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[a038]

Unexpected result of reaction of b-halogen-a-tosyl-substituted ureas with b-oxoesters and 1,3-diketones. Synthesis of 3-acyl-substituted 5-ureido-4,5-dihydrofurans

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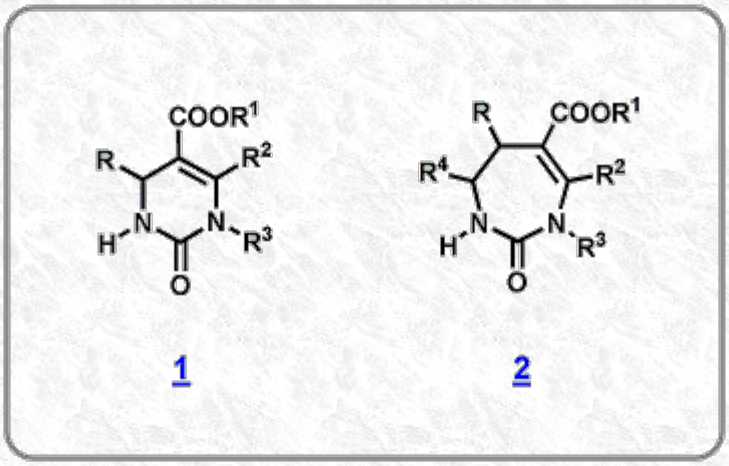
Abstract: Reaction of b-halogen-a-tosyl-substituted ureas with enolates of b-oxoesters and 1,3-diketones gives earlier unknown 3-acyl-substituted 5-ureido-4,5-dihydrofurans instead of expected 5-acyl-6-(halogenomethyl)-4-hydroxyhexahydropyrimidin-2-ones.

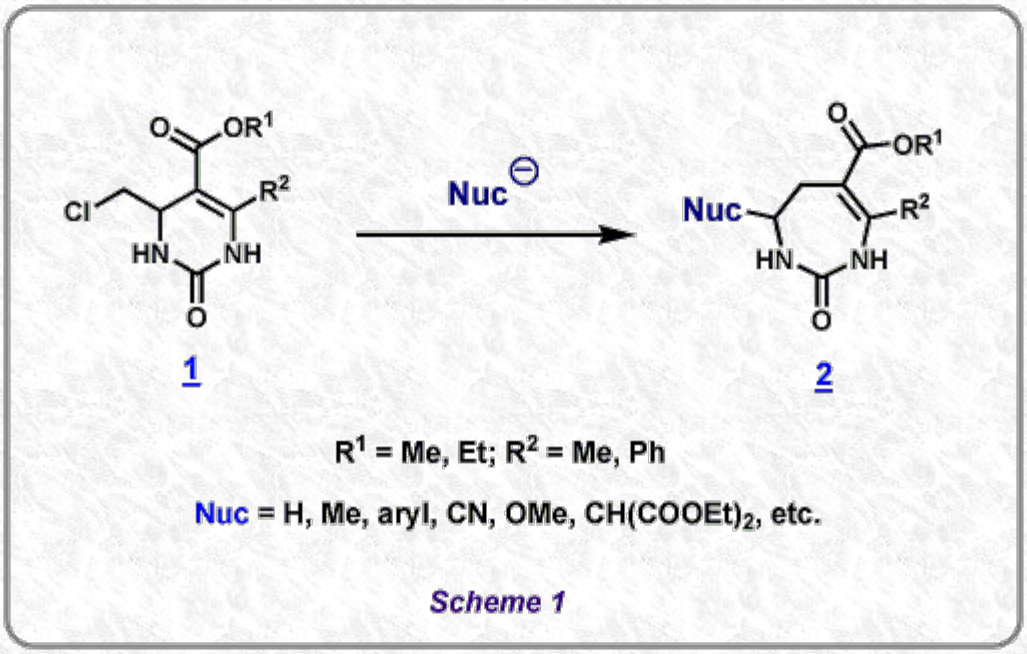
Keywords: a-halogenaldehydes, b-halogen-a-tosyl-substituted ureas, b-oxoesters, 1,3-diketones, 5-ureido-4,5-dihydrofurans, N-carbamoylpyrroles.

Introduction

Alkyl 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (**1**, "Biginelli compounds") are well studied type of heterocycles possessing remarkable pharmacological efficiency (for reviews see [1-3]).

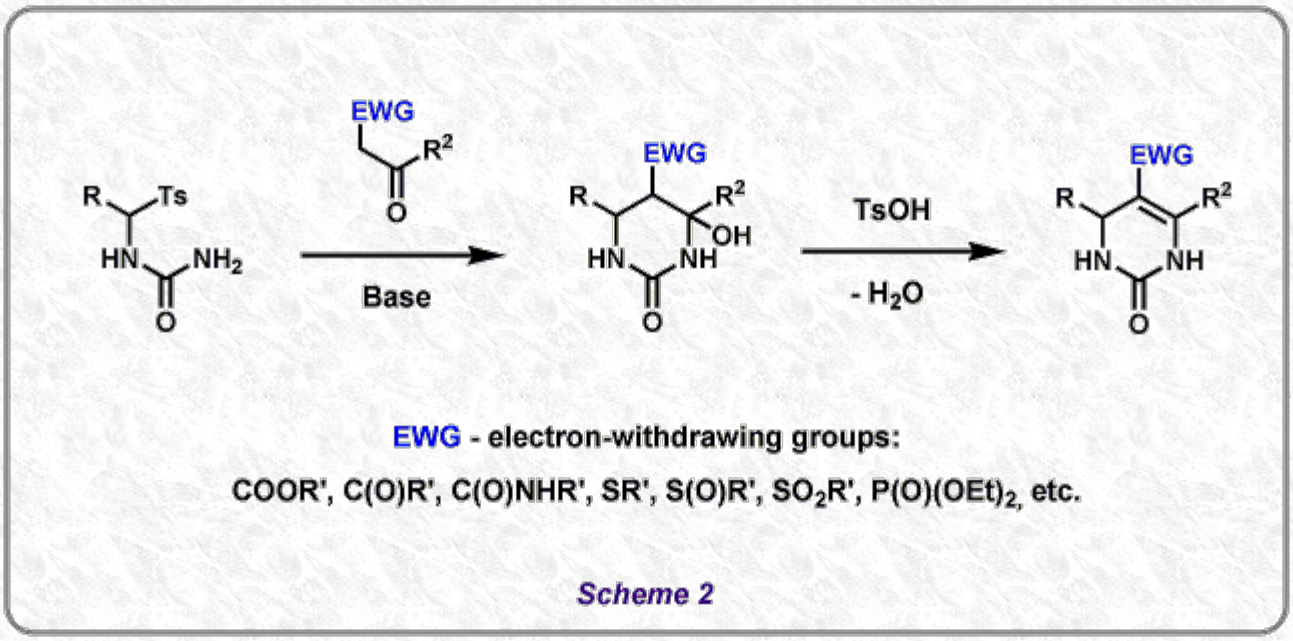


However, hitherto homo-analogues of Biginelli compounds, namely alkyl 2-oxo-2,3,6,7-tetrahydro-1H-1,3-diazepine-5-carboxylates (**2**) remain practically unexplored. It is caused by absence of the general convenient methods of their synthesis. Indeed, diazepines **2** can be prepared by the only method involving reaction of alkyl 4-(chloromethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (**1**, R = CH_2Cl) with nucleophiles (*Scheme 1*) [4-7]. However, this method suffers from the extremely limited diversity of the starting pyrimidines **1**.



Scheme 1

Recently [8-10] we have developed a general approach to the synthesis of a large variety of 5-functionalized 1,2,3,4-tetrahydropyrimidin-2-ones, particularly **1**, based on reaction of a-tosyl-substituted ureas with enolates of a-functionally substituted aldehydes and ketones followed by acid-catalyzed dehydration of the obtained 4-hydroxyhexahydropyrimidin-2-ones (*Scheme 2*).

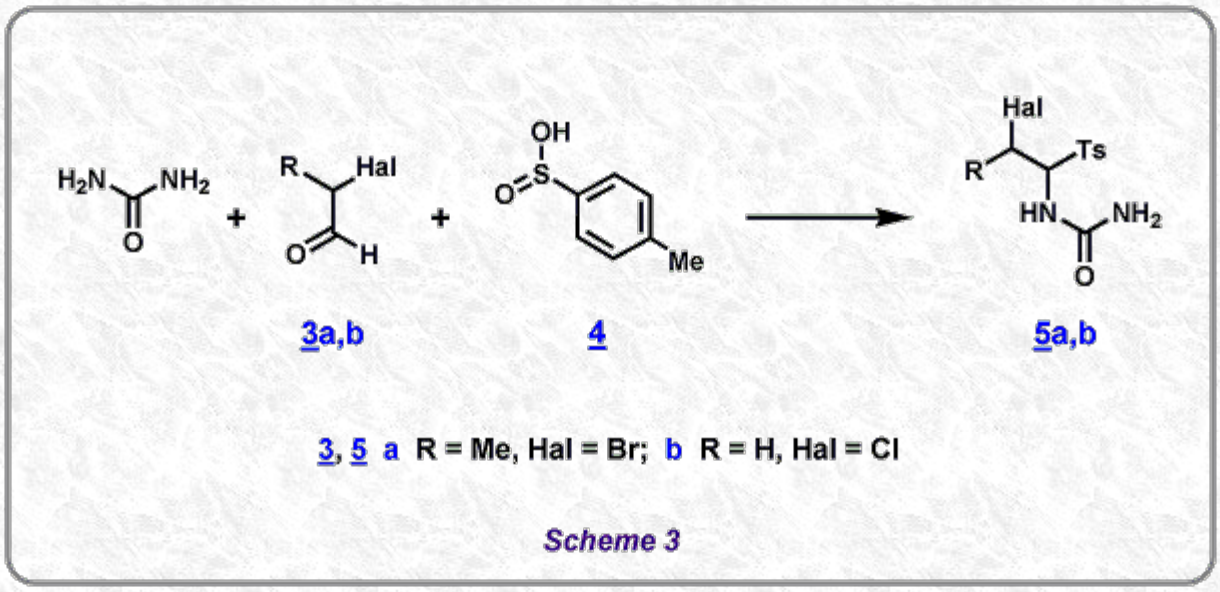


Scheme 2

In continuation of our studies on hydrogenated heterocycles with two heteroatoms at the 1,3 positions we hypothesized that application of b-halogen-a-tosyl-substituted ureas in reaction with enolates of carbonyl compounds could give access to various 4-(1-halogenoalkyl)-1,2,3,4-tetrahydropyrimidin-2-ones. Then the latter could be transformed into a large variety of 2-oxo-2,3,6,7-tetrahydro-1H-1,3-diazepin-2-ones. In this communication we describe preliminary results of our investigation in this direction.

Results and Discussion

N-[(2-Bromo-1-tosyl)prop-1-yl]urea (**5a**) and N-[(2-chloro-1-tosyl)ethyl]urea (**5b**) served as starting materials. They were prepared by reaction of urea with 2-bromopropanal (**3a**) or 2-chloroethanal (**3b**) and *p*-toluenesulfinic acid (**4**) (3:1:1 molar ratio respectively) in water at 20 °C for 3 h in 82-85 % yields (*Scheme 3*).

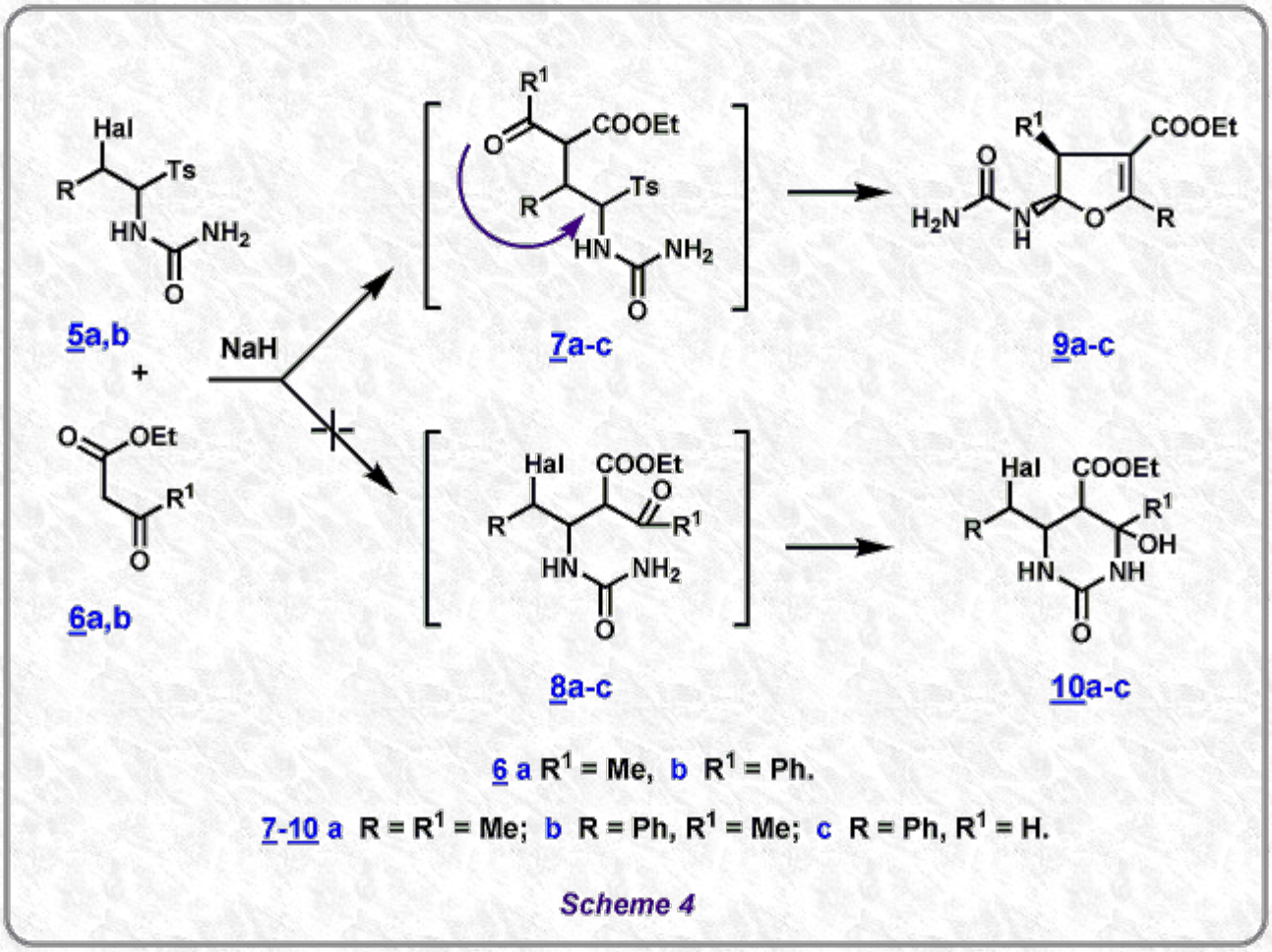


Scheme 3

Compound **5a,b** possessing two electrophilic centers at a- and b-positions to nitrogen can react with

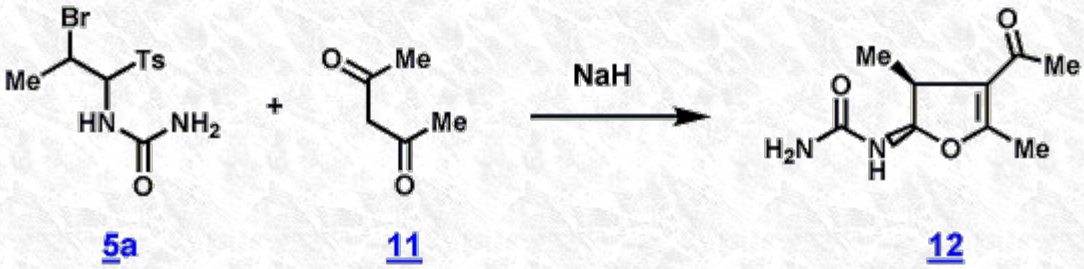
nucleophiles to produce products of halogen or tosyl group substitution. However we believed that substitution of tosyl group is more possible.

Surprisingly we found that the reaction of **5a** with ethyl acetoacetate (**6a**) or ethyl benzoylacetate (**6b**) in the presence of NaH (MeCN, r.t.) gave only products of halogen substitution **7a,b** which spontaneously undergo heterocyclization to produce earlier unknown ethyl 5-ureido-4,5-dihydrofuran-3-carboxylates (**9a,b**) in 68-77 % yields (*Scheme 4*). Similarly, treatment of urea **5b** with ethyl benzoylacetate (NaH, MeCN, r.t.) led to the formation of dihydrofuran **9c** in 44 % yield. It should be noted that compounds **9a,b** were obtained exclusively as single diastereomers as evidenced by their NMR spectra (see below).



Scheme 4

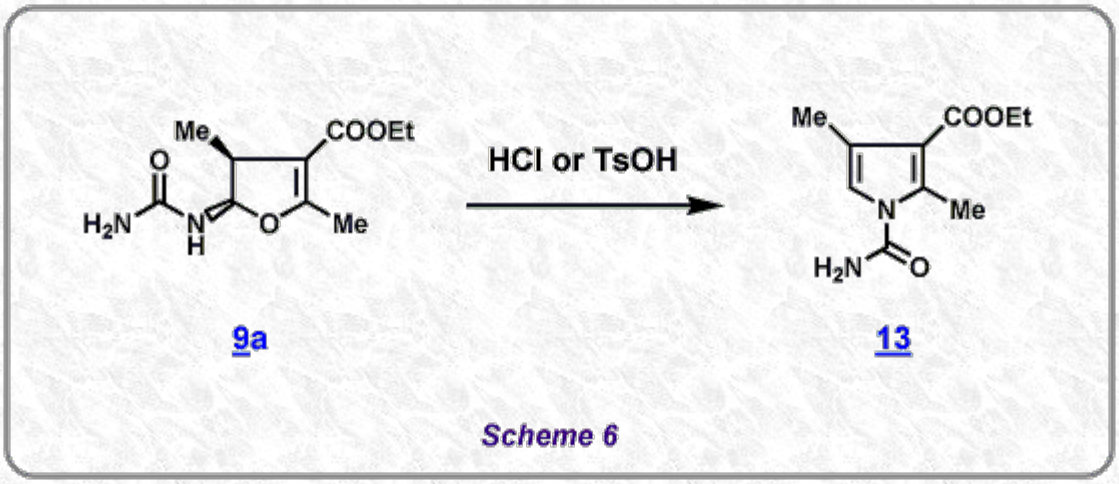
Described above synthesis of 5-ureido-4,5-dihydrofurans is quite general. Indeed, application of acetylacetone **11** instead of **6a,b** in the reaction with **5a** gave 5-acetyl-substituted dihydrofuran **12** (*Scheme 5*).



5a 11 12

Scheme 5

The obtained 3-acyl-substituted 5-ureido-4,5-dihydrofurans can serve as starting compounds for heterocyclic syntheses. Particularly, it was demonstrated by transformation of **9a** into N-carbamoylpyrrole **13** (87-91 % yields) after treatment with acids (HCl or TsOH, EtOH, reflux) (*Scheme 6*).



9a 13

Scheme 6

Structures of dihydrofurans **9a-c** were unambiguously determined by ^{1}H- and ^{13}C-NMR spectroscopy. The following spectra using Bruker DPX-300 (BBO probe) and Bruker AVANCE-600 (BBO probe with Z-grad) spectrometers were registered: ^{1}H; ^{1}H with homodecoupling; ^{13}C{^{1}H, cpd waltz16}; ^{13}C without decoupling; ^{13}C{1H, selective decoupling}; ^{13}C-DEPT (with 45°, 90° and 135° read pulses); ^{1}H,^{1}H-COSY; ^{1}H,^{1}H-NOESY (*Figure 2*); ^{1}H,^{13}C-HSQC; ^{1}H,^{13}C-HMBC (opt. for nJ_{CH}=4 Hz) (*Figure 1*). Particularly, *trans*-configuration of dihydrofurans **9a,b** was established according to ^{1}H,^{1}H-NOESY.

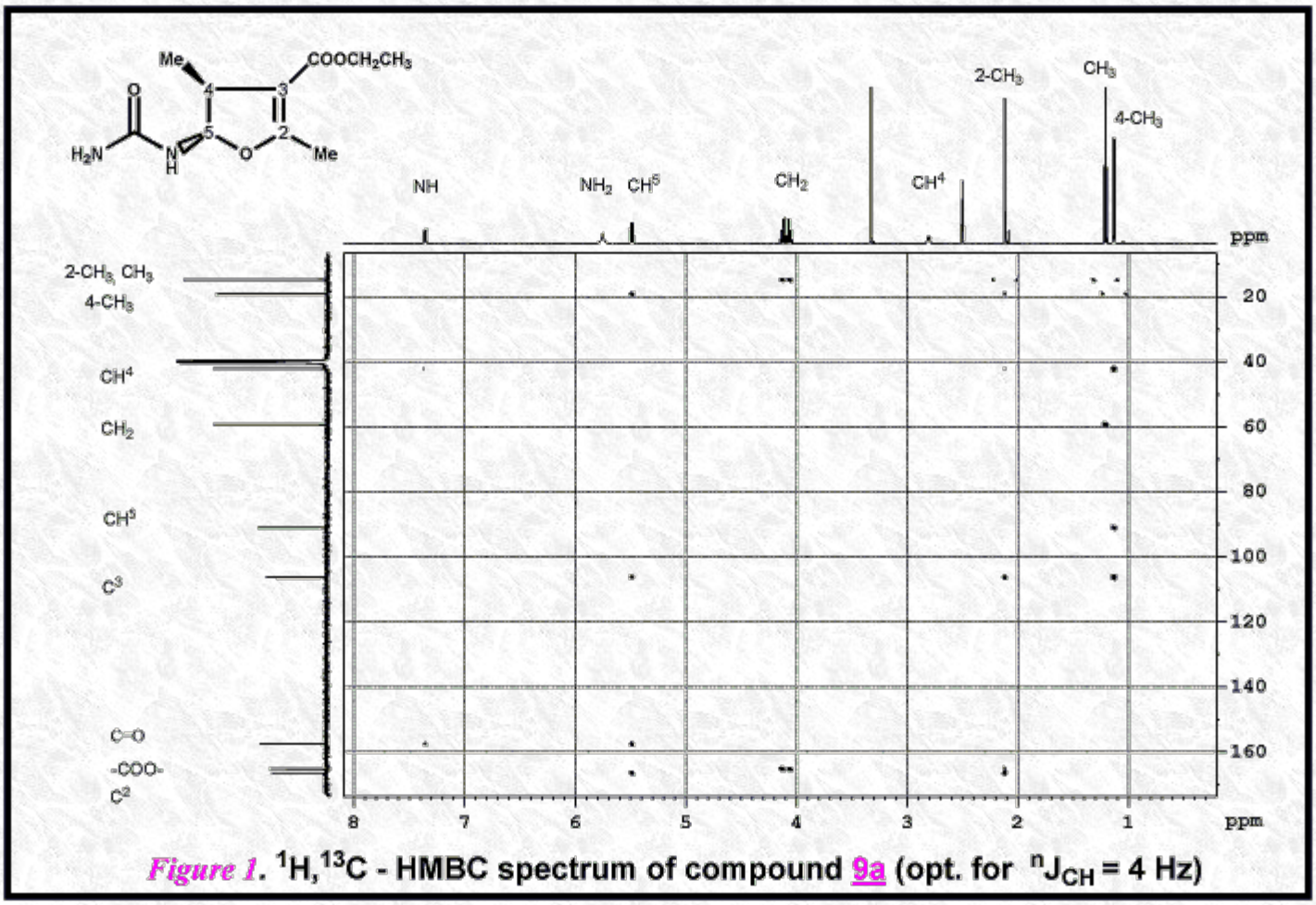


Figure 1. $^{1}H,^{13}C$ - HMBC spectrum of compound 9a (opt. for $^{n}J_{CH}$ = 4 Hz)

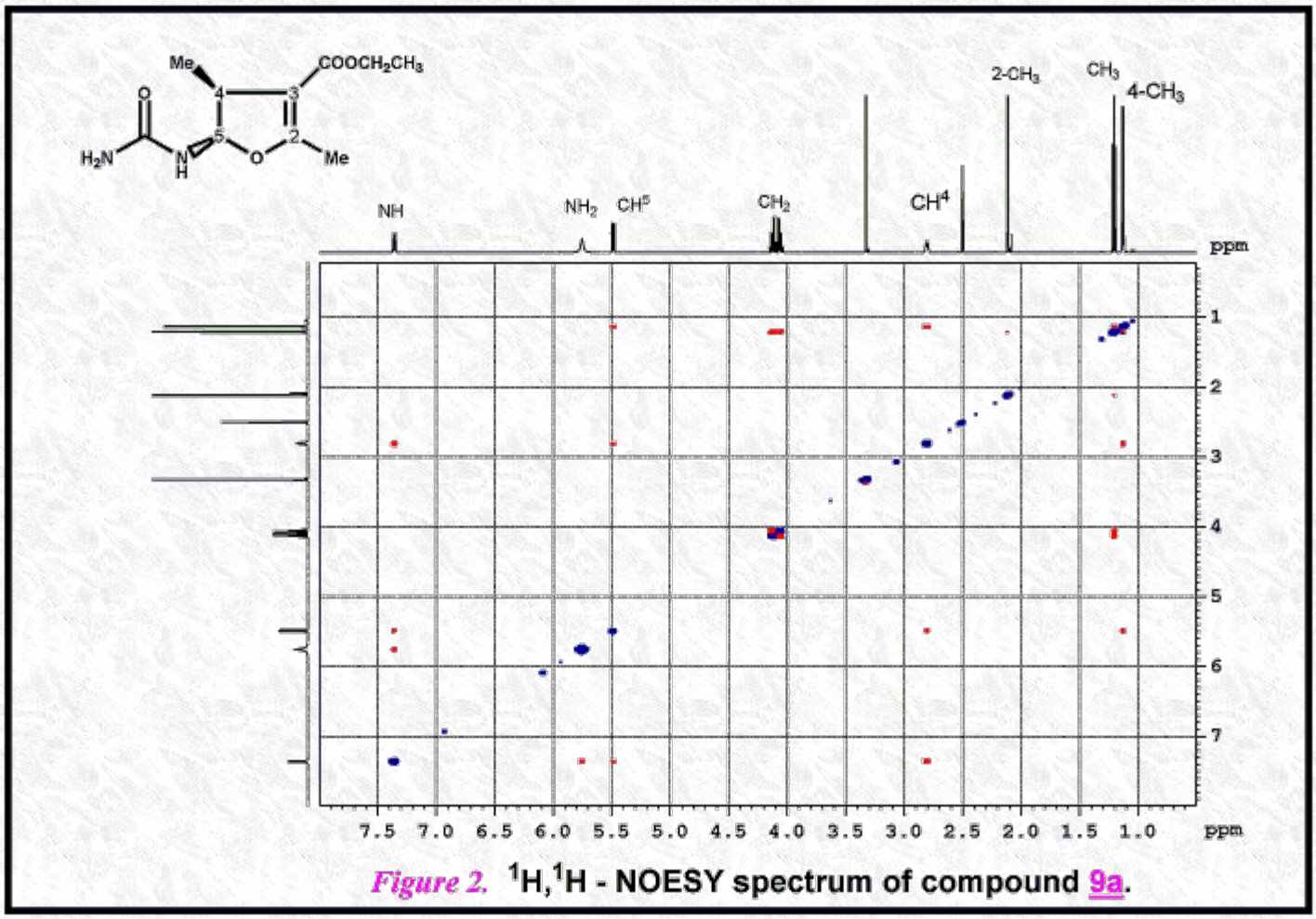


Figure 2. $^{1}H,^{1}H$ - NOESY spectrum of compound 9a.

Conclusion

Thus, reaction of b-halogen-a-tosyl-substituted ureas with enolates of b-oxoesters and 1,3-diketones failed to give expected substituted 5-acyl-6-(halogenomethyl)-4-hydroxyhexahydropyrimidin-2-ones. Earlier unknown 3-acyl-substituted 5-ureido-4,5-dihydrofurans were produced in this reaction. This synthesis can be considered as new general approach to these type of heterocycles.

References

1. Kappe C.O. *Tetrahedro*n, 1993, **49**, 6937.

2. Kappe C.O. *Acc. Chem. Res*., 2000, **33**, 879.

3. Kappe C.O. *Eur. J. Med. Chem*., 2000, **35**, 1043.

4. Ashby, J.; Griffiths, D. *J. Chem. Soc. Perkin I*, 1975, 657.

5. Claremon, D.A.; Rosenthal, S.A. *Synthesis*, 1986, 8 664.

6. Bullock, E.; Carter R.A.; Cochrane R.M.; Gregory B.; Schields D.C. *Can. J. Chem*., 1977, **55**, 895.

7. Baldwin J.J.; McClure D.T.; Claremon, D.A. *US Patent* 4677102 (1987).

8. Shutalev, A.D.; Kuksa, V.A. *Khim. Geterotsicl. Soedin*., 1995, 97 (*Chem. Heterocycl. Compd*., 1995, **31**, 86).

9. Shutalev A.D. *Khim. Geterotsicl. Soedin*., 1997, 1696 (*Chem. Heterocycl. Compd*., 1997, **33**, 1469).

10. Shutalev, A.D.; Kishko, E.A.; Sivova, N.V.; Kuznetsov, A. Yu. *Molecule*s, 1998, 3, 100.