Synthesis of α-(Methylthio)arylacetamides and Their Conversion into Some Biologically Active Arylethylamines

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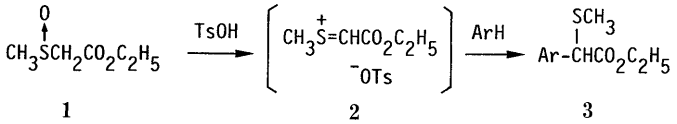
A series of (methylsulfinyl)acetamides 4 reacted with electron-rich arenes in the presence of *p*-toluenesulfonic acid to give α-(methylthio)arylacetamides 5, 6, and 7, some of which were transformed into biologically active arylethylamines such as (±)-macromerine.

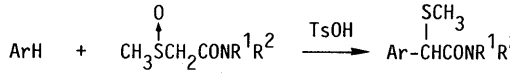
Keywords sulfoxide; Pummerer rearrangement; electrophilic aromatic substitution; arylacetamide; arylglyoxamide; arylethylamine; (±)-macromerine

In a previous paper,[1] we reported that the thionium ion intermediate **2** generated by a Pummerer-like rearrangement of ethyl (methylsulfinyl)acetate (**1**) with *p*-toluenesulfonic acid (PTSA), reacts with aromatic compounds to produce α-(methylthio)arylacetic esters **3**. The present paper describes an extension of this reaction to the synthesis of α-(methylthio)arylacetamides with a series of (methylsulfinyl)acetamides **4a**—**c**. An application of this method to the synthesis of some biologically active arylethylamines is also described.

When a benzene solution of 2-(methylsulfinyl)acetamide (**4a**) was heated under reflux in the presence of anhydrous PTSA, the expected α-(methylthio)phenylacetamide was not formed; 2,2-bis(methylthio)acetamide was the predominant product. However, the acetamide **4a** was found to react in refluxing toluene in the presence of PTSA (2 eq) to afford 2-(methylthio)-2-*p*-tolylacetamide (**5**) in 47% yield (based on **4a**) after recrystallization of the crude material. The reactions with high-boiling electron-rich arenes such as veratrole and 1,3-benzodioxole were performed by refluxing equimolar amounts of **4a** and the arene in 1,2-dichloroethane containing PTSA (2 eq) to give **6a** and **7a** in 41 and 50% yields, respectively, after chromatographic purification. Similarly, the *N*-methylacetamide **4b** and *N*,*N*-dimethylacetamide **4c**, on reacting with veratrole and 1,3-benzodioxole, gave the corresponding arylacetamides **6b** (42%), **6c** (42%), **7b** (71%), and **7c** (93%), respectively.



1 **2** **3**

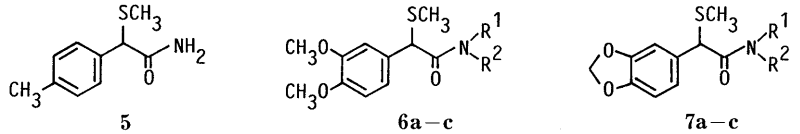


4a—c

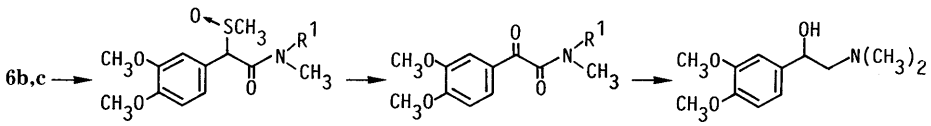
a : R^1=R^2=H, b : R^1=H; R^2=CH_3, c : R^1=R^2=CH_3

Chart 1

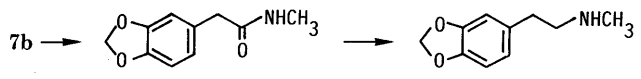
Arylglyoxamides have been shown to be useful intermediates for the synthesis of arenes having an α-hydroxy-β-aminoethyl side chain.[2] Oxidation of **6b** with sodium metaperiodate followed by heating the resultant sulfoxide **8b** in 1,2-dichloroethane in the presence of PTSA monohydrate afforded *N*-methylveratrylglyoxamide (**9b**) in 53% yield. *N*,*N*-Dimethylveratrylglyoxamide (**9c**) was obtained in high yield (95%) by brief heating of the sulfoxide **8c** with an excess of acetic anhydride followed by chromatography on silica gel.[3] Reduction of **9c** with $LiAlH_4$ afforded a racemic mixture of macromerine (**10**), which is a naturally occurring alkaloid displaying hallucinogenic and sympatholytic activities.[4]



5 **6a—c** **7a—c**



8b,c **9b,c** **10**



11 **12**

a : R^1=R^2=H, b : R^1=H; R^2=CH_3, c : R^1=R^2=CH_3

Chart 2

On the other hand, desulfurization of **7b** with zinc dust in refluxing acetic acid afforded the arylacetamide **11** in 73% yield. Reduction of **11** with $LiAlH_4$–$AlCl_3$ afforded the amine **12** which has been shown to exhibit antitussive activity.[5]

In summary, the present method offers an alternate efficient route for the synthesis of biologically important arenes having an α-hydroxy-β-aminoethyl or β-aminoethyl moiety starting from common aromatic compounds.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO A-100 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined with a JEOL JNM-PMX 60 (60 MHz) spectrometer, and δ values are quoted relative to tetramethylsilane. Column chromatography was performed on Silica gel 60 PF_{254} (Merck) under pressure.

2-(4-Methylphenyl)-2-(methylthio)acetamide (5) PTSA monohydrate (962 mg, 5.1 mmol) was added to toluene (10 ml) and the mixture was heated under reflux with azetropic removal of water for 1 h, then cooled to room temperature under a nitrogen atmosphere. 2-(Methylsulfinyl)-acetamide (**4a**)[6] (306 mg, 2.5 mmol) was added to the above solution containing anhydrous PTSA and the mixture was heated again under reflux with azeotropic removal of water for 1 h. The reaction mixture was washed with water and dried over $MgSO_4$. The solvent was evaporated off and the residue was recrystallized from benzene to give **5** (244 mg, 49%), whose physical data are listed in Table I.

General Procedure for the Preparation of α-(Methylthio)arylacetamides 6a—c and 7a—c PTSA (571 mg, 6 mmol) was added to 1,2-dichloroethane (15 ml) and the mixture was heated under reflux with azeotropic removal of water for 1 h, then cooled to room temperature under a nitrogen atmosphere. The (methylsulfinyl)acetamide **4a**, **4b**,[6] or **4c**[6] (3 mmol) and an arene such as veratrole or 1,3-benzodioxole (3 mmol) were successively added to the above solution containing anhydrous PTSA and the mixture was heated again under reflux with azeotropic removal of water for 1 h. The reaction mixture was washed with water and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel using a mixed solvent of benzene and ethyl acetate (1 : 1—4 : 1) as an eluent to give **6a** (41%), **6b** (42%), **6c** (42%), **7a** (50%), **7b** (71%), or **7c** (93%), whose physical data are listed in Table I.

***N*-Methyl-3,4-dimethoxyphenylglyoxamide (9b)** A solution of sodium metaperiodate (224 mg, 1.04 mmol) in water (8 ml) was added dropwise to a solution of **6b** (242 mg, 0.95 mmol) in methanol (8 ml) at room temperature and the mixture was stirred at the same temperature for 15 h. The precipitated salts were removed by filtration and the filtrate was concentrated *in vacuo*. 1,2-Dichloroethane (10 ml) was added to the residue containing the crude sulfoxide **8b** and the mixture was heated under reflux in the presence of PTSA monohydrate (268 mg, 1.4 mmol) for 18 h. The reaction mixture was washed with water and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane : ethyl acetate = 1 : 1) to give **9b** (112 mg, 53%), whose physical data are listed in Table I.

***N,N*-Dimethyl-3,4-dimethoxyphenylglyoxamide (9c)** By using the same procedure as that described for the preparation of **8b**, the sulfide **6c** (229 mg, 0.85 mmol) was oxidized with sodium metaperiodate (182 mg, 0.85 mmol). The resultant crude sulfoxide **8c** was dissolved in acetic anhydride (1 ml) and the mixture was heated under reflux for 30 min. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel (benzene : ethyl acetate = 3 : 1) to give **9c** (128 mg, 95%), whose physical data are listed in Table I.

1-(3,4-Dimethoxyphenyl)-2-(dimethylamino)ethanol [(±)-macromerine] (10) A solution of **9c** (133 mg, 0.56 mmol) in dry tetrahydrofuran (THF) (2 ml) was added to a suspension of $LiAlH_4$ (64 mg) in dry THF (6 ml) and the mixture was heated under reflux for 1 h. Usual work-up followed by purification of the crude product with chromatography on silica gel ($CHCl_3$: MeOH = 9 : 1) gave **10** (111 mg, 88%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1615, 1595. ^{1}H-NMR ($CDCl_3$) δ: 2.3—2.8 (2H, m, NCH_2), 2.40 (6H, s, NMe_2), 3.83, 3.86 (3H each, both s, OMe × 2), 4.22 (1H, s, OH), 4.67 (1H, dd, J = 9, 4.5 Hz, CH), 6.75—7.0 (3H, m, ArH). Its picrate had mp 145.5—146.5 °C (hexane–ethyl acetate), lit.[4] 146—147 °C.

2-(1,3-Benzodioxol-5-yl)-*N*-methylacetamide (11) Zinc dust (3.5 g) was added to a solution of **7b** (415 mg, 1.75 mmol) in acetic acid (10 ml) and the mixture was heated under reflux with vigorous stirring for 15 h. Dichloromethane (20 ml) was added to the reaction mixture and the inorganic materials were filtered off. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel (ethyl acetate) to give **11** (250 mg, 73%), whose physical data are listed in Table I.

2-(1,3-Benzodioxol-5-yl)-*N*-methylethylamine (12) A solution of $AlCl_3$ (1.15 g, 8.6 mmol) in dry ethyl ether (5.8 ml) was added to a suspension of $LiAlH_4$ (327 mg) in dry THF (9.7 ml) at −15 °C and the mixture was stirred at the same temperature for 30 min. A third of the resultant mixture (*ca.* 5 ml) was added to a solution of **11** (133 mg, 0.7 mmol) in dry THF

TABLE I. Physical Properties and Spectral Data for Compounds **5**, **6a—c**, **7a—c**, **9b**, **c** and **11**

Compd. No.	mp (°C) (Solvent)	Analysis (%) Calcd (Found) C	H	N	Formula	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
5	138.5—139 (Benzene)	61.51 (61.27)	6.71 (6.80)	7.17 (7.02)	$C_{10}H_{13}NOS$	3375, 3180, 1655	2.13 (3H, s, SMe), 2.30 (3H, s, ArMe), 4.36 (1H, s, SCH), 5.9—6.7 (2H, br, NH_2), 7.01, 7.16 (2H each, ABq, J = 8 Hz, ArH)
6a	146.5—147 (AcOEt)	54.75 (54.53)	6.27 (6.13)	5.80 (5.82)	$C_{11}H_{15}NO_3S$	3500, 3400, 1680	2.13 (3H, s, SMe), 3.83 (6H, s, OMe × 2), 4.36 (1H, s, SCH), 5.6—6.6 (2H, br, NH_2), 6.6—7.0 (3H, m, ArH)
6b	103.5—104 (AcOEt)	56.45 (56.69)	6.71 (6.90)	5.49 (5.65)	$C_{12}H_{17}NO_3S$	3425, 3380, 1665	2.10 (3H, s, SMe), 2.83, 2.92 (total 3H, both s, NMe), 3.87 (6H, s, OMe × 2), 4.43 (1H, s, SCH), 6.3—7.0 (1H, m, NH), 6.8—7.0 (3H, m, ArH)
6c	Oil	57.97 (57.69)	7.11 (7.40)	5.20 (4.94)	$C_{13}H_{19}NO_3S$	1640[a]	2.00 (3H, s, SMe), 2.96 (6H, s, NMe_2), 3.83 (6H, s, OMe × 2), 4.66 (1H, s, SCH), 6.7—7.0 (3H, m, ArH)
7a	145—146 (AcOEt)	53.32 (53.33)	4.92 (5.19)	6.22 (6.16)	$C_{10}H_{11}NO_3S$	3375, 3180, 1650	2.14 (3H, s, SMe), 4.45 (1H, s, SCH), 5.9—7.0 (2H, br, NH_2), 5.97 (2H, s, OCH_2O), 6.8—7.1 (3H, m, ArH)
7b	93—93.5 (Benzene–AcOEt)	55.21 (55.03)	5.48 (5.57)	5.85 (5.74)	$C_{11}H_{13}NO_3S$	3370, 1660	2.10 (3H, s, SMe), 2.80, 2.88 (total 3H, both s, NMe), 4.36 (1H, s, SCH), 5.89 (2H, s, OCH_2O), 6.3—6.9 (4H, m, NH, ArH)
7c	78.5—79 (Benzene–AcOEt)	56.90 (57.05)	5.97 (5.01)	5.53 (5.47)	$C_{12}H_{15}NO_3S$	1630	2.01 (3H, s, SMe), 3.01 (6H, s, NMe_2), 4.69 (1H, s, SCH), 5.95 (2H, s, OCH_2O), 6.6—7.1 (3H, m, ArH)
9b	119—120.5 (CCl_4)	59.19 (59.00)	5.87 (5.98)	6.27 (6.44)	$C_{11}H_{13}NO_4$	3385, 1685, 1650	2.90, 2.98 (total 3H, both s, NMe), 3.93 (6H, s, OMe × 2), 6.87 (1H, d, J = 8 Hz, ArH), 7.0—7.6 (1H, br, NH), 7.83 (1H, d, J = 2 Hz, ArH), 8.16 (1H, dd, J = 8, 2 Hz, ArH)
9c	124—125 (Benzene–AcOEt)	60.75 (60.49)	6.37 (6.55)	5.90 (6.05)	$C_{12}H_{15}NO_4$	1670, 1640	2.94, 3.10 (total 6H, both s, NMe_2), 3.93 (6H, s, OMe × 2), 6.86 (1H, d, J = 9 Hz, ArH), 7.35—7.60 (2H, m, ArH)
11	99—101 (Hexane–AcOEt)	62.17 (62.06)	5.74 (6.02)	7.25 (7.40)	$C_{10}H_{11}NO_3$	3320, 1645	2.71, 2.79 (total 3H, both s, NMe), 3.45 (2H, s, $COCH_2$), 5.2—5.9 (1H, br, NH), 5.93 (2H, s, OCH_2O), 6.72 (3H, s, ArH)

a) Measured in $CHCl_3$

(4 ml) and the mixture was stirred at room temperature for 15 h. Water (1 ml) and 5% NaOH solution (10 ml) were added successively to the reaction mixture and the whole was extracted with ethyl ether. The extract was washed with water and dried over Na_2SO_4. The solvent was evaporated off to give **12**[5] (98 mg, 80%), which was homogeneous by ^{1}H-NMR. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3220 (weak), 1610. ^{1}H-NMR ($CDCl_3$) δ: 1.2—1.6 (1H, br, NH), 2.44 (3H, s, NMe), 2.76 (4H, s, CH_2CH_2), 5.90 (2H, s, OCH_2O), 6.68 (3H, s, ArH).

References and Notes

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