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# Coupling of 1,2-bis(alkoxyamino)cyclohexanes with 1,3-dicarbonyl compounds: first synthesis of 1,4-dialkoxy-2,3-dihydro-1,4-diazepinium salts

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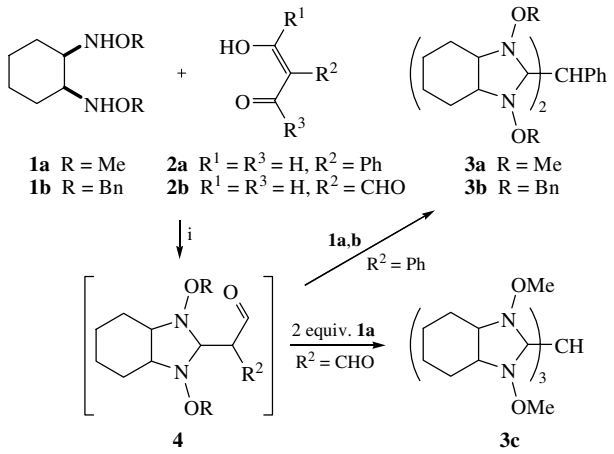
**The reactions of two 1,2-bis(alkoxyamino)cyclohexanes with 2-substituted malonic aldehydes, acetylacetaldehyde and acetylacetone gave rise to imidazolidine derivatives, whereas 1,4-dialkoxy-2,3-dihydro-2,3-cyclohexano-1,4-diazepinium salts were the only products in acidic media.**

New vicinal nitrogen bases are attractive building blocks in the synthesis of heterocyclic systems. 1,2-Bis(alkoxyamines)[1] occupy a unique position among nitrogen binucleophiles, which allows us to synthesise a wide range of heterocyclic compounds containing an N–O moiety, such as *N*-alkoxy derivatives of imidazolidine,[1(a)] piperazine[1(a)] and 1,2,3-triazole.[1(b),(c)] The chemistry of *N*-alkoxy derivatives is attractive for many reasons, which can be divided conventionally into three categories. First, some of the compounds were found biologically active. For example, *N*-methoxyindole-3-carbinol derivatives such as neoascorbigen are natural substances from plants of the *Cruciferae* family, which exhibited pronounced anti-cancer[2] and cytochrome P 450 modulating activities.[3] *N*-Alkoxybenzimidazoles are known as anti-HIV agents.[4] The electron-withdrawing alkoxy group attached to the nitrogen atom in iminoglycosides of the piperidine family can potentially bridge two units of saccharides for a unique class of multisubstrate glycosidase inhibitors.[5] On the other hand, the *N*-alkoxyl substituent in a heterocyclic framework could be regarded as a protective group for the *N*-hydroxy functionality. Despite the fact that powerful reductants such as $SmI_2$ are able to split the N–O bond in alkoxyamines,[6] convenient conditions were found for the successful selective debenzylation[7] and demethylation[8] of the N–O–R-moiety (R = Me, Bn). Finally, sterically hindered alkoxyamines are not only excellent agents for long-lived polymerization processes[9] but also effective initiators of radical intramolecular cyclizations in the synthesis of pyrrole and indole derivatives.[10]

Therefore, the use of new reagents for the synthesis of alkoxyamines is desirable. Recently, it was shown that the reaction of enone Mannich bases and *cis*-1,2-bis(methoxyamino)cyclohexane leads to formation of 1,4-dimethoxyperhydro-1,4-diazepine derivatives.[11] Such compounds are of interest because of biological activity of their 1,4-dialkylated analogues. For instance, *N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-pyridine-3-carboxamides possess potent serotonin 5-$HT_3$ and dopamine $D_2$ receptor antagonistic activity.[12] We realised that another approach to 1,4-dialkoxy-1,4-diazepine derivatives could be achieved by the reaction of 1,2-bis(alkoxyamines) with 1,3-dicarbonyl compounds.

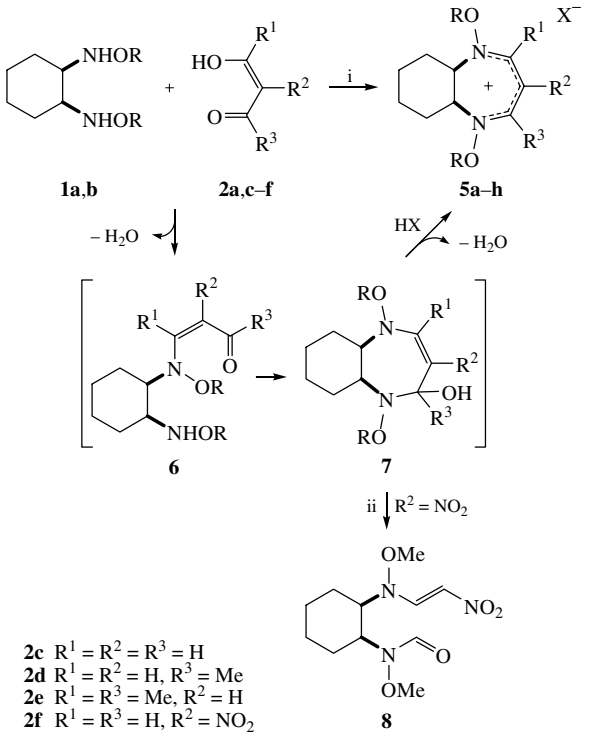
The reaction of model useful compounds *cis*-1,2-bis(alkoxyamino)cyclohexanes **1a**,**b** with phenylmalonic aldehyde[13] **2a** under neutral conditions at room temperature led to bis(imidazolidine)methane derivatives **3a**,**b**.† Triformylmethane[14] **2b** reacts with bis(alkoxyamine) **1a** under similar conditions to form a complex mixture from which tris(imidazolidine)methane **3c** was isolated in 42% yield (Scheme 1).




**Scheme 1** *Reagents and conditions*: i, EtOH, room temperature, 24–96 h, 42–61%.

The coupling of **1a**,**b** with 1,3-dialdehydes proceeded quite differently in the presence of strong acids. Thus, the addition of a mixture of **1a** and an excess of hydrochloric acid to a solution of phenylmalonic aldehyde **2a** in ethanol led to the formation of a stable yellow product. This compound was identified as 1,4-dimethoxy-2,3-dihydro-2,3-cyclohexano-1,4-diazepinium chloride **5a** (Scheme 2). A similar result was observed when $HClO_4$

† Compound **3a**: a solution of **1a** (0.18 g, 1.02 mmol) and phenylmalonic aldehyde **2a** (0.15 g, 1.02 mmol) in 2 ml of EtOH was kept at room temperature for 24 h. Precipitate was filtered off and washed with EtOH. Filtrate was diluted by 2 ml of EtOH and kept at –12 °C for a few days. The resulting colourless crystals were filtered off. Total yield, 136 mg (61%); mp 118–120 °C (EtOH). Found (%): C, 65.4; H, 9.3; N, 12.0. Calc. for $C_{25}H_{40}N_4O_4$ (%): C, 65.2; H, 8.8; N, 12.2. $^1$H NMR (200.13 MHz, $CDCl_3$) $\delta$: 0.85–1.62 [m, 16H, $(CH_2)_4$], 2.99 (t, 1H, C*H*Ph, *J* 7.0 Hz), 3.03 (s, 6H, OMe), 3.10–3.32 [m, 4H, $(CH)_2$], 3.62 (s, 6H, OMe), 4.58 (d, 2H, NCHN, *J* 7.0 Hz), 7.10–7.26, 7.28–7.48 (m, 5H, Ph). $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$: 22.2, 22.3, 26.7, 26.8 [$(CH_2)_4$], 53.9 (C*H*Ph), 60.7, 61.3 (OMe), 63.2, 64.5 [$(CH)_2$], 92.5 (NCHN), 125.9, 126.2, 132.7 ($C_{para}$, $C_{meta}$, $C_{ortho}$, Ph), 137.4 ($C_{ipso}$, Ph). Analogous procedure was applied for compounds **3b**,**c** (yields are 84 and 42%, respectively).




**1a**,**b** **2a**,**c**–**f** **5a**–**h** **6** **7** **8**

**2c** $R^1 = R^2 = R^3 = H$
**2d** $R^1 = R^2 = H$, $R^3 = Me$
**2e** $R^1 = R^3 = Me$, $R^2 = H$
**2f** $R^1 = R^3 = H$, $R^2 = NO_2$

**5a** R = Me, $R^1 = R^3 = H$, $R^2 = Ph$, X = Cl
**5b** R = Me, $R^1 = R^3 = H$, $R^2 = Ph$, X = $ClO_4$
**5c** R = Bn, $R^1 = R^3 = H$, $R^2 = Ph$, X = Cl
**5d** R = Bn, $R^1 = R^3 = H$, $R^2 = Ph$, X = $ClO_4$
**5e** R = Bn, $R^1 = R^2 = R^3 = H$, X = $ClO_4$
**5f** R = Bn, $R^1 = Me$, $R^2 = R^3 = H$, X = $ClO_4$
**5g** R = Me, $R^1 = R^3 = Me$, $R^2 = H$, X = $ClO_4$
**5h** R = Bn, $R^1 = R^3 = Me$, $R^2 = H$, X = $ClO_4$

**Scheme 2** *Reagents and conditions*: i, EtOH, HX (X = Cl, $ClO_4$), room temperature, 24–96 h, 63–93%; ii, R = Me, $R^1 = R^3 = H$, $R^2 = NO_2$, EtOH, HCl, room temperature, 24 h, 28%.

was used.‡ Perchloric acid is used instead of hydrochloric acid because the obtained salts are not so hygroscopic. Using less reactive 1,3-dicarbonyl compounds in place of 1,3-dialdehydes does not influence the nature of the corresponding products. 3-Oxobutanal **2d** and pentane-2,3-dione **2e** react smoothly with **1a**,**b** in the presence of an excess of $HClO_4$ to form diazepinium salts **5f**–**h**. A plausible explanation of this result is initial condensation to give unstable intermediate alkoxyamine **6**, intramolecular cyclization to form hydroxytetrahydro-1,4-diazepine **7** and dehydration evoked by a mineral acid.

The NMR spectra of cations **5a**–**g** indicate the total equivalence of C(5) and C(7) on the NMR time scale; this implies that the extensive delocalization of π electrons between the two nitrogen atoms of the diazepine ring is due to vinamidinium system.

The data observed in an X-ray study of perchlorate **5b** show that the cyclohexane and diazepine rings are *cis*-fused§ (Figure 1). In fact, the vinamidinium system is not fully planar because of the influence exerted by the cyclohexane ring and two alkoxyl groups at the nitrogen atoms. The UV spectra of diazepines **5a**–**h** have three absorption maxima at 200–210, 227–260 and 340–386 nm and are similar to those of their 1,4-dialkylated analogues obtained from 1,2-disubstituted 1,2-diamines.[15] In the IR spectra of these compounds, there are two absorption bands with highest intensities around 1580–1600 and 1500–1540 $cm^{-1}$ due to the vinamidinium system. Owing to the presence of two alkoxyl groups, 1,4-diazepinium salts **5a**–**h** are easily soluble in both polar and nonpolar solvents, and this feature allows easy purification of these salts by flash chromatography.

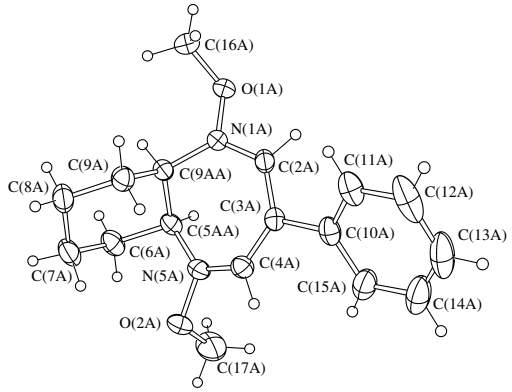



**Figure 1** Crystal structure of compound **5b** (only one cation is shown from two independent).

The reaction of 1,2-bis(methoxyamino)cyclohexane **1a** with nitromalonic aldehyde sodium salt[16] **2f** in the presence of two equivalents of HCl proceeded without the formation of corresponding 1,4-diazepinium salt. We suppose that in this case, a C–C bond rupture in intermediate **7** (Scheme 2) takes place. The main product isolated from the reaction mixture has the structure of open-chain derivative **8**. The structure of this compound was deduced from X-ray analysis.

Thus, we found that 1,2-bis(alkoxyamino)cyclohexanes can be used as analogues of *N*,*N*′-dialkylated-1,2-diamines for the synthesis of new 1,4-dialkoxy-2,3-dihydro-1,4-diazepinium salts. Additional examples in this series of reactions of 1,2-bis(alkoxyamines), as well as investigations of the reactivity of the obtained 1,4-diazepinium salts, are under study.

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‡ Compound **5b**: a solution of **1a** (0.18 g, 1.02 mmol) and 0.15 ml of concentrated $HClO_4$ in 1 ml of EtOH was added to a solution of **2a** (0.15 g, 1.02 mmol) in 2 ml of EtOH at room temperature with stirring. After 24 h at room temperature reaction mixture was evaporated *in vacuo* and product **5b** was purified by column chromatography on $SiO_2$ ($CHCl_3$–MeOH, 20:1). Yield 0.27 g (63%), mp 98–100 °C ($Pr^iOH$). Found (%): C, 52.8; H, 6.0; Cl, 9.3; N, 7.2. Calc. for $C_{17}H_{23}ClN_2O_6$ (%): C, 52.8; H, 6.0; Cl, 9.2; N, 7.2. UV [EtOH, $\lambda_{max}$/nm (lg ε)]: 203 (3.22), 234 (3.01), 248 (3.00), 386 (2.86). IR (KBr, $\nu$/$cm^{-1}$): 1625, 1598, 1537 (ν, C=C–C=N). $^1$H NMR (400.13 MHz, $CDCl_3$) δ: 1.40–1.55, 1.65–1.78, 1.79–1.92 [m, 8H, $(CH_2)_4$], 3.85 (s, 6H, OMe), 4.53 [d, 2H, $(CH)_2$, *J* 8.4 Hz], 7.05–7.21 (m, 5H, Ph), 7.71 (s, 2H, 2-H and 4-H). $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ: 21.9, 27.4 [$(CH_2)_4$], 62.7 [$(CH)_2$], 65.2 (OMe), 97.1 (C-6), 127.4, 127.5, 129.0 ($C_{para}$, $C_{meta}$, $C_{ortho}$, Ph), 136.4 ($C_{ipso}$, Ph), 153.3 (C-5, C-7). Analogous procedure was applied for compounds **5a**,**c**–**h**.

§ *X-ray crystallographic data for compound* **5b**. The fragment N(1B)–O(1B)–C(16B) is disordered over two positions in the second independent cation, $[C_{17}H_{23}N_2O_2]^+[ClO_4]^-$, $M_r$ = 386.82, orthorhombic, $Pca2_1$, *a* = = 30.374(4), *b* = 9.257(2) and *c* = 13.2396(14) Å, *V* = 3722.6(11) Å$^3$, *Z* = 8, $d_{calc}$ = 1.380 g $cm^{-3}$, $\mu$(MoKα) = 0.241 $mm^{-1}$, *T* = 296 K, $wR_2$ = = 0.1706, *S* = 1.060 for all 3829 *hkl* [*R* = 0.0540 for observed 3055 $I > 2\sigma(I)$].

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 286076. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2007.

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