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Studies on the Selective Preparation of Aromatic Compounds. 14. An Attempt to Prepare All the Possible Deuterated Phenols by the Reductive Dehalogenation of the Corresponding Halophenols with Raney Alloys in an Alkaline Deuterium Oxide Solution[1]

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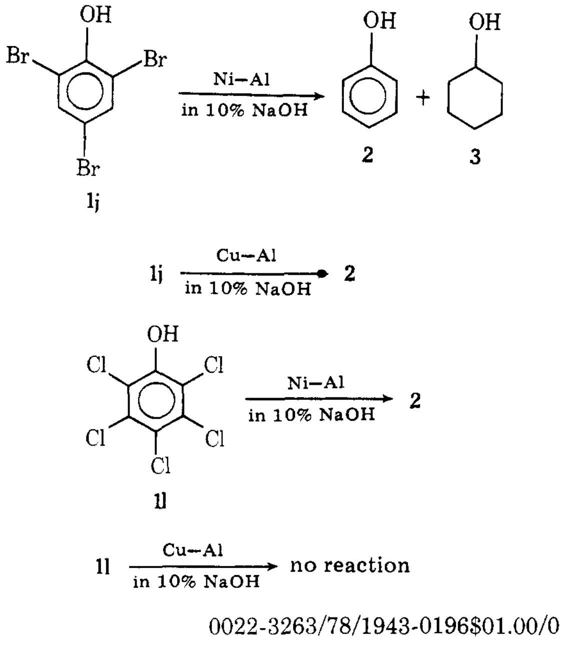
The reductive dehalogenation of the 19 halophenols **1a–s** was carried out with Raney alloys such as Ni–Al and Cu–Al in 10% NaOD–D_2O solution in order to obtain all the possible deuterated phenols. It was found that the reaction of the bromophenols with Raney Cu–Al alloy gives fairly selectively the corresponding deuterated phenols, but chlorophenols and bromochlorophenols give extensive further exchange of phenyl hydrogen atoms. 2-Bromophenoxyacetic acid (**6**) was reduced with Raney Ni–Al alloy to afford phenoxyacetic-*2-d* acid (**8**) in high purity without the further exchange of hydrogen atoms.

It has been known that[2–7] some halophenol derivatives could be reduced with Raney Ni–Al alloy in alkaline solution to afford the corresponding phenols. However, we recently found that[8] (i) the reduction of 2,4,6-tribromophenol (**1j**) with Raney Ni–Al alloy in 10% NaOH solution at 80 °C afforded phenol (**2**) with the formation of cyclohexanol (**3**) as a byproduct, (ii) Raney Cu–Al alloy gave only **2** without any amount of **3**, and (iii) the former alloy was active for the reduction of chlorophenols as well as bromophenols; however, the latter alloy could reduce only bromophenols but not chlorophenols (Scheme I).

These results suggest that the desired deuterated phenols may be prepared by the reduction of the corresponding halophenols with the Raney alloys in an alkaline deuterium oxide solution.

Scheme I

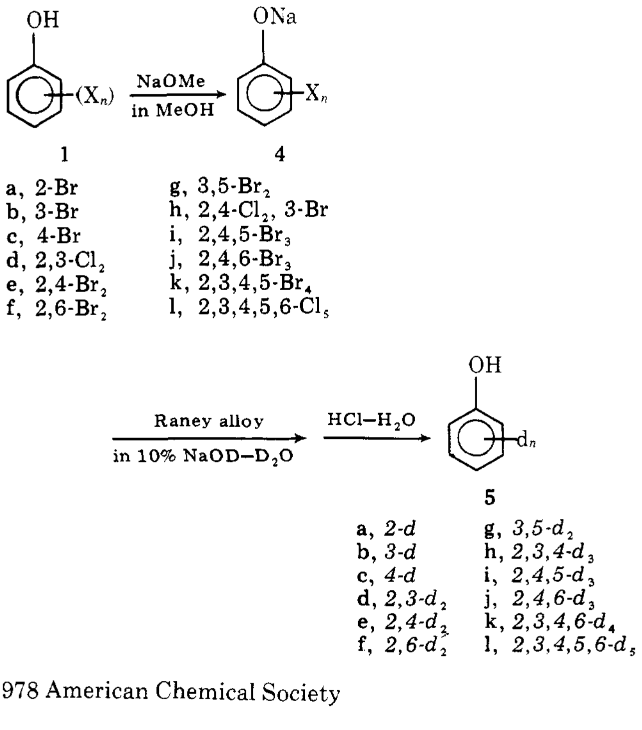


We wish to report the use of the Raney alloys for the reduction of halophenols (**1a–s**) in 10% NaOD–D_2O solution.

Results and Discussion

There are 19 possible isomers of the deuterated phenols. In order to obtain all of the possible deuterated phenols, the corresponding halophenols **1a–s** were reduced with Raney alloys such as Ni–Al and Cu–Al in 10% NaOD–D_2O solution which was prepared from D_2O (99.8%) and the calculated amount of NaOMe. To keep the D_2O solution in high isotopic purity, the halophenols **1** were converted to their sodium salts

Scheme II



a, 2-Br
b, 3-Br
c, 4-Br
d, 2,3-Cl_2
e, 2,4-Br_2
f, 2,6-Br_2
g, 3,5-Br_2
h, 2,4-Cl_2, 3-Br
i, 2,4,5-Br_3
j, 2,4,6-Br_3
k, 2,3,4,5-Br_4
l, 2,3,4,5,6-Cl_5

a, *2-d*
b, *3-d*
c, *4-d*
d, *2,3-d_2*
e, *2,4-d_2*
f, *2,6-d_2*
g, *3,5-d_2*
h, *2,3,4-d_3*
i, *2,4,5-d_3*
j, *2,4,6-d_3*
k, *2,3,4,6-d_4*
l, *2,3,4,5,6-d_5*

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Table I. The Reduction of Halophenols (1) Via Their Sodium Salts (4) with Raney Alloy in 10% NaOD–D$_2$O Solution[a]

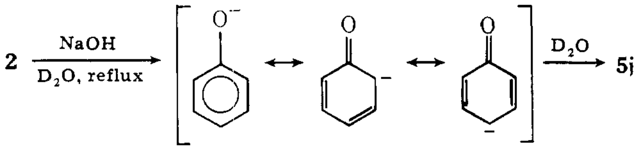
Run	Substance (g)	Registry no.	Alloy (g)	Registry no.	5 (yield %)[b]	Registry no.	Composition of 5 (%)[c]					
							d_0	d_1	d_2	d_3	d_4	d_5
1	**1a** (2.0)	95-56-7	Cu–Al (0.5)	11099-19-7	**5a** (94)	23951-01-1	15	83	2	0	0	0
2	**1b** (2.0)	591-20-8	Cu–Al (0.5)		**5b** (77)	23951-02-2	3	92	5	0	0	0
3	**1c** (2.0)	106-41-2	Cu–Al (0.5)		**5c** (69)	23951-03-3	3	92	5	0	0	0
4	**1d** (3.0)	576-24-9	Ni–Al (4.2)	11114-68-4	**5d** (92)	64045-90-5	2	13	35	31	16	3
5	**1e** (1.72)	615-58-7	Cu–Al (0.8)		**5e** (88)	64045-89-2	1	9	85	5	0	0
6	**1b** (3.5)	608-33-3	Cu–Al (2.0)		**5f** (83)	64045-88-1	0	17	80	3	0	0
7	**1g** (2.22)	06-41-5	Cu–Al (1.00)		**5g** (89)	6264045-87-0	0	12	84	4	0	0
8	**1h** (2.0)	13659-21-7	Ni–Al (4.5)		**5h** (80)	64045-86-9	3	9	27	45	13	3
9	**1i** (4.0)	14401-61-7	Cu–Al (2.0)		**5i** (82)	64045-85-8	0	1	6	92	1	0
10	**1j** (3.38)	118-79-6	Cu–Al (2.0)		**5j** (65)	7329-50-2	0	1	16	80	3	0
11	**1k** (4.5)	4526-58-3	Cu–Al (3.0)		**5k** (77)	64045-84-7	0	0	2	14	82	2
12	**1l** (5.0)	87-86-5	Ni–Al (7.5)		**5l** (74)	4165-62-2	0	0	0	1	13	86

[a] Reaction time was 60 min. [b] The yields isolated are shown. The yields determined by gas chromatographic analyses are almost quatitative in respective cases. [c] The compositions were obtained by mass spectroscopic method.

4 which were obtained from 1 by treatment with the calculated amount of dry NaOMe in MeOH and then dried in vacuo.

The results of the reduction are summarized in Table I. The data of Table I show that the expected deuterated phenols **5a–f** were obtained in good yields, respectively. Although the desired deuterated phenols such as **5a–c,e–g,i–k** were formed in high purities (80–90%) from the corresponding bromophenols with Raney Cu–Al alloy, respectively, **5d** and **5h** were obtained in lower purities (40–50%) from the corresponding halophenols containing one or more chloro atoms with Raney Ni–Al alloy. Also, the reduction of 2,5-dichloro- (**1m**), 3,4-dichloro-(**1n**), 3,5-dibromo-2-chloro- (**1o**), 3-bromo-2,6-dichloro- (**1p**), 3,5-dibromo-4-chloro- (**1q**), 3,5-dibromo-2,4-dichloro- (**1r**), and 3,5-dibromo-2,6-dichlorophenol (**1s**) with Raney Ni–Al alloy gave only in lower purities the deuterated phenols, respectively. However, the expected **5l** was obtained in high purity in the presence of the latter alloy. The former alloy was less active than the latter one so it could not reduce the halophenols containing the chloro atoms.

It should be noted that use of Raney Ni–Al leads to the introduction of more than the expected number of deuterium atoms. It has been reported that[9,10] phenol 2 was refluxed for a long time in D$_2$O in the presence of NaOH to afford 2,4,6-trideuterated phenol **5j**.



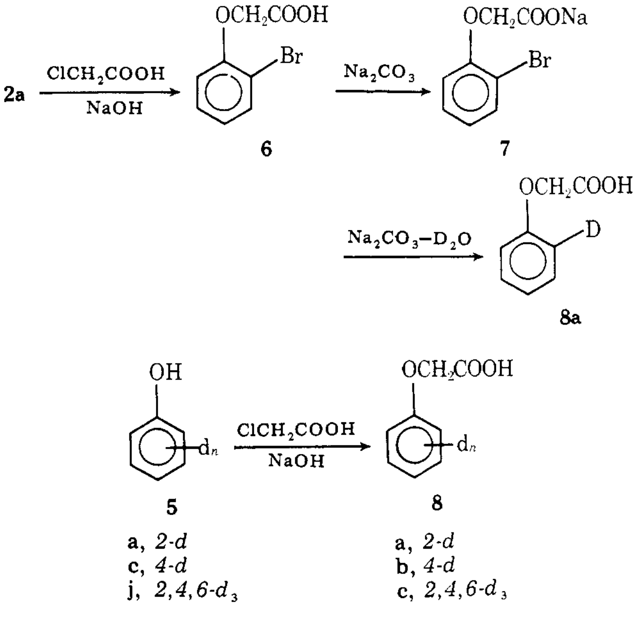
The above reaction might take place in the reduction with Raney Ni–Al as one of the side reactions, since the reaction temperature was somewhat increased when the alloy was added in the alkaline solution.

When sodium 2-bromophenoxyacetate (7), which was easily prepared from 2-bromophenoxyacetic acid (6) with Na$_2$CO$_3$, was treated with Raney Ni–Al in 10% Na$_3$CO$_3$–D$_2$O solution in a similar manner, phenoxyacetic-*2-d* acid (8) was obtained in good yield and in high purity (>90%). The deuterated phenoxyacetic acid 8 was also obtained from **5a** and chloroacetic acid in the usual manner.

The result of reduction of 6 with Raney Ni–Al alloy suggests that this reductive method for the introduction of deuterium atoms on the desired position of aromatic ring might be applied to carboxylic compounds as well as phenolic compounds.

The ^{1}H NMR spectra of **5a–c,g,i–l**, and **8b,c** are shown in Figures 1 and 2. The purities of **8b** and **8c** were calculated from the relative intensities of their methylene and aromatic protons, and agreed well with those obtained from the mass spectra of **5c** and **5j**. The data of Figures 1 and 2 show also that the deuterium atoms were introduced on the desired positions of the ring of 2 in the reductive system of Cu–Al alloy and bromophenols.

Scheme III



Based on the results described above it might be concluded that, although the attempt to prepare all of the possible deuterated phenols in high purity was not successful, the reduction of bromophenols with Raney Cu–Al alloy in 10% NaOD–D$_2$O solution might be more a convenient preparative method for the introduction of deuterium atoms on the desired position of aromatic rings than the previously reported methods.[9–14]

Experimental Section

All melting points are uncorrected. Mass spectra were obtained on a Hitachi RMS-4 mass spectrometer with a direct inlet (ionization energy 70 eV). NMR spectra were determined at 60 MHz with a Hitachi R-20 NMR spectrometer and Me$_4$Si as an internal reference.

Materials. The halophenols such as **1a–e,m,n,j,l** of commercial grade were used without further purification. The other halophenols were prepared by the reported method and were purified by fractional distillation and/or recrystallization. **1f**:[4,15] mp 57–59 °C; **1q**:[16] mp 81 °C; **1h**:[17] mp 85 °C; **1o**:[18] mp 68 °C; **1p**:[19] mp 67 °C; **1i**:[20] mp 79 °C; **1q**:[18] mp 121 °C; **1r**:[18] mp 121 °C; **1k**:[21] mp 123–125 °C; **1s**:[18] mp 128 °C.

Analytical Procedure. The analyses were carried out by gas chromatography using a Yanagimoto gas chromatograph, Yanaco

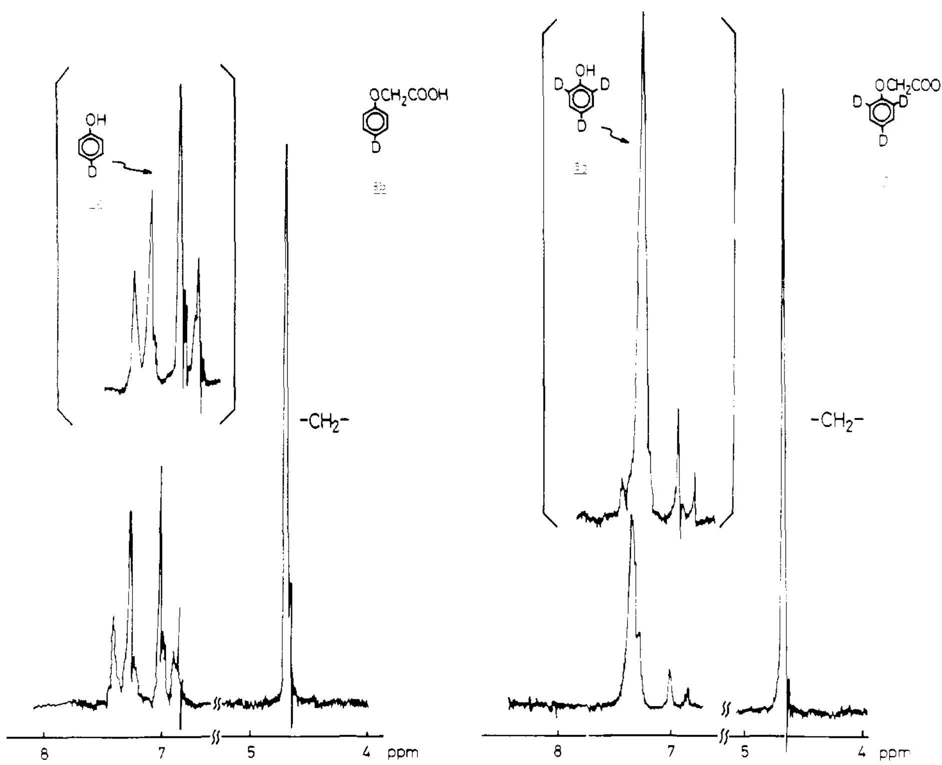


Figure 1. The ^{1}H NMR spectra of **5c–j** and **8b–c** (Solvent: CDCl$_3$).

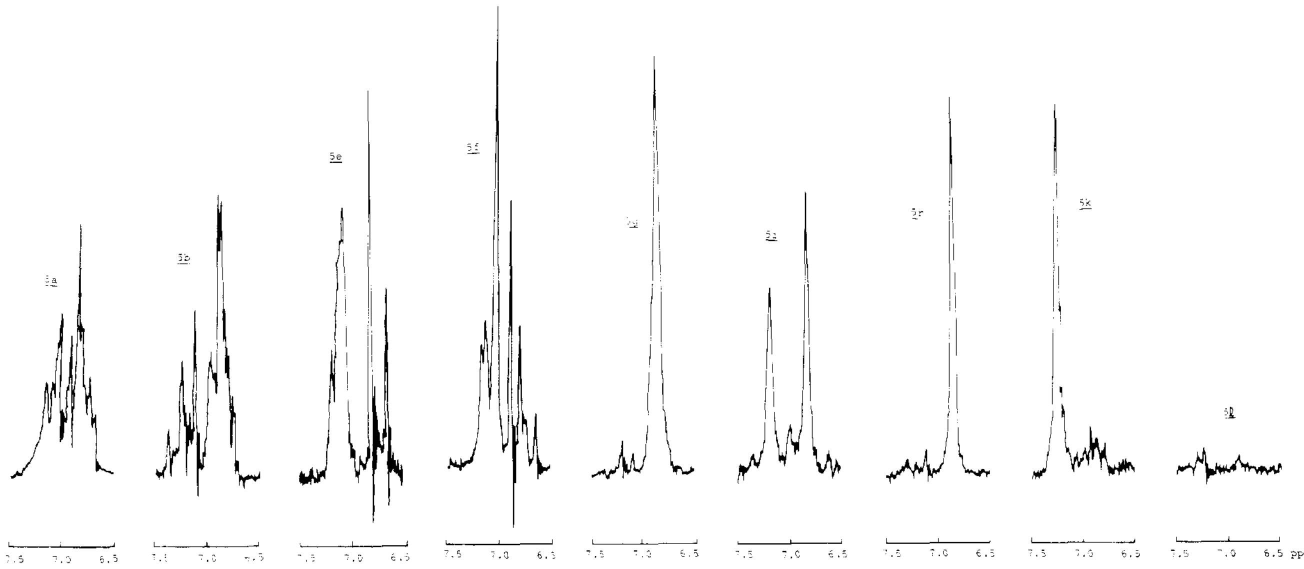


Figure 2. The ^{1}H NMR spectra of **5a,–l** (solvent CDCl$_3$).

YR-101: column 30% high-vacuum silicon grease, 75 cm; increase rate of column temperature, 12 °C/min; carrier gas, helium, 30 mL/min.

The Typical Procedure for Reduction of 1. To a solution of NaOMe in 50 mL of MeOH, which was prepared from 0.24 g (10.4 mmol) of Na in 50 mL of MeOH, was added 3.38 g (10.2 mmol) of 2,4,6-tribromophenol (**1j**), and then the excess MeOH was evaporated in vacuo to leave the residue which was dried by heating at 120–130 °C over night under reduced pressure affording dry **4j**. The sodium salt **4j** was dissolved in 50 mL of 10% NaOD-D$_2$O solution which was prepared from 7.37 g of NaOMe and 50 mL of D$_2$O. To the solution was gradually added at room temperature 2 g of Cu–Al alloy over a period of 10 min. After the reaction mixture was stirred for an additional 50 min, excess D$_2$O was distilled under reduced pressure, 20—30 mL of D$_2$O was recovered. The insoluble material was separated by filtration. The filtrate was acidified with 10% HCl solution and extracted with ether. The ether solution was dried over Na$_2$SO$_4$ and evaporated to afford **5j** which was analyzed by GC and MS.

The Reduction of 2-Bromophenoxyacetic Acid (6). After 0.2 g of **6** was dissolved in 10 mL of 2 N Na$_2$CO$_3$, the solution was evaporated in vacuo to leave colorless crystals (**7**) which were dried at 120 °C for 3 h under reduced pressure. The crystals were dissolved in 10 mL of D$_2$O and then 0.2 g of Raney Ni–Al alloy was gradually added in a period of 5 min. After the reaction mixture was stirred at 70 °C for 40 min, it was treated and worked up as described above to afford colorless crystals which were recrystallized from *n*-hexane giving 50 mg of phenoxyacetic-2-*d* acid (**8a**), mp 98 °C. The melting point of the unlabeled authentic compound is 99 °C.

Preparation of Deuterated Phenoxyacetic Acid (8) by the Reaction of Chloroacetic Acid with Deuterated Phenols 5a,c,j. The deuterated phenols **5a,c,j** were treated with chloroacetic acid in alkaline solution in the usual manner[22] to afford the corresponding deuterated phenoxyacetic acid.

Registry No.—**4j**, 2666-53-7; **5r**, 64045-83-6; **6**, 1879-56-7; **7**, 13730-99-9; **8a**, 64045-82-5; **8b**, 52199-99-2; **8c**, 21273-28-9.

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Reaction of Silylynamines with Active Triple Bonds

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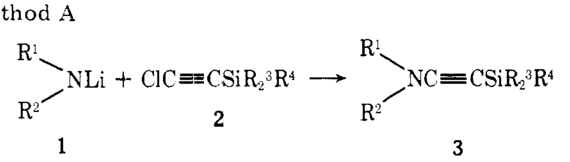
N,N-Disubstituted (triorganosilylethynyl)amines (silylynamines, **3**) reacted with dimethyl acetylenedicarboxylate (**6**), methyl propiolate (**7**), and benzyne (**18**) to give the 1:1 addition products **8**, **9**, and **20**. It appears that these adducts were formed as a result of 1,3-anionic rearrangement of the triorganosilyl group from carbon to carbon in the dipolar intermediates **16** and **19**.

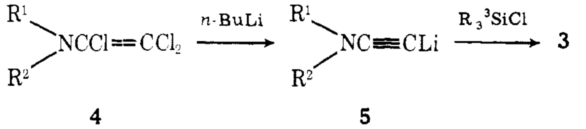
The addition reaction of ynamines with active multibonds provides a versatile tool in the syntheses of amine derivatives.[1] *N,N*-Dialkyl (alkyl or phenylethynyl) amine reacts with dimethyl acetylenedicarboxylate[2] or benzyne[3] in 1:2 mole ratio to give an aniline derivative or a mixture of phenanthrene and anthracene derivatives. These 1:2 addition products may be formed via dipolar intermediates reactive enough to add to another mole of the active triple bond (Scheme I). In this paper, we report the 1:1 addition reaction of N,N-disubstituted (triorganosilylethynyl)amines (silylynamines) with acetylenecarboxylates or benzyne.

Silylynamines **3a–j** were prepared by reaction of lithium diorganoamides **1** with triorganosilylethynyl chlorides **2** (method A[4]) or from *N*-methyl-*N*-(1,2,2-trichlorovinyl)aniline (**4**) via lithium aminoacetylide (**5**) (method B[5]). Method A gave good yields in the preparation of *N*-(triorganosilylethynyl)dialkylamines **3a–f**, and method B was adequate for *N*-(triorganosilylethynyl)arylamines **3g–j**. The results are summarized in Table I.

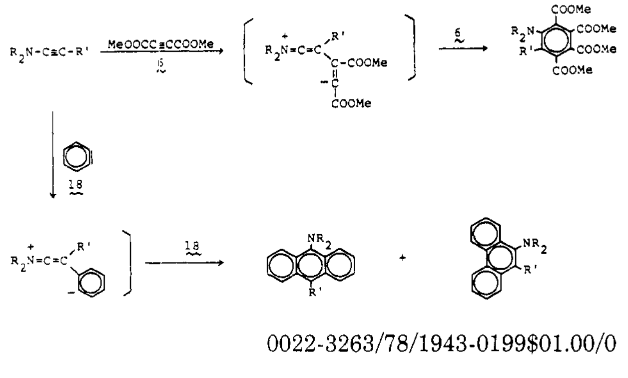
Method A



Method B

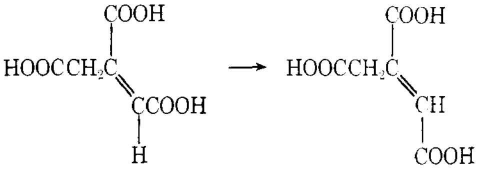


Scheme I



When *N,N*-diethyl(trimethylsilylethynyl)amine (**3a**) was mixed with an equimolar amount of dimethyl acetylenedicarboxylate (**6**) in ether, an exothermic reaction occurred immediately at room temperature to give the sole product **8a**. The elemental, NMR, and mass spectral analyses of **8a** indicated this product to be a 1:1 adduct, $C_{15}H_{25}NO_4Si$, and the IR spectrum showed a band at 2180 cm^{-1} indicating the presence of a triple bond. Thus, the structure of **8a** was assumed as (*E*)-*N,N*-diethyl[3,4-bis(methoxycarbonyl)-4-trimethylsilyl-3-buten-1-ynyl]amine (Scheme II).

Acid hydrolysis of **8a** afforded a mixture of two desilylated amides (**10a**) which were assigned to stereoisomers of *E* and *Z* types based on the NMR. Catalytic hydrogenation of the mixture gave a 90% yield of *N,N*-diethyl-3,4-bis(methoxycarbonyl)butanamide (**13**) as a single product. Attempted separation of the stereomers by silica gel column chromatography failed, because both isomers convert to each other at room temperature. In the presence of water, isomerization of (*Z*)-aconitic acid occurrs at ambient temperature.[6]



(*Z*)-aconitic acid (*E*)-aconitic acid

Similar 1:1 addition reactions of silylynamines with **6** were observed in the cases of *N,N*-diethyl(dimethylethylsilylethynyl)amine (**3b**), *N*-(trimethylsilylethynyl)morpholine (**3e**), and *N*-methyl-*N*-(trimethylsilylethylnyl)aniline (**3g**). *N*-Methyl-*N*-(triphenylsilylethynyl)aniline (**3h**) did not react in ether, but did in acetonitrile (see Table II). Acid hydrolysis

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