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Reactions of 2-bromopropanamides with conjugated bases of representative β-dicarbonyl compounds. Synthesis of 2,5-dioxopyrrolidines and oxazolidine-4-ones☆

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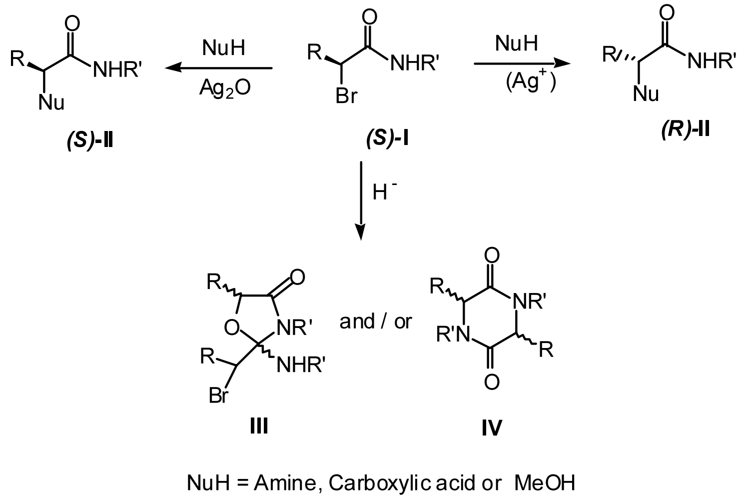
Dedicated to Professor Ferruccio D'Angeli on the occasion of his 76th birthday

Abstract—Reactions of 2-bromopropanamides with potassium enolates of representative β-dicarbonyl compounds provide, in high yields, open and heterocyclic compounds through a C–C or C–O alkylation reaction. Whereas *C*-alkylation products form in all conditions tested under relevant diastereoselectivity, *O*-alkylation takes place only in the presence of silver promoters, and shows partial diastereoselectivity. © 2003 Elsevier Science Ltd. All rights reserved.

Alkyl halides showed paramount importance at unveiling the existence of different substitution patterns, providing (i) stereochemical and kinetic information when starting from single enantiomeric species,[1] as well as (ii) regiochemical information when using ambident nucleophiles such as enolate anions.[2]

In our laboratory, attention has been devoted in recent years to a particular family of halides, i.e. 2-bromoamides **I**. Homochiral **I** were found to react with either an amine, methanol or a carboxylic acid giving the substitution products **II**; stereochemistry of **II** depends upon the presence of a promoter such as Ag$^+$ or Ag$_2$O[3] and different reaction pathways were taken into consideration.[4] On the other hand, 2-bromoamides **I** react with the non-nucleophilic base H$^-$ yielding cyclodimeric oxazolidine-4-ones **III** and/or 2,5-dioxopiperazines **IV** (Scheme 1).[5]



Scheme 1.

Keywords: 2-bromoamides; silver oxide; *C*-alkylation; *O*-alkylation; β-dicarbonyl compounds.

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Continuing our investigation on 2-bromoamides, we here report a preliminary study concerning reactions of protic (**1a**,**b**) or aprotic (**2a**,**b**) 2-bromopropanamides with ambident anions, i.e. potassium enolates of diethylmalonate (**3**), 2,4-pentanedione (**4**) or acetoacetate (**5**) in anhydrous THF (Fig. 1).

When protic **1a**,**b** were treated with diethylmalonate potassium salt (**3**), the formation of a C–C bond in the alkylation step took place both in the presence or absence of a promoter (Ag^+, Ag_2O) (Scheme 2).

2,5-Dioxopyrrolidines (**6a**,**b**), encompassing the C_3–C_4 bond (along with the C_2–N bond), formed with almost complete diastereoselectivity in the three reaction conditions chosen.

On the other hand, 2,4-pentanedione or acetoacetate potassium salts (**4**, **5**) reacted, in turn, with **1a**,**b** only in the presence of a silver promoter. In both oxazolidin-4-ones (**7a**,**b**, **8a**,**b**) and acyclic enol-ethers (**9a**,**b**), a new C–O bond is formed.

In the case of anion **4**, the reaction in the presence of Ag^+ resulted in only one diastereoisomer (*cis*-**7a**,**b**). On the contrary, the reactions of both **4** and **5** in the presence of Ag_2O, gave compounds **7** and **8** as 1:1 *cis*/*trans* mixtures.

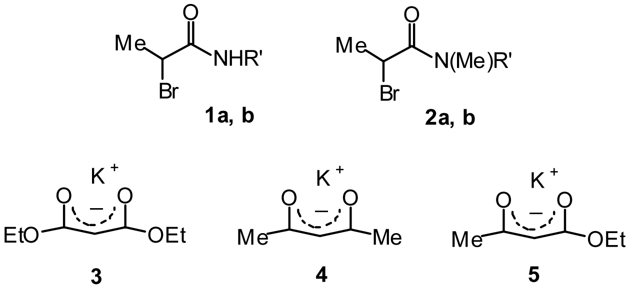


Figure 1. Throughout the paper, compounds **a**, R′ = Ph; **b**, R′ = Bn.

Alkylation at carbon versus oxygen may be related, inter alia,[2] to the relative acid–base properties of all reacting species. Anions **3**–**5** are weaker bases (pK_a of respective conjugated acids: 13, 9, 11, respectively) than the amidate conjugated bases of both 2-propanamides (pK_a of bromoamides **1a**,**b**: 19 and 22)[4] and possibly of the hypothetical primary and final reaction products (**9**–**11a**,**b**) (Fig. 2).

In order to explore the role of ancillary C–N bond formation in heterocyclic products, aprotic amides **2a**,**b** were reacted in the same conditions used for **1a**,**b**. Whereas **2a**,**b** reacted with **3** both in the presence or absence of a promoter yielding the pertinent open *C*-alkylation products **12a**,**b**, no reaction took place from **2a**,**b** and **4** or **5** even in the presence of a promoter (Scheme 3).

Another interesting observation derives from the isolation of **9a**,**b**, **12a**,**b**. These compounds give indirect evidence of the role of **10a**,**b** as intermediates in the formation of **6a**,**b** and suggested that ancillary heterocyclization is not of crucial importance for the isolation of *C*- and *O*-alkylation products.

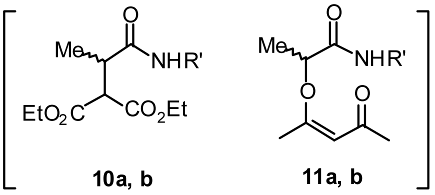
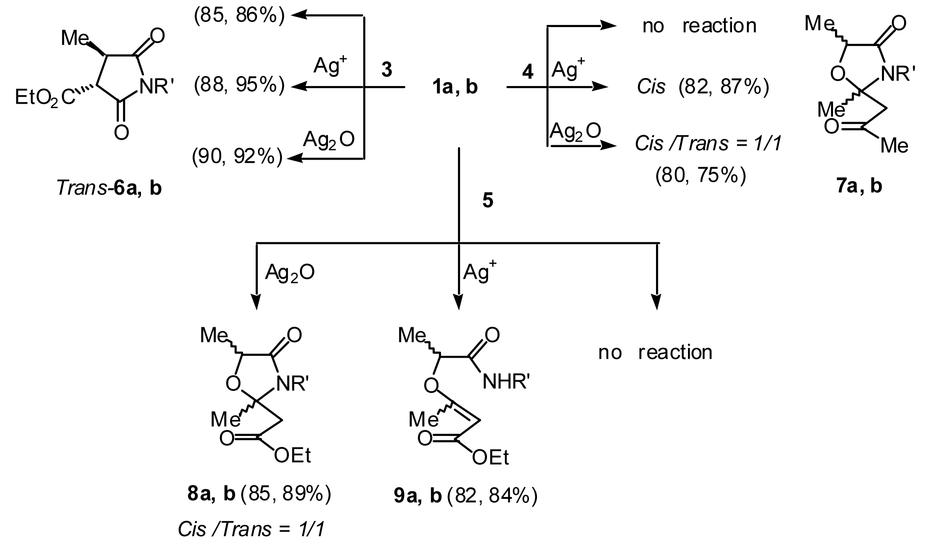
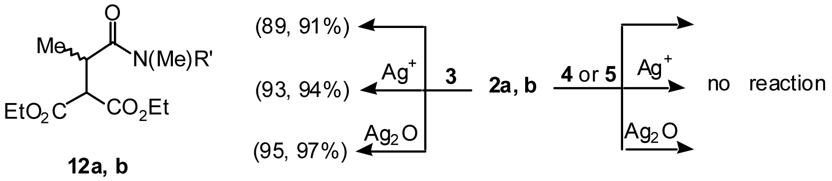


Figure 2.



Scheme 2. Configurations of **6a**,**b** are arbitrary to show *trans*-isomers.



Scheme 3.

In conclusion, in previous studies we have demonstrated that regio- and stereochemistry of the bromine substitution in 2-bromoamides by a variety of oxygen or nitrogen nucleophiles depend on the nucleophile and the presence of a silver promoter. In the present study we have investigated the possibility to form C–C or C–O bonds from 2-bromopropanamides and ambident anions, i.e. alkali metal enolates of β-dicarbonyl compounds. The preliminary results obtained indicate that a new C–C bond results in acyclic compounds (**12a**,**b**) or heterocycles arising through domino reactions (**6a**,**b**); moreover, a C–O bond results in acyclic enol ethers (**9a**,**b**) or oxazolidin-4-ones (**7a**,**b**, **8a**,**b**). The new succinic, pyrrolidine or oxazolidin-4-one derivatives are interesting for further elaboration, stereochemical studies and as models for broadening the scope of the research. Further investigations are currently being conducted in order to study the formation of a C–C bond from 2-bromoamides and other carbon nucleophiles as well as the stereochemistry of the products arising in different experimental conditions.

Acknowledgements

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