** Ar = 4-FC_6H_4; **l** Ar = 2-$O_2NC_6H_4$; **m** Ar = 3-$O_2NC_6H_4$; **n** Ar = 2-C_4H_3O; **o** Ar = 2-C_4H_3S

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In the reaction of 2,3-diaminopyridine (**1**) with dimedone **2**, two isomeric enamines **3** and **4** can be formed. We know [8] that when diamine **1** reacts with 1,3-cyclohexanedione, the product of reaction at the 3-amino group is obtained. In the reaction under discussion of diamine **1** with dimedone, carried out under conditions for azeotropic distillation of water, only one compound is isolated from the reaction mixture and identified. Based on ^{1}H NMR spectra, we have assigned this compound the structure of 3-(2-amino-3-pyridyl)-amino-5,5-dimethylcyclohex-2-en-1-one (**4**). We identified enamine **4** by comparing its spectra with the ^{1}H NMR spectra of 3-(2-amino-3-pyridyl)aminocyclohex-2-en-1-one [8]. The chemical shifts and spin–spin coupling constants in the spectra of both these compounds virtually coincide: the differences between their chemical shifts (Δδ) are 0.07 ppm for the NH_2 group and 0.06 ppm for the =CH– group. The maximum chemical shift difference is observed for the $C_{(3)}$–H protons of the pyridine moiety of the molecule (Δδ = 0.12 ppm), where the chemical shift values for the $C_{(2)}$–H protons (Δδ = 0.05 ppm) and $C_{(3)}$–H protons (Δδ = 0.03 ppm) are virtually the same in both compounds, while the spin–spin coupling constants ($^3J_{H\alpha,H\beta}$ = 5 Hz, $^3J_{H\beta,H\gamma}$ = 7.5 Hz) match within the experimental accuracy limits. In the spectra of both of the compared compounds, we observe a strongly broadened signal from the NH proton relatively upfield at ~7.3 ppm. Chromatographic data for the reaction mixture after isolation of enamine **4** suggest the presence of four more compounds in the mixture, probably also including enamine **3**, which unfortunately we could not isolate.

We carried out the reaction of enamine **4** with aldehydes **5a-d**, containing the functional groups [OH, $N(CH_3)_2$], by boiling equimolar amounts of the reagents in ethanol in the presence of piperidine acetate. We used the same conditions in the reactions of enamine **4** with furfural **5n** and 2-thiophenecarbaldehyde **5o**. In the

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Hal (S)		
4	$C_{13}H_{17}N_3O$	67.30 / 67.50	7.49 / 7.41	18.10 / 18.17		223-224	26
6a	$C_{20}H_{21}N_3O_2$	71.44 / 71.62	6.16 / 6.31	12.60 / 12.53		252-253	82
6b	$C_{20}H_{21}N_3O_2$	71.50 / 71.62	6.33 / 6.31	12.42 / 12.53		291-292	70
6c	$C_{21}H_{23}N_3O_3$	69.19 / 69.02	6.16 / 6.34	11.42 / 11.50		243-244	47
6d	$C_{22}H_{26}N_4O$	66.81 / 66.98	6.49 / 6.64	14.14 / 14.20		252-253	70
6e	$C_{21}H_{23}N_3O_2$	72.01 / 72.18	6.69 / 6.63	11.91 / 12.03		197-198	38
6f	$C_{22}H_{25}N_3O_3$	69.42 / 69.63	6.60 / 6.64	11.11 / 11.07		213-215	43
6g	$C_{22}H_{25}N_3O_3$	69.50 / 69.63	6.73 / 6.64	10.93 / 11.07		126-127	60
6h	$C_{21}H_{21}N_3O_3$	69.21 / 69.40	5.70 / 5.83	11.60 / 11.56		233-234	66
6i	$C_{20}H_{20}BrN_3O$	60.11 / 60.31	5.01 / 5.06	10.66 / 10.55	19.90 / 20.06	237-239	62
6j	$C_{20}H_{20}ClN_3O$	67.71 / 67.89	5.56 / 5.70	11.72 / 11.88	9.80 / 10.02	249-251	38
6k	$C_{20}H_{20}FN_3O$	71.01 / 71.20	6.04 / 5.98	12.33 / 12.45		237-238	73
6l	$C_{20}H_{20}N_4O_3$	65.70 / 65.92	5.50 / 5.53	15.27 / 15.38		196-197	73
6m	$C_{20}H_{20}N_4O_3$	65.77 / 65.92	5.39 / 5.53	15.19 / 15.38		179-181	77
6n	$C_{18}H_{19}N_3O_2$	69.65 / 69.88	6.03 / 6.19	13.42 / 13.58		244-245	74
6o	$C_{18}H_{19}N_3OS$	66.26 / 66.43	5.80 / 5.88	12.73 / 12.91	(9.60) / (9.85)	271-272	83

TABLE 2. IR and ^{1}H NMR Spectra of Synthesized Compounds

Com-pound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm. (SSCC, *J*, Hz)*
1	2	3
4	1666, 1595, 1570, 550-1530; 3400, 3350, 3250-3100	1.03 (6H, s, 2CH_3); 2.18 (2H, s, CH_2); 2.36 (2H, s, CH_2); 4.71 (2H, br. s, NH_2); 5.09 (1H, s, =CH-); 6.64 (1H, dd, ^3J = 7.5, ^4J = 5, C_5H_3N); 7.30 (1H, br. s, NH); 7.38 (1H, dd, ^3J = 7.5, ^4J = 2, C_5H_3N); 7.87 (1H, dd, ^3J = 5, ^4J = 2, C_5H_3N)
6a	1645; 3350-3250; 3200-3080	1.03 (3H, s, CH_3); 1.14 (3H, s, CH_3); 2.11 and 2.17 (2H, two d, ^2J = 14, CH_2); 2.69 (2H, s, CH_2); 5.81 (1H, d, ^3J = 6, CH); 6.00 (1H, d, ^3J = 6, NH); 6.41-6.96 (6H, m, C_6H_4, C_5H_3N); 7.25 (1H, dd, ^3J =7, ^4J = 2, C_5H_3N); 7.56 (1H, dd, ^3J = 5, ^4J = 2, C_5H_3N); 8.94 (1H, br. s, OH); 9.76 (1H, br. s, NH)
6b	1642; 3450-3200; 3150-3050	0.95 (3H, s, CH_3); 1.14 (3H, s, CH_3); 2.12 and 2.20 (2H, two d, ^2J = 14, CH_2); 2.55 (2H, s, CH_2); 5.74 (1H, d, ^3J = 6, CH); 6.49-7.72 (8H, m, C_6H_4, C_5H_3N, NH); 7.77 (1H, br. s, NH); 9.14 (1H, br. s, OH)
6c	1645; 3300-3200; 3150-3050	1.05 (3H, s, CH_3); 1.12 (3H, s, CH_3); 2.12 and 2.20 (2H, two d, ^2J = 14, CH_2); 2.67 (2H, s, CH_2); 3.76 (3H, s, OCH_3); 5.77 (1H, d, ^3J = 6, NH); 6.05 (1H, d, ^3J = 6, CH); 6.25-6.81 (4H, m, C_6H_3, C_5H_3N); 7.34 (1H, dd, ^3J = 7, ^4J = 1.5, C_5H_3N); 7.58 (1H, dd, ^3J = 7, ^4J = 1.5, C_5H_3N); 8.96 (1H, br. s, NH); 9.03 (1H, br. s, OH)
6d	1638; 3300, 3200; 3150-3050	1.01 (3H, s, CH_3); 1.12 (3H, s, CH_3); 2.15 and 2.21 (2H, two d, ^2J = 16, CH_2); 2.54 (2H, s, CH_2); 2.81 (6H, s, NCH_3); 5.77 (1H, d, ^3J = 6, CH); 6.46-6.78 (4H, m, C_6H_4, C_5H_3N, NH); 7.03 (2H, m, ^3J = 8, C_6H_4); 7.27 (1H, dd, ^3J = 7, ^4J = 1.5, C_5H_3N); 7.65 (1H, dd, ^3J = 5, ^4J = 1.5, C_5H_3N); 7.78 (1H, br. s, NH)
6e	1640; 3300, 3200-3100	1.01 (3H, s, CH_3); 1.12 (3H, s, CH_3); 2.13 and 2.21 (2H, two d, ^2J = 14, CH_2); 2.58 (2H, s, CH_2); 3.67 (3H, s, OCH_3); 5.76 (1H, d, ^3J = 6, CH); 6.58-7.27 (6H, m, C_6H_4, C_5H_3N, NH); 7.27 (1H, dd, ^3J = 7, ^4J = 1.5, C_5H_3N); 7.63 (1H, dd, ^3J = 5, ^4J = 1.5, C_5H_3N); 7.87 (1H, br. s, NH)
6f	1645;3350, 3250-3100	1.01 (3H, s, CH_3); 1.09 (3H, s, CH_3); 2.14 and 2.22 (2H, two d, ^2J = 15, CH_2); 2.56 (2H, s, CH_2); 3.58 (3H, s, OCH_3); 3.65 (3H, s, OCH_3); 5.76 (1H, d, ^3J = 6, =CH-); 6.54 (5H, m, C_6H_3, C_5H_3N, NH); 7.25 (1H, dd, ^3J = 7, ^4J = 1.5, C_5H_3N); 7.63 (1H, dd, ^3J = 5, ^4J = 1.5, C_5H_3N); 8.81 (1H, br. s, NH)
6g	1644; 3350, 3260, 3200-3100	1.03 (3H, s, CH_3); 1.12 (3H, s, CH_3); 2.12 and 2.20 (2H, two d, ^2J = 15, CH_2); 2.63 (2H, s, CH_2); 3.67 (3H, s, OCH_3); 3.91 (3H, s, OCH_3); 5.72 (1H, d, ^3J = 6, NH); 5.83 (1H, d, ^3J = 6, CH); 6.21-6.75 (4H, m, C_6H_3, C_5H_3N); 7.27 (1H, m, ^3J = 8, C_6H_3); 7.58 (1H, dd, ^3J = 5, ^4J = 1, C_5H_3N); 8.92 (1H, br. s, NH)
6h	1638; 3300, 3200-3050	1.01 (3H, s, CH_3); 1.12 (3H, s, CH_3); 2.15 and 2.21 (2H, two d, ^2J = 16, CH_2); 2.58 (2H, s, CH_2); 5.74 (1H, d, ^3J = 6, CH); 5.94 (2H, s, CH_2); 6.58-6.82 (5H, m, C_6H_3, C_5H_3N, NH); 7.27 (1H, dd, ^3J = 7, ^4J = 1.5, C_5H_3N); 7.67 (1H, dd, ^3J = 5, ^4J = 1.5, C_5H_3N); 8.85 (1H, br. s, NH)
6i	1638; 3300, 3200-3050	0.98 (3H, s, CH_3); 1.09 (3H, s, CH_3); 2.12 and 2.20 (2H, two d, ^2J = 14, CH_2); 2.56 (2H, s, CH_2); 5.78 (1H, d, ^3J = 6, CH); 6.67 (1H, dd, ^3J = 7, ^3J = 5, C_5H_3N); 6.87 (1H, d, ^3J = 6, NH); 7.04-7.45 (5H, m, C_6H_4, C_5H_3N, NH); 7.67 (1H, dd, ^3J = 5, ^4J = 2, C_5H_3N); 8.89 (1H, br. s, NH)
6j	1638; 3300, 3240-3080	1.03 (3H, s, CH_3); 1.09 (3H, s, CH_3); 2.14 and 2.22 (2H, two d, ^2J = 15, CH_2); 2.65 (2H, s, CH_2); 5.83 (1H, d, ^3J = 6, CH); 6.62 (1H, dd, ^3J = 7, ^3J = 5, C_5H_3N); 6.85 (1H, d, ^3J = 6, NH); 7.18-7.34 (5H, m, C_6H_4, C_5H_3N); 7.69 (1H, dd, ^3J = 5, ^4J = 1.5, C_5H_3N); 8.92 (1H, br. s, NH)
6k	1645; 3300, 3250-3100	1.01 (3H, s, CH_3); 1.11 (3H, s, CH_3); 2.14 and 2.22 (2H, two d, ^2J = 14, CH_2); 2.55 (2H, s, CH_2); 5.83 (1H, d, ^3J = 6, CH); 6.58-7.33 (7H, m, C_6H_4, C_5H_3N, NH); 7.67 (1H, dd, ^3J = 5, ^4J = 1.5, C_5H_3N); 8.89 (1H, br. s, NH)

TABLE 2 (continued)

1	2	3
6l	1640; 3350, 3250-3100	0.98 (3H, s, CH_3); 1.09 (3H, s, CH_3); 2.06 and 2.14 (2H, two d, ^2J = 14, CH_2); 2.67 (2H, s, CH_2); 5.78 (1H, d, ^3J = 6, NH); 6.07 (1H, d, ^3J = 6, CH); 6.78-8.06 (7H, m, C_6H_4, C_5H_3N); 8.89 (1H, br. s, NH)
6m	1643; 3300, 3240-3080	1.01 (3H, s, CH_3); 1.14 (3H, s, CH_3); 2.21 and 2.29 (2H, two d, ^2J = 15, CH_2); 2.63 (2H, s, CH_2); 6.09 (1H, br. s, CH); 6.89 (1H, dd, ^3J = 7, ^3J = 5, C_5H_3N); 7.49-8.12 (7H, m, C_6H_4, C_5H_3N, NH); 9.25 (1H, br. s, NH)
6n	1635; 3320, 3200-3050	0.96 (3H, s, CH_3); 1.07 (3H, s, CH_3); 2.11 and 2.17 (2H, two d, ^2J = 16, CH_2); 2.51 (2H, s, CH_2); 5.81 (1H, d, J = 6, CH); 5.82 (1H, m, C_4H_3O); 6.14 (1H, m, C_4H_3O); 6.67 (2H, m, C_5H_3N, NH); 7.29-7.42 (2H, m, C_4H_3O, C_5H_3N); 7.72 (1H, dd, ^3J = 5, ^4J = 1, C_5H_3N); 8.88 (1H, br. s, NH)
6o	1637; 3350, 3220-3080	0.99 (3H, s, CH_3); 1.05 (3H, s, CH_3); 2.12 and 2.20 (2H, two d, ^2J = 14, CH_2); 2.55 (2H, s, CH_2); 6.03 (1H, d, ^3J = 6, CH); 6.58-6.92 (4H, m, C_5H_3N, C_4H_3S); 7.14-7.34 (2H, m, C_5H_3N, C_4H_3S); 7.69 (1H, dd, ^3J = 5, ^4J = 1.5, C_5H_3N); 8.89 (1H, br. s, NH)

* The ^{1}H NMR spectrum of compound **4** was recorded in $CDCl_3$; the spectra for the rest of the compounds were recorded in DMSO-d_6.

reactions with the aldehydes **5e-m**, the best results were achieved by boiling in ethanol in the presence of sulfuric acid.

In the ^{1}H NMR spectra of the derivatives of pyridodiazepine **6**, the proton at the $C_{(10)}$ atom is characterized by a doublet δ 5.74-6.09 ppm (J = 6 Hz), and the proton at the adjacent $N_{(11)}$ atom gives a doublet δ 5.72-6.87 ppm (J = 6 Hz). The protons of the methylene group at $C_{(8)}$ are magnetically nonequivalent and coupled (geminal spin–spin coupling constant 14-16 Hz), representing an AB spin system.

In the IR spectra, the carbonyl group of compounds **6** is characterized by absorption bands in the interval 1645-1635 cm^{-1}, while the stretching vibrations of the NH bonds are intense bands in the 3350-3100 cm^{-1} region.

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 for suspensions of the compounds in vaseline oil (1800-1500 cm^{-1}, only the absorption bands for the carbonyl group are given) and in hexachlorobutadiene (3600-2000 cm-1, the stretching vibration bands for the C–H bonds in the 3050-2800 cm^{-1} region are not given). The ^{1}H NMR spectra were measured on Bruker WH-90/DS (90 MHz) and Varian-BB Mercury (200 MHz) spectrometers, internal standard HMDS (δ 0.055 ppm)

We used Fluka 2,3-diaminopyridine for synthesis of enamine **4**.

3-(2-Amino-3-pyridyl)amino-5,5-dimethylcyclohex-2-en-1-one (4). A solution of dimedone (2.80 g, 20 mmol) and 2,3-diaminopyridine (2.18 g, 20 mmol) in toluene (100 ml) in the presence of a catalytic amount of *p*-toluenesulfonic acid was boiled for 3 h with a Dean–Stark attachment. Then the toluene was distilled off under vacuum and dry THF (30 ml) was added to the residue. The solution obtained was held for 24 hours in a refrigerator; the precipitate was filtered out and recrystallized one more time from THF. Enamine **4** (1.20 g, 26%) was obtained.

10-(2-Hydroxyphenyl)- (6a), 10-(4-Hydroxyphenyl)- (6b), 10-(2-Hydroxy-3-methoxyphenyl)- (6c), 10-(4-Dimethylaminophenyl)- (6d), 10-(2-Furyl)- (6n), and 10-(2-Thiophenyl)- (6o) 7,7-dimethyl-5,6,7,8,9,10-hexahydro-11H-pyrido[3,2-*b*][1,4]benzodiazepin-9-ones. A solution of enamine **4** (1.5 mmol),

the corresponding aldehyde **5** (1.5 mmol), glacial CH_3COOH (0.15 ml), and piperidine (0.20 ml) in ethanol (15 ml) was boiled for 3 h. The reaction mixture was poured into crushed ice to cool down. When a tarry residue was formed, it was triturated until it solidified; the precipitate formed was filtered out, and the compounds **6a,c,d,n,o** were recrystallized from ethanol and the diazepinone **6b** was recrystallized from 2-propanol.

10-(4-Methoxyphenyl)- (6e), 10-(2,4-Dimethoxyphenyl)- (6f), 10-(3,4-Dimethoxyphenyl)- (6g), 10-(3,4-Methylenedioxyphenyl)- (6h), 10-(4-Bromophenyl)- (6i), 10-(4-Chlorophenyl)- (6j), 10-(4-Fluorophenyl)- (6k), 10-(2-Nitrophenyl)- (6l), and 10-(3-Nitrophenyl)- (6m) 7,7-dimethyl-5,6,7,8,9,10-hexahydro-11H-pyrido[3,2-*b*][1,4]benzodiazepin-9-ones. A solution of enamine **4** (1.5 mmol), the corresponding aldehyde **5** (1.5 mmol), and conc. H_2SO_4 (0.15 ml) in ethanol (15 ml) was boiled for 3 h. Then the solvent (7-10 ml) was distilled off under vacuum. The residue was poured into crushed ice and an aqueous KOH solution was added until pH 7 was achieved; after 24 hours, the precipitate was filtered out and compounds **6e-g,j-m** were recrystallized from 2-propanol, the diazepinone **6h** was recrystallized from ethanol, and the diazepinone **6i** was recrystallized from dioxane.

REFERENCES

1. A. Strakovs, M. V. Petrova, N. N. Tonkikh, E. E. Brooks, S. J. Biehle, and G. P. Kreishman, *J. Org. Chem.*, **64**, 1462 (1999).
2. N. N. Tonkikh, A. Strakovs, M. V. Petrova, V. V. Chernyshev, and H. Schenk, *Khim. Geterotsikl. Soedin.*, 822 (2002).
3. R. Martinez, E. Angeles, and F. Martinez, *Heterocycl. Commun.*, **2**, 47 (1996).
4. N. Rashed, M. Sayed, and E. S. H. El-Ashry, *J. Chin. Chem. Soc.*, **40**, 189 (1993); *Chem. Abstr.* **119**, 139194 (1993).
5. E. J. J. Vanden, A. Mayence, A. Magnestian, and E. Andrs, *Bull. Soc. Chim. Belg.*, **101**, 801 (1992).
6. M. A. Lukhate and P. S. Fernandes, *J. Indian Chem. Soc.*, **67**, 609 (1990).
7. S. Miyano and N. Abe, *Chem. Pharm. Bull.*, **20**, 1588 (1972).
8. Y. Blache, M. Hichour, G. Di Blasi, J.-M. Chezal, H. Viols, O. Chavignon, J.-C. Taulade, and J.-P. Chapat, *Heterocycles*, **51**, 1003 (1999).
9. T. Watanabe, I. Kinoyama, K. Takizawa, S. Hirano, and T. Shibanuma, *Chem. Pharm. Bull.*, **47**, 672 (1999).
10. T. Watanabe, I. Kinoyama, A. Kakefuda, T. Okazaki, K. Takizawa, S. Hirano, H. Shibata, and I. Yanagisawa, *Chem. Pharm. Bull.*, **45**, 996 (1997).
11. F. X. Woolard, J. Paetsch, and J. A. Ellman, *J. Org. Chem.*, **62**, 6102 (1997).