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A new entry towards the synthesis of 1-substituted 3-azetidinones

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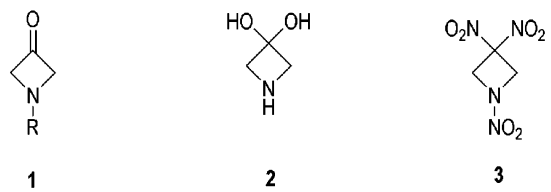
Abstract—The synthesis of 1-substituted 3-azetidinones, starting from readily accessible *N*-(alkylidene)- or *N*-(arylidene)-2,2,3-tribromopropylamines, is disclosed. © 2001 Published by Elsevier Science Ltd.

Azetidine derivatives, carrying a carbonyl group at position 2, occupy a special place in heterocyclic chemistry. Natural and synthetic azetidin-2-one derivatives are known as antibiotic compounds.[1–4] Much less widespread are azetidin-3-one derivatives (Fig. 1), e.g. **1**, which are not yet found in nature. However, very recently, 3,3-dihydroxyazetidine **2**, the hydrate of azetidin-3-one, has been isolated from the supernatant of a culture of *Bacillus cereus* and has been found to act as a growth-promoting factor for several strains of *Bifidobacterium*.[5]

Considerable research in this area has been done towards the synthesis of 1,3,3-trinitroazetidine **3** (TNAZ), an energetic material which is sensitive to detonation on impact.[6–10] Most syntheses of this compound start from the 2,4-unsubstituted azetidin-3-one, which is converted to the oxime and treated with nitric acid.[6–8]

The most important synthetic routes towards azetidin-3-ones include cyclization of α-amino-α′-diazoketones,[11] ring closure of α-amino-α′-halo-[12] or α-amino-α′,β′-epoxyketones,[13] oxidation of 3-azetidinols[14] and ozonization of 3-alkylidene-1-substituted azetidines.[15]



1 2 3

Figure 1.

In this communication, we wish to present an easy entry towards 2,4-unsubstituted azetidin-3-ones **9** starting from *N*-(alkylidene)- or *N*-(arylidene)-2,2,3-tribromopropylamines **6**. The new tribromoimines **6** were synthesized from 2-bromoallylamine **4**, which can easily be synthesized via a well-established procedure, starting from allyl bromide.[16] Two pathways can be followed in the synthesis of imines **6** (Scheme 1). Condensation of 2-bromoallylamine **4** with benzaldehyde and subsequent bromination of the intermediate *N*-(benzylidene)-2-bromoallylamine **5** yields imine **6a**.

With the use of other aldehydes, this pathway is not useful since the necessary prolonged bromination of the corresponding imines leads to partial hydrolysis to the aldehyde again. An alternative route can be followed where the 2-bromoallylamine is first protected as the hydrobromide salt, then brominated to give the intermediate **7** and afterwards condensed with the aldehyde, giving the corresponding tribromoimines **6** in excellent yields. It was noticed by the authors that the latter compounds **6** exhibit an irritating effect on the eyes.

The cyclization of *N*-(alkylidene)- or *N*-(arylidene)-2,2,3-tribromo-propylamines **6** with excess sodium borohydride in methanol under reflux, results in the azetidine derivatives **8** (Scheme 2). Under the applied conditions, the imino function of compounds **6** was reduced and the resulting intermediate γ-bromoamines were cyclized to afford the corresponding 3,3-dibromoazetidines. The latter intermediates were not isolated but were found to be converted readily by methanolysis to aminoacetals **8** in isolated yields of 47–54%. This synthetic scheme gives the possibility of creating new

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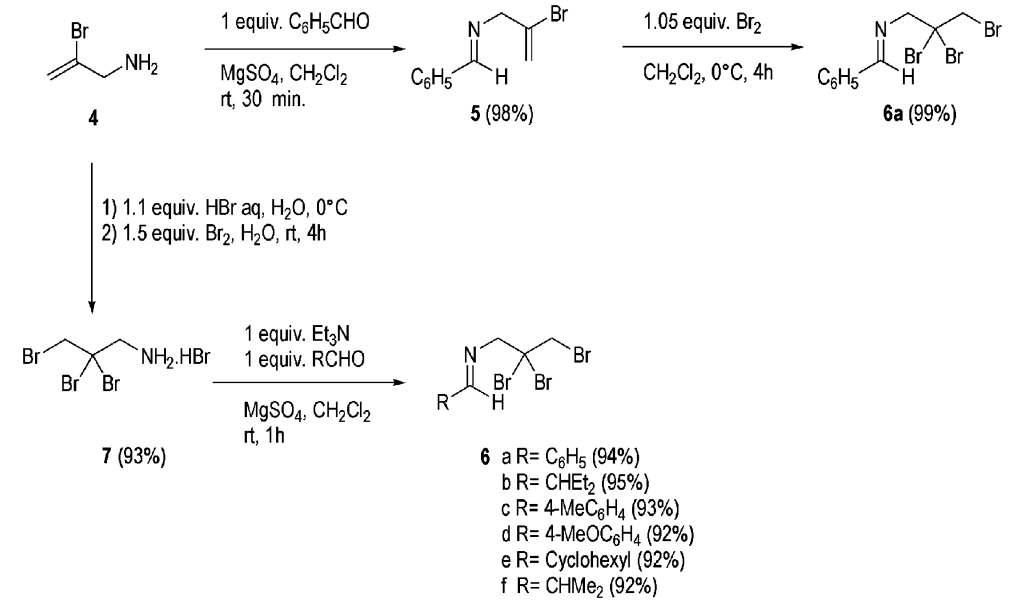
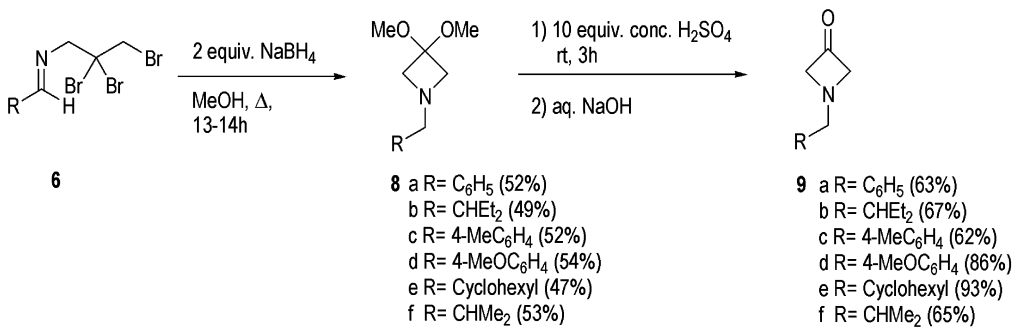


Scheme 1.



Scheme 2.

access to azetidin-3-ones by hydrolysis of the acetal. Previously, the hydrolysis of ethyl 3-methoxy-2-phenyl-3-[(trimethylsilyl)oxy]-1-azetidine carboxylate by aqueous hydrochloric acid has been reported.[17]

In the present case, hydrochloric acid seemed to have a destructive effect on the 3,3-dimethoxyazetidine substrates **8**. Several hydrolytic conditions for the conversion of acetals to the corresponding ketones were tried out without success (e.g. 5 equiv. 2 M HCl, 4 h reflux; 10 equiv. 2 M HCl, 4 h reflux; 5 equiv. 4 M HCl, 4 h reflux; 5 equiv. 12 M HCl, 4 h reflux, …). However, the use of concentrated sulfuric acid permitted us to perform the desired transformation of acetals **8** into azetidin-3-ones **9**. The azetidin-3-ones **9a–f** were obtained in 62–93% yield.[18] The 1-substituted azetidin-3-ones **9** so obtained are labile compounds and start decomposing after 8 hours at room temperature. According to literature references, only azetidin-3-one derivatives with sterically demanding[14b,c] or electron-withdrawing[11b,c,14] substituents on nitrogen are stable towards self condensation.

Currently, further transformations of these 2,4-unsubstituted azetidin-3-ones are under investigation.

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18. Spectroscopic data for **9a**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.89 (2H, s, $C_6H_5CH_2N$), 4.08 (4H, s, CH_2NCH_2), 7.33 (5H, broad s, C_6H_5); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 63.45 ($C_6H_5CH_2N$), 75.06 (CH_2NCH_2), 127.51 ($=C_{para}$), 128.37 and 128.57 ($=C_{ortho}$ and $=C_{meta}$), 138.04 ($C_{quat.}$), 201.24 (C=O); IR (NaCl, cm^{-1}): 1810 ($\nu_{C=O}$); MS (70 eV) m/z (%): 161 (M^+, 2), 160(2), 134(7), 133(40), 132(12), 106(2), 105(4), 104(4), 103(4), 91(59), 89(5), 84(4), 77(4), 65(16), 63(5), 51(7), 44(5), 43(4), 42(100), 41(9).