An Expedient Synthesis of Vicinal Diamines from Alkenes and Cycloalkenes

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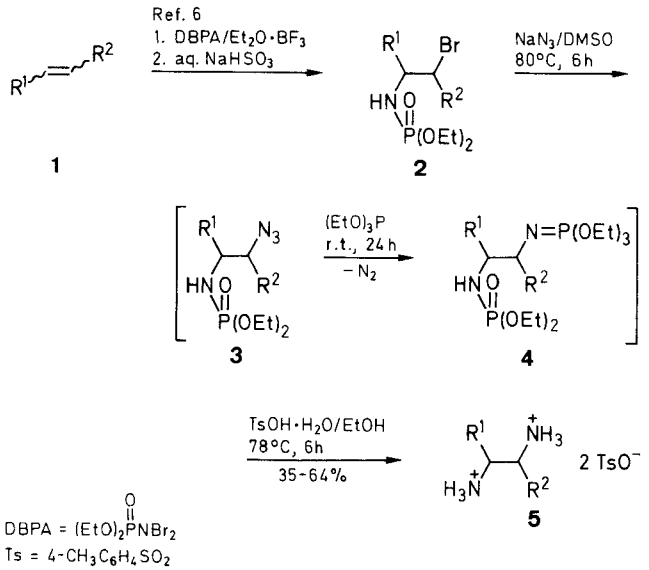
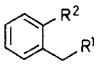
A new procedure for the facile preparation of various vicinal diamines is developed that utilizes diethyl *N*-(β-bromoalkyl)phosphoramidates **2** easily accessible by ionic addition of diethyl *N,N*-dibromophosphoramidate (DBPA) to alkenes and cycloalkenes 1. Crude phosphoramidates **2** are readily transformed into the corresponding ammonium ditosylates **5** by sequential azidation, Staudinger reaction with triethyl phosphite, and deprotection by refluxing with *p*-toluenesulfonic acid in aqueous ethanol. Diamination of cyclohexene and indene proceeds stereospecifically affording *cis*-1,2-diaminocyclohexane and *cis*-1,2-diaminoindane, respectively. Open-chain olefins do not react stereospecifically under conventional conditions yielding mixtures of diastereoisomers. Full stereochemical control of azidation can be, however, achieved when β-bromoamine hydrochlorides instead of diethyl *N*-(β-bromoalkyl)phosphoramidates are used as starting materials for this reaction.

The vicinal diamino group is an ubiquitous structural unit commonly present in various naturally occuring compounds and medicinal agents. Despite the importance of this functionality, which renders it an interesting synthetic target, only few general methods exist for the preparation of vicinal diamines.[1] In the majority of cases the synthetic approach is an extension and/or modification of the procedures conventionally used for introduction of a single amino group into an organic molecule. The overall conversions to vicinal diamines or their derivatives occur in low yield, proceed without stereochemical control, and often require the preparation of potentially hazardous intermediates. Recently Jung and Kohn[1] described an elegant, four-step sequence for the preparation of vicinal primary diamines from unactivated alkenes via 2,3-dihydroimidazole intermediates. Some diamination procedures mediated by organometallic reagents have been also reported.[2-4] The most recent work describes the synthesis of various 3-substituted-1,2-diaminopropane compounds from the corresponding *N,N*-bis-protected-2-(aminomethyl)aziridine derivatives by nucleophilic opening of the aziridine ring.[5] Except Kohn's work[1] all current methods suffer from severe disadvantages, for example, the lack of general character,[4,5] application of explosive *vic*-diazides,[2] and the use of rather sophisticated starting materials.[3]

As an alternative to the existing methodology of double bond diamination,[1] it was envisaged that diethyl *N*-(β-bromoalkyl)phosphoramidates **2** readily accessible by ionic addition of diethyl *N,N*-dibromophosphoramidate (DBPA) to alkenes and cycloalkenes,[6] might serve as convenient precursors for vicinal diamines **6**. The synthetic protocol is outlined in Scheme **A**.

Diethyl *N*-(β-bromoalkyl) phosphoramidates **2**, the precursors of vicinal diamines, were obtained according to



1–5	R^1	R^2
a	n-C_3H_7	H
b	n-C_4H_9	H
c	CH_3	CH_3 (*Z*-)isomer
d	CH_3	CH_3 (*E*-)isomer
e	Ph	H
f	Ph	CH_3 (*E*-)isomer
g	$-(CH_2)_4-$	
h		

Scheme **A**

Table 1. Ammonium Ditosylates **5** and Vicinal Diamines **6** Prepared

Product	Yield[a] (%)	mp (°C) or bp (°C)/mbar and/or n_D^{20}	Molecular Formula[b] or Lit. mp (°C)
5a	55	274–278	$C_{19}H_{30}N_2O_6S_2$ (446.6)
5b	47	285–287	$C_{20}H_{32}N_2O_6S_2$ (460.6)
5c	40[c]	341–342	$C_{18}H_{28}N_2O_6S_2$ (432.6)
5d	45[c]	328–330	$C_{18}H_{28}N_2O_6S_2$ (432.6)
5e	64	269–273	$C_{22}H_{28}N_2O_6S_2$ (480.6)
5f	43[d]	277–280	$C_{23}H_{30}N_2O_6S_2$ (494.6)
5g	35	238–241	$C_{20}H_{30}N_2O_6S_2$ (458.6)
5h	47	261–263	$C_{23}H_{28}N_2O_6S_2$ (492.6)
6a	64	80/57 1.4540	$C_5H_{14}N_2$ (102.2)
6b	67	59–60/4 1.4490	$C_6H_{16}N_2$ (116.2)
6e	64	180/3.3 1.5415	$C_8H_{12}N_2$ (136.2)
6f	72	122/4 1.5422	$C_9H_{14}N_2$ (150.2)
6g	75[e]	309–310	310–312[2]
6h	66	45–46	43–47[12]

[a] Yield of isolated products.
[b] Satisfactory microanalyses obtained: C ±0.38, H ±0.27, N ±0.31.
[c] Mixture of *meso*- and *dl*-isomers.
[d] Mixture of *threo*- and *erythro*-isomers.
[e] Yield of 1,2-diaminocyclohexane dihydrochloride obtained from crude **5g**.

Table 2. Spectrometric Data of Vicinal Diamines **6**

Product	IR (neat) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS (70 eV) m/z (%)
6a	3340, 3300 (NH_2), 2960, 2930, 2870, 1600, 1460, 1035, 920	0.73–1.08 (t,[a] 3H), 1.35 (s, 4H), 1.17–1.50 (m, 4H), 2.25–2.90 (m, 3H)	72 (M – 30, 80)
6b	3380, 3300 (NH_2), 2980, 2940, 2880, 1605, 1475, 1045, 875	0.66–1.07 (t,[a] 3H), 1.30 (s, 4H), 1.07–1.50 (m, 6H), 2.26–2.86 (m, 3H)	86 (M – 30, 100)
6e	3380, 3300 (NH_2), 2940, 2860, 1610, 1460, 1040, 870, 720	1.37 (s, 4H), 2.60–2.90 (m, 1H), 3.73 (d, 1H, J = 7.0), 3.83 (d, 1H, J = 7.0), 7.30 (s, 5H)	106 (M – 30, 100)
6f	3380, 3300 (NH_2), 2960, 2870, 1610, 1455, 900, 720	0.90, 0.98 (2d, 3H, J = 6.0), 1.40 (s, 4H), 2.70, 2.97 (2q, 1H, J = 6.0), 3.50, 3.67 (2d, 1H, J = 6.0), 7.26 (s, 5H)	106 (M – 44, 69), 44 (M – 106, 100)
6h	3360, 3315, 3270 (NH_2), 2940, 2840, 1600, 1475, 1015, 940, 910, 850, 750	1.37 (s, 4H), 2.66 (dd, 1H, J = 15.7, 4.0), 3.02 (dd, 1H, J = 15.7, 6.0), 3.58 (q, 1H, J = 6.0), 4.12 (d, 1H, J = 6.0), 7.17–7.31 (m, 4H)	148 (M^+, 14), 130 (M – 18, 100)

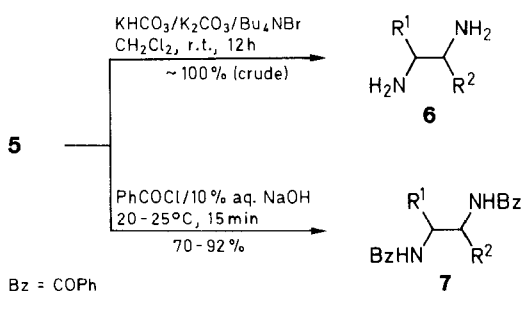
[a] Distorted triplet.

the previously described procedure[6] by electrophilic addition of *N,N*-dibromophosphoramidate (DBPA) to numerous terminal and non-terminal alkenes as well as cycloalkenes. The reaction afforded solely the *anti*-addition products.

The monosubstituted terminal alkenes **1a,b** yield mixtures of the Markovnikov and the *anti*-Markovnikov adducts **2a,b** in the ratio of 65:35, but both of these regioisomers were finally converted into the same vicinal diamine.

The second step in our synthetic strategy required the conversion of phosphoramidates **2** into the corresponding ammonium ditosylates **5** by sequential azidation, reduction of azides via the Staudinger reaction, and deprotection of both nitrogen atoms. All these transformations could be conveniently achieved by a one-pot sequence, which entirely eliminates hazardous isolation and purification of the intermediate azides **3** (Scheme **A**).

Ammonium ditosylates **5** are convenient starting materials for the preparation of free vicinal diamines **6** as well as their dibenzoyl derivatives **7** (Scheme **B**). A suspension of **5** in dichloromethane treated with an excess of potassium bicarbonate and potassium carbonate in the presence of 20 mol% of tetrabutylammonium bromide as phase-transfer catalyst at ambient temperature affords the corresponding free vicinal diamines **6** in quantitative crude yield. Free bases **6**, which can be purified by distillation *in vacuo*, are unstable at room temperature but can be stored unchanged for several weeks at −20 °C.



Scheme **B**

The yields and physical data of ammonium ditosylates **5a–h** and free diamines **6a–h** are listed in Table 1. All diamines reported give IR, MS, and ^{1}H-NMR spectra (see Table 2) fully compatible with the anticipated structures. Ammonium ditosylates **5** reacted smoothly with benzoyl chloride under typical Schotten–Baumann reaction conditions to give the corresponding dibenzoyl derivatives **7** in high yields. The corresponding data for **7** are given in Table 3.

Table 3. Dibenzoyl Compounds **7** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a]
7a	77	190–191	$C_{19}H_{22}N_2O_2$ (310.4)
7b	92	180–181	$C_{20}H_{24}N_2O_2$ (324.4)
7e	82	223–225	$C_{22}H_{20}N_2O_2$ (344.4)
7f	89	235–245	$C_{23}H_{22}N_2O_2$ (358.4)
7g	70	352–354	$C_{20}H_{22}N_2O_2$ (322.4)
7h	86	236–237	$C_{23}H_{20}N_2O_2$ (356.4)

[a] Satisfactory microanalyses obtained: C ±0.40, H ±0.26, N ±0.15.

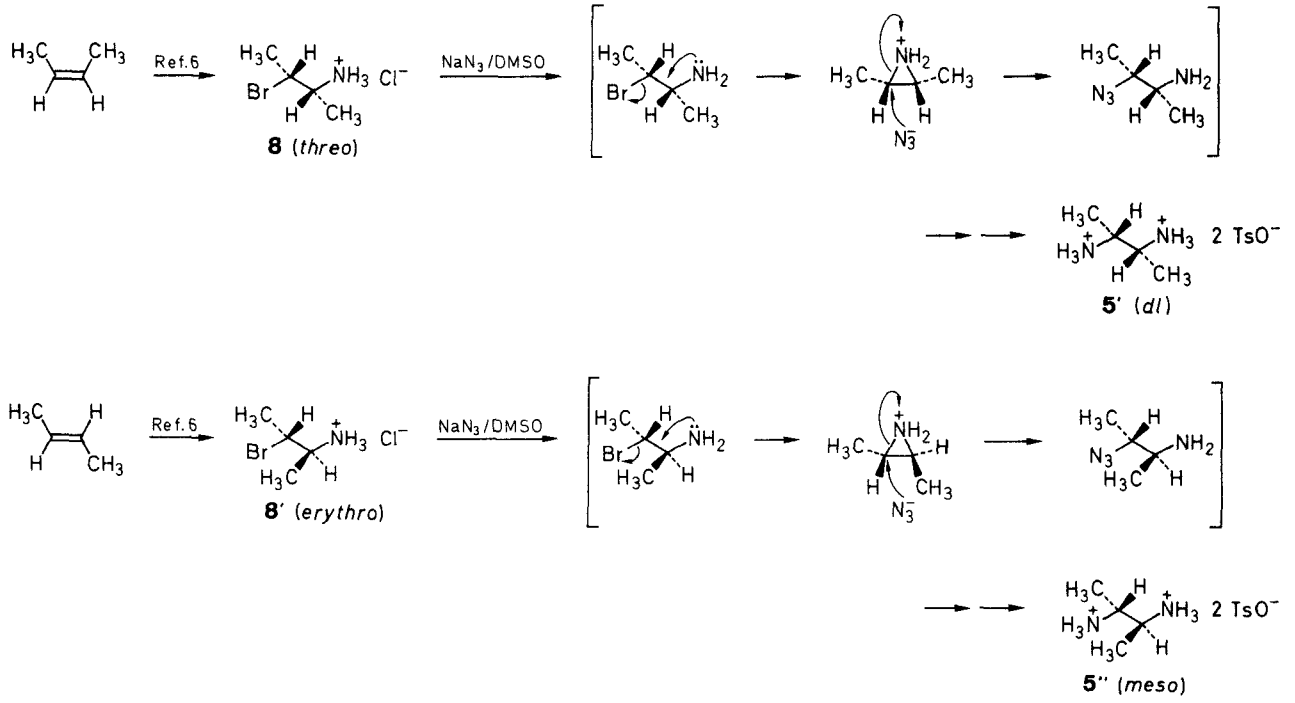
In our synthetic strategy (Scheme **A**) diastereoisomerically pure diethyl *N*-(β-bromoalkyl) phosphoramidates **2** of known configuration[6] were used as starting materials. On the route from **2** to ammonium ditosylates **5** only azidation of **2** involves a bond cleavage at the chiral center. This displacement of bromine by a strongly nucleophilic azide ion should occur, however, by a well-defined stereochemical course, i.e. with inversion.[9] According to this assumption ammonium ditosylates **5c,d,f** should be single diastereoisomers with the relative configuration opposite to that of their initial precursors **2**. Clean stereochemical outcome in this sequence was observed only in the case of cycloalkenes, **1g,h**. *trans*-1-*N*-(Diethoxyphosphoryl)-2-bromocyclohexane (**2g**) was

thus converted into *cis*-1,2-diaminocyclohexane dihydrochloride in 26% yield via the corresponding ditosylate **5g** and free diamine **6g**. The configuration of this dihydrochloride was established by comparison of its physical and spectroscopic data with those reported.[1,10] Similarly *cis*-1,2-diaminoindane (**6h**) was obtained in 31% yield from indene via the corresponding intermediates **2–5h**. Physical data for **6h** is in agreement with published values;[11] the configuration of **6h** is confirmed by its ^{1}H-NMR data. In 1,2-disubstituted indanes the shift difference between the protons at C-3 is generally smaller in the *cis*-compound than in the corresponding *trans*-isomer.[12] The chemical shifts for H-3 in **6h** are $\delta = 2.66$ (dd, $J = 15.7$, 4.0 Hz) and $\delta = 3.02$ (dd, $J = 15.7$, 6.0 Hz), the $\Delta\delta$ being 0.36. The recently reported[13] values of $\Delta\delta$ for H-3 resonances in relative *trans*-1,2-disubstituted indanes are 0.60 and 0.58.

Contrary to the expectations the overall diamination reaction (alkene → ammonium ditosylate) was not stereospecific in the case of open-chain olefins. Although (*Z*)- and (*E*)-2-butenes (**1c** and **1d**), selected as model substrates, reacted with diethyl *N,N*-dibromophosphoramidate (DBPA) in a stereospecific manner,[6] they could not be transformed into the corresponding ammonium ditosylates **5c** and **5d** with full stereochemical control. Examination of the ^{1}H-NMR spectra showed that the ammonium ditosylates **5c** and **5d**, obtained from phosphoramidates **2c** and **2d**, were diastereoisomeric mixtures of meso- and *dl*-isomers. The appearance of two upfield doublets centered at $\delta = 1.40$ and 1.45 indicates the existence of nonequivalent methyl groups in the *dl*- and *meso* diastereoisomers respectively. The isomer ratio, was estimated to be 6:1 (*meso*/*dl*-isomer)[14] from (*Z*)-2-butene (**1c**) and 1:4 from (*E*)-2-butene (**1d**). This result suggests a complex stereochemistry for the azidation step. The formation of considerable amounts of diastereoisomers having the same relative configuration as the starting phosphoramidates **2** suggests that azidation at least partially involves neighboring group participation by the amidophosphoryl group, resulting in two consecutive S_N2 reactions, leading to retention. This assistance can be reasonably explained in terms of the intermediacy of a five-membered cyclic quasiphosphonium type structure. If this is the case, the P–N bond rupture in phosphoramidates **2c** and **2d** prior to azidation should entirely change the reaction course possibly leading to pure diastereoisomers.

This assumption was verified experimentally opening a new simple route to stereospecific diamination of open-chain olefins. *threo*-2-Amino-2-bromobutane hydrochloride (**8**) prepared from (*Z*)-2-butene (**1c**) could be easily transformed into pure *dl*-2,3-diaminobutane ditosylate (**5′**).[15] Similarly *erythro*-2-amino-3-bromobutane hydrochloride (**8′**) obtained from (*E*)-2-butene (**1d**) delivered only *meso*-2,3-diaminobutane ditosylate (**5″**).[1] These results can be plausibly interpreted by assuming preliminary deprotonation of the hydrochlorides by an azide anion resulting in stereospecific ring closure to provide the corresponding aziridines that can be opened stereospecifically with an azide anion. Ring closure and subsequent opening occuring with inversion lead to net retention of configuration. Both transformations are outlined in Scheme C. In each case the ^{1}H-NMR spectra of **5′** and **5″** exhibited only one upfield doublet centered at $\delta = 1.38$ and 1.46, respectively.

The overall diamination procedure reported herein is a useful alternative to other methods due to its simplicity, versatility, and the possibility of stereochemical control. Its major disadvantage is that it cannot be used in the case of sterically congested olefins, which cannot undergo aminobromination.[6]



Scheme C

IR spectra were recorded on a Specord 71 IR (C. Zeiss) spectrophotometer. ^{1}H-NMR spectra were measured at 80 MHz using a Tesla BS 487 spectrometer (**6a,b,e**) and at 300 MHz on a Bruker MSL-300 spectrometer (**6f,h**). Mass spectra were recorded on a LKB 2091 mass spectrometer.

Ammonium Ditosylates 5; General Procedure:

A mixture of crude diethyl *N*-(β-bromoalkyl)phosphoramidate **2** (0.05 mol) prepared according to the previously described procedure,[6] NaN_3 (6.5 g, 0.1 mol), Bu_4NBr (1.6 g, 0.005 mol), and DMSO (25 mL) is stirred at 80 °C for 6 h. The product is poured into cold water (250 mL) and the resultant solution is extracted with benzene (3 × 10 mL). The extract is dried ($MgSO_4$), filtered, and treated with $(EtO)_3P$ (8.3 g, 0.05 mol). The mixture is stirred at r.t. for 24 h. Benzene is then removed under reduced pressure. A solution of $TsOH \cdot H_2O$ (19.0 g, 0.1 mol) in EtOH (15 mL) containing water (1.8 g, 0.1 mol) is added to the residue and the resultant mixture is refluxed gently for 6 h. Colorless crystals of ammonium ditosylate **5** separate on cooling and are isolated by suction filtration. A second crop of **5** can be sometimes obtained by evaporation on the mother liquor and addition of Et_2O. Crude ditosylates **5** are recrystallized from EtOH or $EtOH/H_2O$ to give analytically pure samples.

Vicinal Diamines 6; General Procedure:

A mixtures of the ammonium ditosylate (**5**; 0.05 mol) $KHCO_3$ (50 g, 0.5 mol), K_2CO_3 (69 g, 0.5 mol), Bu_4NBr (3.2 g, 0.01 mol), and CH_2Cl_2 (200 mL) is stirred vigorously at r.t. for 12 h. The suspension is then filtered and the filtrate is evaporated under reduced pressure. The residue is distilled *in vacuo* to give pure diamines **6** as colorless, mobile liquids, which quickly become dark when stored at r.t.

Benzoylation of Ammonium Ditosylates 5 to Dibenzoyl Derivatives 7; General Procedure:

Benzoyl chloride (3.1 g, 0.022 mol) is added to the solution of ammonium ditosylate **5** (0.01 mol) in water (20 mL) containing NaOH (1.8 g, 0.044 mol). The resultant mixture is stirred at 20–25 °C (occasional cooling) for 15 min. The precipitated product **7** is isolated by filtration and recrystallized from MeOH or MeOH/DMF to give analytically pure samples.

Conversion of *threo*-2-Amino-3-bromobutane Hydrochloride (8) to *dl*-2,3-Diaminobutane Ditosylate (5′); Typical Procedure:

NaN_3 (2.6 g, 0.04 mol) is added to a solution of crude *threo*-2-amino-3-bromobutane hydrochloride[6] (**8**; 3.77 g, 0.02 mol) in DMSO (10 mL). The mixture is stirred at 80 °C for 6 h, then cooled to r.t., and dissolved in water (100 mL). The solution is made alkaline (pH = 11) with solid NaOH and then extracted with benzene (2 × 10 mL). The extract is dried ($MgSO_4$), filtered, treated with $(EtO)_3P$ (3.3 g, 0.02 mol), and stirred at r.t. for 24 h. Benzene is then removed under reduced pressure. The residue is dissolved in EtOH (10 mL), and $TsOH \cdot H_2O$ (7.6 g, 0.04 mol) is added. The mixture is refluxed gently for 6 h. On cooling to r.t. the product crystallizes spontaneously. It is isolated by filtration and washed well with Et_2O; yield: 3.98 g (46%); mp 293–295 °C.

$C_{18}H_{28}N_2O_6S_2$	calc.	C 49.98	H 6.52	N 6.47
(432.6)	found	49.80	6.50	6.48

IR (KBr): ν = 3100, 1630, 1615, 1540, 1410, 1340, 1260, 1180, 1140, 1085, 1050, 1025, 835, 700 cm^{-1}.

^{1}H-NMR (D_2O/TMS_{ext}): δ = 1.38 (d, 6 H, *J* = 6.6 Hz, CH_3), 2.30 (s, 6 H, Ar-CH_3), 3.73–3.78 (m, 2 H, CH), 7.25–7.71 (m, 4 H_{arom}).

Conversion of *erythro*-2-Amino-3-bromobutane Hydrochloride (8′) to *meso*-2,3-Diaminobutane Ditosylate (5″):

The same typical procedure and the same amount of reagents as described immediately above are applied; yield: 3.80 g (44%); mp 324–326 °C (dec).

$C_{18}H_{28}N_2O_6S_2$	calc.	C 49.98	H 6.52	N 6.47
(432.6)	found	49.70	6.60	6.61

IR (KBr): ν = 3050, 1655, 1630, 1570, 1420, 1220, 1145, 1055, 1025, 835, 705 cm^{-1}.

^{1}H-NMR (D_2O/TMS_{ext}): δ = 1.46 (d, 6 H, *J* = 6.6 Hz, CH_3), 2.39 (s, 6 H, Ar-CH_3), 3.65–3.71 (m, 2 H, CH), 7.35–7.74 (m, 4 H_{arom}).

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(15) Both structural assignments have been confirmed by X-ray crystallographic analysis: Wieczorek, M.W.; Bujacz, G.; Osowska-Pacewicka, K.; Zwierzak, A. *J. Cryst. Spectr. Res.*, in preparation.