

Formation of Thioureas by Reaction of Isothiocyanates with Weakly Basic or Betaine Amines Promoted by DMAP

P. Pazdera^{a,b}, J. Šimbera^a, K. Sedláček^b and J. Havel^c

^aDepartment of Organic Chemistry, Masaryk University Brno, Kotlářská 2, CZ-611 37 Brno, Czech Republic

^bComin.cz, s. r. o., Táborská 23, Prague, CZ-130 87, Czech Republic

^cDepartment of Analytical Chemistry, Masaryk University Brno, Kotlářská 2, CZ-611 37 Brno, Czech Republic

E-mail: pazdera@chemi.muni.cz

Introduction

Several thousand papers and patents refer since 1970s that activation of acyl, alkoxycarbonyl or aryloxy carbonyl synthons for their coupling with N, O, C nucleophiles may be very effectively realized by an addition of 4-*N,N*-dialkylaminopyridine (DMAP) in catalytic amount [1].

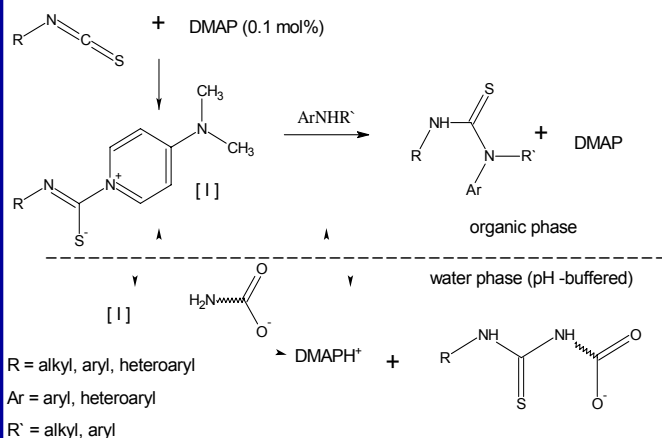
On the other hand, formation of thioureas is not easy for reactions starting from small reactive isothiocyanates (*e. g.* alkyl-, electron donor substituted aryl- or heteroaryl isothiocyanates) and/or weakly basic or betaine amines. The last mentioned betaines are insoluble in non-polar organic solvents and reactions must be frequently carried out for the most part in two phase systems or in water – organic solvents solution very often with poor yields.

Results and discussion

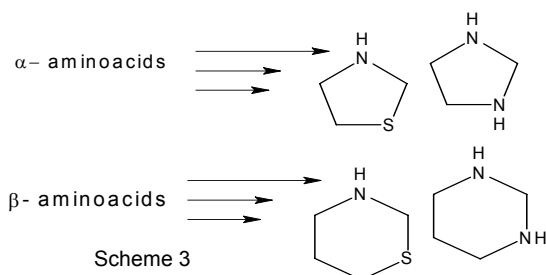
Now we found that these problems can be solved under a promotion by DMAP addition to both reacting components (Scheme 1). Syntheses can be realized successfully for small active isothiocyanates (phenyl-, allyl-, methylisothiocyanate, rhodamin B - isothiocyanate) and/or weakly basic amines (2-, 3-, 4-nitroaniline, 2,4-, 2,6-dinitroaniline in different organic solvents, for betaine amines (glycine, α -, β -alanine, proline, tryptophane, sulfanilic and orthonilic acid) in two phase systems consisting buffered water and organic solvent. Under this condition the thioureas are formed fast (reaction times 15 – 60 min) and in very good yields (about 80%).

We assume that the reaction course proceeds *via* quick formation of the key betaine intermediate I (detected by TLC and UV-VIS methods): structure of I determines its solubility for reaction in both water and organic solvent, on the other hand the carbon atom of thiocarbonyl group in I is activated for nucleophilic attack by nitrogen of amino group and thiourea product is formed.

Further part of the DMAP during this process is N – H deprotonation of very weakly basic amines, *e. g.* EWG substituted anilines and related compounds (Scheme 2).



Scheme 1

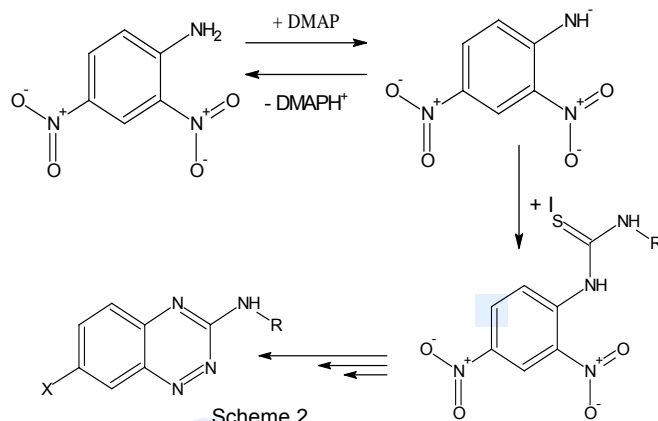


Scheme 3

Prospects

This observation enables new applications of this method in heterocyclic syntheses (*e. g.* 1,2,4-benzotriazine [2, 3], thiazole, imidazole, thiazine and pyrimidine skeletons – Scheme 2, 3), anyhow for final determination of amino acids, proteins and related structures after their separation by spectrophotometric or luminescent analytical methods after a derivatization with suitable isothiocyanate reagents [4].

Key words: DMAP, molecules activation, green synthesis



Scheme 2

Literature

1. Marugan R., Scriven E.F.V., *Aldrich Chim. Acta* **36** (1), 21 (2003).
2. Pazdera P., Potáček M., *Chem. Papers* **43** (1), 97 (1989).
3. Pazdera P., Potáček M., *Chem. Papers* **43** (1), 107 (1989).
4. Chen R. F., *Arch. Biochem. Biophys.* **133**, 263 (1969).