Tetrahedron Letters 52 (2011) 88–91

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Unexpected pathway of the reaction of *N*-[(β-halogeno-α-tosyl)alkyl]ureas with β-oxoester enolates. Synthesis of ethyl 5-ureido-4,5-dihydrofuran-3-carboxylates and *N*-carbamoylpyrrole-3-carboxylates

Nikolay N. Kurochkin [a], Anastasia A. Fesenko [a], Dmitry A. Cheshkov [b], Musa M. Davudi [a], Anatoly D. Shutalev [a,*]

[a] Department of Organic Chemistry, Moscow State Academy of Fine Chemical Technology, 86 Vernadsky Ave., 119571 Moscow, Russian Federation
[b] State Scientific Research Institute of Chemistry and Technology of Organoelement Compounds, 38 Entuziastov shosse, 111123 Moscow, Russian Federation

ARTICLE INFO

Article history:
Received 1 September 2010
Revised 18 October 2010
Accepted 29 October 2010
Available online 4 November 2010

Keywords:
β-Halogeno-α-tosyl-substituted *N*-alkylureas
Nucleophilic substitution
α-Halogeno *N*-acylimines
Dihydrofurans
Pyrroles

ABSTRACT

Reaction of β-halogeno-α-tosyl-substituted *N*-alkylureas with sodium enolates of β-oxoesters proceeds predominantly via nucleophilic substitution of the halogen rather than the tosyl group followed by spontaneous cyclization to give ethyl 5-ureido-4,5-dihydrofuran-3-carboxylates. The latter are transformed into ethyl *N*-carbamoylpyrrole-3-carboxylates under acidic conditions.

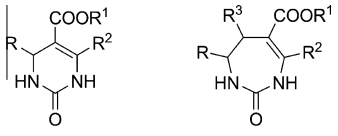
Biginelli compounds (e.g., **1**; Fig. 1) are readily available heterocycles[1] with a wide range of biological activity.[2] In contrast, the biological activity of their seven-membered analogs (e.g., **2**) hitherto remains almost unknown because of their limited availability, and only for some examples of compounds **2** has cardiovascular activity been described.[3]

The reported approach to diazepinones **2** involves reaction of **1** (R = CH_2Cl; R^1 = Me, Et) with nucleophiles.[3,4] However, this procedure suffers from poor availability of the starting materials. Indeed, only three 4-chloromethyl-substituted pyrimidines **1** ($R^1 = R^2$ = Me; R^1 = Et; R^2 = Me; R^1 = Et; R^2 = Ph) have been obtained in low to moderate yields (2–65%).[4b,c]

Recently, we described a general synthesis of 5-functionalized 1,2,3,4-tetrahydropyrimidin-2-ones/thiones **3** based on reaction of α-tosyl-substituted *N*-alkylureas and *N*-alkylthioureas **4** with enolates of α-substituted ketones followed by acid-catalyzed dehydration of the obtained 4-hydroxyhexahydropyrimidin-2-ones/thiones **5** (Scheme 1).[5]

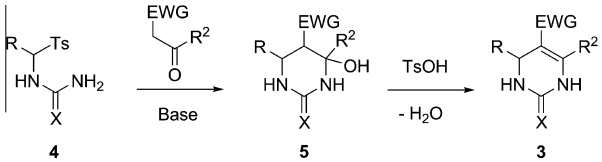
We hypothesized that the use of β-halogeno-α-tosyl-substituted alkyl ureas (**4**, X = O, R = CH(Hal)R′) in this synthesis might give access to various 4-(1-halogenoalkyl)-1,2,3,4-tetrahydropyrimidin-2-ones, which could then be transformed into 2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones. Herein, we describe the preliminary results of our investigation of this synthetic process.

The starting materials, ureas **6a**,**b**, were prepared by the reaction of urea with 2-chloroethanal (**7a**) or 2-bromopropanal (**7b**)



1 2

Figure 1. Structures of Biginelli compounds **1** and seven-membered analogs **2**.



4 5 3

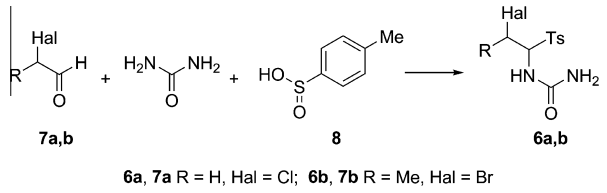
X = O, S

EWG = COOR', C(O)R', C(O)NHR', CN, SR', S(O)R', SO_2R', $P(O)(OEt)_2$, etc.

Scheme 1. General synthesis of 5-functionalized 1,2,3,4-tetrahydropyrimidin-2-ones/thiones **3**.

* Corresponding author. Tel.: +7 495 936 8908; fax: +7 495 936 8909.
E-mail address: shutalev@orc.ru (A.D. Shutalev).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.10.162



Scheme 2. Synthesis of β-halogeno-α-tosyl-substituted alkyl ureas **6a**,**b**.

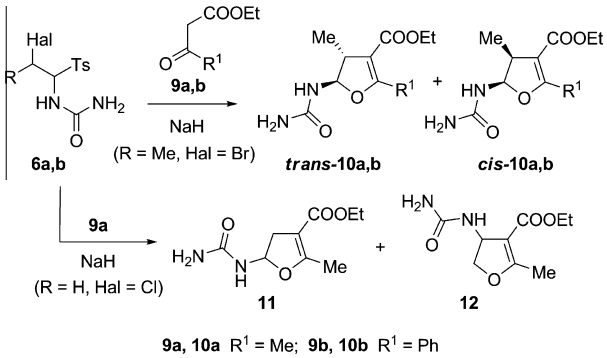
and *p*-toluenesulfinic acid (**8**) (3:1:1 molar ratio) in water at room temperature for 15–16 h in 84–86% yields (Scheme 2).[6] Compound **6b** was obtained as a mixture of two diastereomers in a ratio of 67:33.

Ureas **6a,b** possess electrophilic centers at the α- and β-positions with respect to the nitrogen. Hence, these compounds could react with nucleophiles to give products of halogen or tosyl group substitution. However, based on our experience,[5] we assumed that substitution of the tosyl group, especially in the case of β-chloro-substituted ethyl urea **6a**, would be preferable.

Unexpectedly, we found that treatment of **6a**,**b** with enolates of ethyl acetoacetate (**9a**) or ethyl benzoylacetate (**9b**) in MeCN at room temperature failed to give the products of tosyl group substitution, 6-(1-halogenoalkyl)-4-hydroxyhexahydropyrimidin-2-ones (or their acyclic precursors). Thus, reaction of **6b** with 2 equiv of sodium enolates **9a**,**b** led to the formation of ethyl 5-ureido-4,5-dihydrofuran-3-carboxylates **10a**,**b** in 69–80% yields (Scheme 3).[7] Reaction of **6a** with the sodium enolate of **9a** (2 equiv, MeCN, rt) proceeded in a more complex manner and gave a regioisomeric mixture of 5-ureidodihydrofuran **11** and 4-ureidodihydrofuran **12** in a ratio of 80:20 (71%).[8] Pure **11** was obtained after crystallization of the mixture from MeCN. The yields of dihydrofurans **10** were reduced significantly when 1 equiv of enolate **9a**,**b** was used instead of 2 equiv.

According to ^{1}H NMR data, dihydrofurans **10a**,**b** were formed with high diastereoselectivity. Compound **10a** was obtained as a single isomer with *trans*-configuration as evidenced by a ^{1}H, ^{1}H-NOESY experiments. NOEs were observed between 4-CH_3 and 5-H, and between the N–H and 4-H protons. Compound **10b** was obtained as a mixture of trans- and cis-isomers in a ratio of 85:15. The structural assignment in this case was based on the close values of the vicinal coupling constants $J_{4\text{-H},5\text{-H}}$ for the major isomer of **10b** and *trans*-**10a** (4.2 and 4.6 Hz, respectively). The value of $J_{4\text{-H},5\text{-H}}$ for the minor diastereomer of **10b** was 8.6 Hz.

The structures of dihydrofurans **10**–**12** were confirmed unambiguously by IR, ^{1}H, and ^{13}C NMR data[7–9] including 2D NMR spectral data (^{1}H, ^{1}H-COSY, ^{1}H, ^{13}C-HSQC, ^{1}H, ^{13}C-HMBC) for *trans*-**10a**. The presence of the *N*,*O*-acetal functionality in compounds **10a**,**b** and **11** was proved by the downfield resonances of the 5-H proton

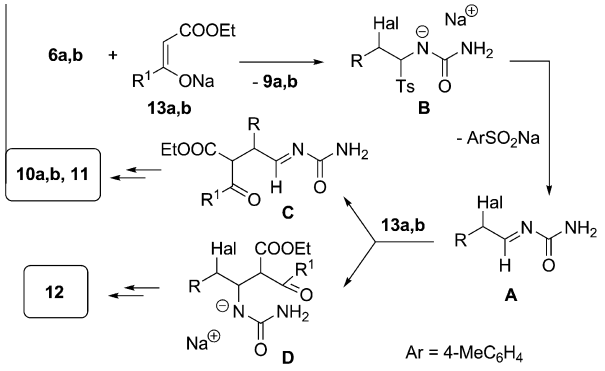


Scheme 3. Reaction of β-halogeno-α-tosyl-substituted alkyl ureas **6a**,**b** with the sodium enolates of β-oxoesters **9a**,**b**.

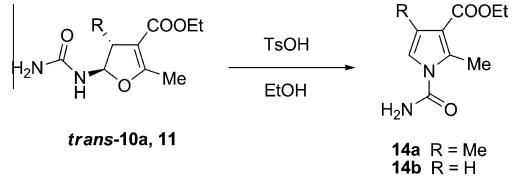
(5.49–6.22 ppm; doublet of doublets of doublets in **10a**,**b** and a doublet of doublets of doublets in **11**) and the C5 carbon (84.32–90.53 ppm) in the ^{1}H and ^{13}C NMR spectra in DMSO-d_6. The location of the urea moiety at C4 in **12** was clearly evident from its ^{1}H and ^{13}C NMR spectra. In particular, the signals for the C5 and C4 carbons in the ^{13}C NMR spectrum of **12** are shifted upfield (78.32 ppm) and downfield (52.16 ppm) compared with those for its regioisomer **11** (84.32 and 34.12 ppm, respectively). A feature of the ^{1}H NMR spectra of *trans*-**10a**, **11**, and **12** were the long-range couplings of 1.1–1.7 Hz between the 2-CH_3 and 4-H proton (for *trans*-**10a** and **12**) and between 2-CH_3 and each of the 4-H protons (for **11**).

Formally, compounds **10**–**11** result from nucleophilic substitution of the halogen in **6a**,**b** with the β-oxoester enolates **13a**,**b** followed by intramolecular nucleophilic substitution of the tosyl group. However, direct substitution of the halogen in **6a**,**b** seems unlikely because the reaction of **6a**,**b** with **13a**,**b** proceeds under mild conditions. One possible explanation for the formation of **10**–**12** is presented in Scheme 4. The principal stage of this pathway involves reaction of **13a**,**b** with α-halogeno acylimines **A** which result from the base-induced elimination of *p*-toluenesulfinic acid from starting ureas **6a**,**b** according to an E1cB mechanism (via **B**).[10,11] Transformation of **6a**,**b** into acylimines **A** leads to a significant increase of the electrophilicity of the β-carbon. α-Halogeno acylimines **A** react further with **13a**,**b** to give predominantly the products of nucleophilic substitution of the halogen, acylimines **C**. The products of nucleophilic addition to the C=N bond of **A**, compounds **D**, partly form only in the case of **6a** containing a relatively poor chlorine leaving group. According to this mechanism 2 equiv of the nucleophile are necessary for the full conversion of **6a**,**b** in agreement with the experimental data.

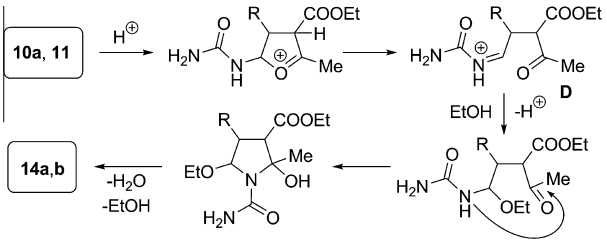
An interesting structural feature of the obtained 5-ureido-4,5-dihydrofurans **10a**,**b** and **11** is their ability to give acyclic isomeric forms **C** (Scheme 4). Indeed, according to ^{1}H NMR spectroscopy, gradual formation of *cis*-**10a** was observed upon prolonged storage of a DMSO-d_6 solution of *trans*-**10a**.[12] The molar ratios of *cis*- to *trans*-**10a** after 3, 31, and 55 days were 2:98, 6:94, and 10:90, respectively. Obviously, the transformation of *trans*-**10a** into *cis*-**10a** proceeds via the respective acyclic form. However, this form



Scheme 4. Plausible pathways for the reactions of **6a**,**b** with the sodium enolates of **9a**,**b**.



Scheme 5. Synthesis of ethyl *N*-carbamoyl-1*H*-pyrrole-3-carboxylates **14a**,**b**.



Scheme 6. Plausible pathway for the transformation of *trans*-**10a** and **11** into **14a**,**b**.

was not detected by ^{1}H NMR spectroscopy, possibly due to its presence in low concentration.

We found that dihydrofurans *trans*-**10a** and **11** on being treated with TsOH in EtOH under reflux readily gave *N*-carbamoylpyrroles **14a**,**b** in 69–87% yields (Scheme 5).[13]

This reaction can also be explained by the intermediate formation of the respective acyclic forms **D** followed by their recyclization into **14a**,**b** (Scheme 6).

In summary, the reaction of the readily available β-halogeno-α-tosyl-substituted *N*-alkylureas with sodium enolates of β-oxoesters proceeds via predominant nucleophilic substitution of the halogen to give previously unknown ethyl 5-ureido-4,5-dihydrofuran-3-carboxylates. This unexpected reaction pathway has been explained in terms of the intermediate formation of α-halogeno acylimines. The obtained dihydrofurans are rare representatives of 3-acyl-substituted 4,5-dihydrofurans possessing a C(5)–N bond.[14] They are of interest as versatile precursors in heterocycle syntheses. This was demonstrated by their transformation into ethyl *N*-carbamoyl-1*H*-pyrrole-3-carboxylates under acidic conditions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.162.

References and notes

1. For reviews, see: (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963; (b) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879–888.
2. For reviews, see: Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052.
3. Baldwin, J. J.; McClure, D. E.; Claremon, D. A. U.S. Patent 4,677,102, 1987; *Chem. Abstr.* **1988**, *109*, 54794.
4. (a) Ashby, J.; Griffiths, D. *J. Chem. Soc., Chem. Commun.* **1974**, 607–608; (b) Ashby, J.; Griffiths, D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 657–662; (c) Bullock, E.; Garter, R. A.; Cochrane, R.; Gregory, B.; Shields, D. C. *Can. J. Chem.* **1977**, *55*, 895–905; (d) Claremon, D. A.; Rosenthal, S. A. *Synthesis* **1986**, 664–665.
5. (a) Shutalev, A. D.; Kuksa, V. A. *Chem. Heterocycl. Compd.* **1997**, *33*, 91–95; (b) Shutalev, A. D. *Chem. Heterocycl. Compd.* **1997**, *33*, 1469–1470; (c) Shutalev, A. D.; Kishko, E. A.; Sivova, N. V.; Kuznetsov, A. Y. *Molecules* **1998**, *3*, 100–106; (d) Fesenko, A. A.; Shutalev, A. D. *Tetrahedron Lett.* **2007**, *48*, 8420–8423; (e) Fesenko, A. A.; Cheshkov, D. A.; Shutalev, A. D. *Mendeleev Commun.* **2008**, *18*, 51–53.
6. *Synthesis of* **6a**: To a stirred solution of chloroethanal (**7a**) (6.094 g, 77.63 mmol) in H_2O (56 mL) was added *p*-toluenesulfinic acid (12.123 g, 77.61 mmol) and the resulting suspension was stirred at rt for 5 min, then urea (13.993 g, 233.00 mmol) and H_2O (50 mL) were added. The obtained suspension was stirred at rt for 15 h 45 min, and the resulting solid was filtered, washed with ice-cold water, light petroleum ether, and dried to give 18.465 g (86%) of **6a**, which was used without further purification. An analytically pure sample was obtained by recrystallization from MeCN. Mp 126–127 °C (decomp., MeCN). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.70–7.75 (2H, m, AA′ part of an AA′XX′ spin system, C(2)H and C(6)H in 4-MeC_6H_4), 7.41–7.47 (2H, m, XX′ part of an AA′XX′ spin system, C(3)H and C(5)H in 4-MeC_6H_4), 7.17 (1H, d, $^3J_{NH,CH}$ = 10.2 Hz, N–H), 5.86 (2H, s, NH_2), 5.26 (1H, ddd, $^3J_{CH,NH}$ = 10.2, $^3J_{CH,CH(B)}$ = 8.5, $^3J_{CH,CH(A)}$ = 3.6 Hz, CH–N), 4.10 (1H, dd, $^2J_{CH(A),CH(B)}$ = 11.8, $^3J_{CH(A),CH}$ = 3.6 Hz, CH(A) in OCH_2), 3.88 (1H, dd, $^2J_{CH(B),CH(A)}$ = 11.8, $^3J_{CH(B),CH}$ = 8.5 Hz, CH(B) in OCH_2), 2.41 (3H, s, CH_3). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 156.49 (C=O), 144.91 (C(4) in 4-MeC_6H_4), 134.12 (C(1) in 4-MeC_6H_4), 129.80 (C(3) and C(5) in 4-MeC_6H_4), 128.94 (C(2) and C(6) in 4-MeC_6H_4), 70.58 (N–CH), 41.16 (CH_2–Cl), 21.19 (CH_3). IR (Nujol) ν, cm^{-1}: 3464 s, 3437 s, 3358 s, 3300 s, 3211 m (ν NH), 3009 w (ν CH_{arom}), 1668 s (amide-I), 1594 m (ν CC_{arom}), 1539 s (amide-II), 1493 w (ν CC_{arom}), 1287 s (ν_{as} SO_2), 1145 s (ν_s SO_2). Anal. Calcd for $C_{10}H_{13}ClN_2O_3S$: C, 43.40; H, 4.74; N, 10.12. Found: C, 43.49; H, 4.88; N, 10.32.
Compound **6b** (13.860 g, 84%) was prepared as a mixture of two diastereomers (67:33) in the same way as **6a** from 2-bromopropanal (6.779 g, 49.49 mmol), *p*-toluenesulfinic acid (7.730 g, 49.49 mmol), and urea (8.917 g, 148.48 mmol) in H_2O (50 mL). Mp 109–109.5 °C (decomp., acetone). ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 7.69–7.75 (2H, m, AA′ part of an AA′XX′ spin system, C(2)H and C(6)H in 4-MeC_6H_4), 7.39–7.45 (2H, m, XX′ part of an AA′XX′ spin system, C(3)H and C(5)H in 4-MeC_6H_4), 6.93 (1H, d, $^3J_{NH,CH}$ = 10.5 Hz, N–H), 6.03 (2H, s, NH_2), 5.26 (1H, dd, $^3J_{CH,NH}$ = 10.5, $^3J_{CH,CH}$ = 2.6 Hz, CH–N), 4.89 (1H, dq, $^3J_{CH,CH3}$ = 6.8, $^3J_{CH,CH}$ = 2.6 Hz, CH–Br), 2.39 (3H, s, CH_3 in Ts), 1.63 (3H, d, $^3J_{CH3,CH}$ = 6.8 Hz, CH_3). ^{1}H NMR of the minor isomer (300.13 MHz, DMSO-d_6) δ: 7.37 (1H, d, $^3J_{NH,CH}$ = 10.9 Hz, N–H), 5.84 (2H, s, NH_2), 5.36 (1H, dd, $^3J_{CH,NH}$ = 10.9, $^3J_{CH,CH}$ = 2.6 Hz, CH–N), 5.00 (1H, dq, $^3J_{CH,CH3}$ = 6.9, $^3J_{CH,CH}$ = 2.6 Hz, CH–Br), 2.40 (3H, s, CH_3 in Ts), 1.79 (3H, d, $^3J_{CH3,CH}$ = 6.9 Hz, CH_3). Signals of aromatic protons overlap with signals of the analogous protons of the major isomer. ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 156.60 (C=O), 144.51 (C(4) in 4-MeC_6H_4), 135.22 (C(1) in 4-MeC_6H_4), 129.60 (C(3) and C(5) in 4-MeC_6H_4), 128.69 (C(2) and C(6) in 4-MeC_6H_4), 72.58 (N–CH), 45.43 (CH–Br), 23.94 (CH_3), 21.11 (CH_3 in Ts). ^{13}C NMR of the minor isomer (75.48 MHz, DMSO-d_6) δ: 156.43 (C=O), 144.84 (C(4) in 4-MeC_6H_4), 134.66 (C(1) in 4-MeC_6H_4), 129.77 (C(3) and C(5) in 4-MeC_6H_4), 128.69 (C(2) and C(6) in 4-MeC_6H_4), 73.90 (N–CH), 44.49 (CH–Br), 21.14 (CH_3 in Ts), 21.02 (CH_3). IR (Nujol) ν, cm^{-1}: 3473 s, 3375 s, 3281 s, 3198 m (ν NH), 3060 w, 3045 w (ν CH_{arom}), 1698 m, 1665 s (amide-I), 1588 m (ν CC_{arom}), 1529 s (amide-II), 1289 s (ν_{as} SO_2), 1156 s (ν_s SO_2). Anal. Calcd for $C_{11}H_{15}BrN_2O_3S$: C, 39.41; H, 4.51; N, 8.36. Found: C, 39.75; H, 4.87; N, 8.41.
7. *Synthesis of trans*-**10a**: To a stirred and cooled (ice bath) suspension of NaH (0.402 g, 16.75 mmol) in anhydrous MeCN (15 mL) was added dropwise a solution of ethyl acetoacetate (2.178 g, 16.74 mmol) in anhydrous MeCN (9 mL). After 10 min, sulfone **6b** (2.550 g, 7.61 mmol) was added and then anhydrous MeCN (3 mL). The obtained suspension was stirred at rt for 5 h 10 min and the solvent was removed under vacuum. To the white solid residue was added a saturated aqueous solution of $NaHCO_3$ (7 mL). The obtained mixture was left at rt for 12 h. After cooling to 0 °C, the precipitate was filtered, washed with ice-cold water, light petroleum ether, and dried to give 1.195 g (69%) of *trans*-**10a**. Mp 176.5–177 °C (MeCN). ^{1}H NMR (600.13 MHz, DMSO-d_6) δ: 7.36 (1H, d, $^3J_{NH,5\text{-}H}$ = 9.8 Hz, N–H), 5.75 (2H, s, NH_2), 5.49 (1H, dd, $^3J_{5\text{-}H,NH}$ = 9.8, $^3J_{5\text{-}H,4\text{-}H}$ = 4.6 Hz, 5-H), 4.12 (1H, dq, $^2J_{CH(A),CH(B)}$ = 10.9, $^3J_{CH(A),CH3}$ = 7.1 Hz, CH(A) in OCH_2), 4.07 (1H, dq, $^2J_{CH(B),CH(A)}$ = 10.9, $^3J_{CH(B),CH3}$ = 7.1 Hz, CH(B) in OCH_2), 2.81 (1H, dqq, $^3J_{4\text{-}H,4\text{-}CH3}$ = 6.8, $^3J_{4\text{-}H,5\text{-}H}$ = 4.6, $^5J_{4\text{-}H,2\text{-}CH3}$ = 1.3 Hz, 4-H), 2.12 (3H, d, $^5J_{2\text{-}CH3,4\text{-}H}$ = 1.3 Hz, 2-CH_3), 1.21 (3H, t, $^3J_{CH3,CH(A)}$ = $^3J_{CH3,CH(B)}$ = 7.1 Hz, CH_3 in COOEt), 1.13 (3H, d, $^3J_{4\text{-}CH3,4\text{-}H}$ = 6.8 Hz, 4-CH_3). ^{13}C NMR (150.91 MHz, DMSO-d_6) δ: 166.01 (C(2)), 164.77 (C=O in COOEt), 157.06 (N–C=O), 105.78 (C(3)), 90.53 (C(5)), 58.81 (OCH_2), 41.59 (C(4)), 18.61 (4-CH_3), 14.29 (CH_3 in COOEt), 14.27 (2-CH_3). IR (Nujol) ν, cm^{-1}: 3437 s, 3355 m, 3305 m, 3208 s, 3067 m (ν NH), 1681 s (ν C=O in COOEt), 1651 s (amide-I), 1619 s (ν C=C), 1546 s (amide-II), 1282 s, 1213 s, 1147 s, 1076 s (ν C–O). Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.71; H, 7.01; N, 12.23.
Compound **10b** (1.313 g, 80%) was prepared as a mixture of trans- and cis-isomers (85:15, respectively) in the same way as *trans*-**10a** from sulfone **6b** (1.891 g, 5.64 mmol), ethyl benzoylacetate (2.382 g, 12.39 mmol), and NaH (0.298 g, 12.42 mmol) in anhydrous MeCN (20 mL) at rt in 7 h. Mp 168.5–169 °C (MeCN). ^{1}H NMR of the *trans*-isomer (600.13 MHz, DMSO-d_6) δ: 7.63–7.66 (2H, m, C(2)H and C(6)H in Ph), 7.54 (1H, d, $^3J_{NH,5\text{-}H}$ = 9.8 Hz, N–H), 7.39–7.48 (3H, m, C(3)H, C(4)H and C(5)H in Ph), 5.79 (2H, s, NH_2), 5.64 (1H, dd, $^3J_{5\text{-}H,NH}$ = 9.8, $^3J_{5\text{-}H,4\text{-}H}$ = 4.2 Hz, 5-H), 4.01–4.10 (2H, m, OCH_2), 3.03 (1H, dq, $^3J_{4\text{-}H,4\text{-}CH3}$ = 6.9, $^3J_{4\text{-}H,5\text{-}H}$ = 4.2 Hz, 4-H), 1.25 (3H, d, $^3J_{4\text{-}CH3,4\text{-}H}$ = 6.9 Hz, 4-CH_3), 1.12 (3H, t, $^3J_{CH3,CH2}$ = 7.1 Hz, CH_3 in COOEt). ^{1}H NMR of the *cis*-isomer (600.13 MHz, DMSO-d_6) δ: 7.59–7.62 (2H, m, C(2)H and C(6)H in Ph), 7.09 (1H, d, $^3J_{NH,5\text{-}H}$ = 11.0 Hz, N–H), 6.25 (1H, dd, $^3J_{5\text{-}H,NH}$ = 11.0, $^3J_{5\text{-}H,4\text{-}H}$ = 8.6 Hz, 5-H), 5.95 (2H, s, NH_2), 3.31 (1H, dq, $^3J_{4\text{-}H,5\text{-}H}$ = 8.6, $^3J_{4\text{-}H,4\text{-}CH3}$ = 7.1 Hz, 4-H), 1.18 (3H, d, $^3J_{4\text{-}CH3,4\text{-}H}$ = 7.1 Hz, 4-CH_3), 1.10 (3H, t, $^3J_{CH3,CH2}$ = 7.1 Hz, CH_3 in COOEt). Signals for C(3)H, C(4)H, C(5)H of Ph and OCH_2 overlap with the signals for the analogous protons of the *trans*-isomer. ^{13}C NMR of the *trans*-isomer (150.91 MHz, DMSO-d_6) δ: 164.02 (C=O in COOEt), 162.56 (C(2)), 157.07 (N–C=O), 130.25 (C(4) in Ph), 130.07 (C(1) in Ph), 129.01 (C(3) and C(5) in Ph), 127.57 (C(2) and C(6) in Ph), 106.50 (C(3)), 89.89 (C(5)), 59.09 (OCH_2), 43.16 (C(4)), 18.60 (4-CH_3), 13.96 (CH_3 in COOEt). IR (Nujol) ν, cm^{-1}: 3455 s, 3343 s, 3277 s, 3217 m, 3082 m (ν NH), 1688 s (ν C=O in COOEt), 1667 s (amide-I), 1616 m (ν C=C), 1595 m (ν CC_{arom}), 1553 s (amide-II), 1490 m (ν CC_{arom}), 1295 s, 1266 s, 1199 s, 1093 s (ν C–O), 770 s, 699 s (δ CH_{arom}). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.83; H, 6.13; N, 9.84.
8. *Synthesis of* **11**: To a stirred and cooled (ice bath) suspension of NaH (0.208 g, 8.67 mmol) in anhydrous MeCN (5 mL) was added dropwise a solution of ethyl acetoacetate (1.137 g, 8.74 mmol) in anhydrous MeCN (6 mL). After 5 min, sulfone **6a** (1.143 g, 4.13 mmol) was added and then anhydrous MeCN (4 mL). The obtained suspension was stirred at rt for 9 h and the solvent was removed under vacuum. To the white solid residue was added a saturated aqueous solution of $NaHCO_3$ (3 mL). The obtained mixture was left at 35 °C for 1 h. Upon cooling to 0 °C, the precipitate was filtered, washed with ice-cold water, light petroleum ether, and dried to give a mixture of dihydrofurans **11** and **12** in a ratio of 80:20 (0.628 g, 71%). Pure **11** was obtained after crystallization of the mixture from MeCN. Mp 177.5–178 °C (decomp., MeCN). ^{1}H NMR (300.13 MHz,

DMSO-d_6) δ: 7.35 (1H, d, $^3J_{NH,5\text{-}H}$ = 9.8 Hz, N–H), 6.00 (1H, ddd, $^3J_{5\text{-}H,NH}$ = 9.8, $^3J_{5\text{-}H,4\text{-}H(A)}$ = 9.5, $^3J_{5\text{-}H,4\text{-}H(B)}$ = 6.0 Hz, 5-H), 5.78 (2H, s, NH_2), 4.08 (2H, q, $^3J_{CH2,CH3}$ = 7.1 Hz, OCH_2), 3.02 (1H, ddq, $^2J_{4\text{-}H(A),4\text{-}H(B)}$ = 15.1, $^3J_{4\text{-}H(A),5\text{-}H}$ = 9.5, $^5J_{4\text{-}H(A),2\text{-}CH3}$ = 1.7 Hz, 4-H(A)), 2.49 (1H, ddq, $^2J_{4\text{-}H(B),4\text{-}H(A)}$ = 15.1, $^3J_{4\text{-}H(B),5\text{-}H}$ = 6.0, $^5J_{4\text{-}H(B),2\text{-}CH3}$ = 1.6 Hz, 4-H(B)), 2.11 (3H, dd, $^5J_{2\text{-}CH3,4\text{-}H(A)}$ = 1.7, $^5J_{2\text{-}CH3,4\text{-}H(B)}$ = 1.6 Hz, 2-CH_3), 1.19 (3H, t, $^3J_{CH3,CH2}$ = 7.1 Hz, CH_3 in COOEt). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 166.25 (C(2)), 164.89 (C=O in COOEt), 157.01 (N–C=O), 99.96 (C(3)), 84.32 (C(5)), 58.93 (OCH_2), 34.12 (C(4)), 14.40 (CH_3 in COOEt), 13.97 (2-CH_3). IR (Nujol) ν, cm^{-1}: 3425 s, 3317 s, 3218 s (ν NH), 1683 s (ν C=O in COOEt), 1657 s (amide-I), 1613 s (ν C=C), 1558 s (amide-II), 1273 s, 1202 s, 1130 s (ν C–O). Anal. Calcd for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.57; H, 6.58; N, 13.21.

9. *Spectral characteristics of* ***12***: ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 6.17 (1H, d, $^3J_{NH,4\text{-}H}$ = 6.3 Hz, NH), 5.42 (2H, s, NH_2), 4.82 (1H, dddq, $^3J_{4\text{-}H,5\text{-}H(A)}$ = 8.0, $^3J_{4\text{-}H,NH}$ = 6.3, $^3J_{4\text{-}H,5\text{-}H(B)}$ = 3.0, $^5J_{4\text{-}H,CH3}$ = 1.1 Hz, 4-H), 4.40 (1H, dd, $^2J_{5\text{-}H(A),5\text{-}H(B)}$ = 10.1, $^3J_{5\text{-}H(A),4\text{-}H}$ = 8.0 Hz, 5-H(A)), 4.12 (1H, dd, $^2J_{5\text{-}H(B),5\text{-}H(A)}$ = 10.1, $^3J_{5\text{-}H(B),4\text{-}H}$ = 3.0 Hz, 5-H(B)), 4.09 (2H, q, $^3J_{CH2,CH3}$ = 7.1 Hz, OCH_2), 2.18 (3H, d, $^5J_{CH3,4\text{-}H}$ = 1.1 Hz, 2-CH_3), 1.20 (3H, t, $^3J_{CH3,CH2}$ = 7.1 Hz, CH_3 in COOEt). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 170.97 (C(2)), 164.47 (C=O in COOEt), 158.09 (N–C=O), 103.47 (C(3)), 78.32 (C(5)), 58.96 (OCH_2), 52.16 (C(4)), 14.23 (CH_3 in COOEt), 13.12 (2-CH_3).
10. It has been reported,[15] that *N*-acylimines form as intermediates in the amidoalkylation reactions of various nucleophiles in basic media with amido alkylating reagents derived from primary amides.
11. For reviews on α-halogenated imino compounds, see: (a) De Kimpe, N.; Schamp, N. *Org. Prep. Proceed Int.* **1979**, *11*, 115–199; (b) De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Org. Prep. Proceed Int.* **1980**, *12*, 49–180.
12. ^{1}H NMR spectrum of *cis*-**10b** (300.13 MHz, DMSO-d_6) δ: 6.93 (1H, d, $^3J_{NH,5\text{-}H}$ = 11.0 Hz, N–H), 6.09 (1H, dd, $^3J_{5\text{-}H,NH}$ = 11.0, $^3J_{5\text{-}H,4\text{-}H}$ = 8.7 Hz, 5-H), 5.94 (2H, s, NH_2), 3.06 (1H, dqq, $^3J_{4\text{-}H,5\text{-}H}$ = 8.7, $^3J_{4\text{-}H,4\text{-}CH3}$ = 7.0, $^5J_{4\text{-}H,2\text{-}CH3}$ = 1.2 Hz, 4-H), 2.09 (3H, d, $^5J_{2\text{-}CH3,4\text{-}H}$ = 1.2 Hz, 2-CH_3), 1.05 (3H, d, $^3J_{4\text{-}CH3,4\text{-}H}$ = 7.0 Hz, 4-CH_3). The signals of the OEt protons overlap with the signals of the analogous protons of the *trans*-isomer. The *cis*-configuration was determined via a ^{1}H, ^{1}H-NOESY experiment. An NOE was observed between the 4-CH_3 and N–H protons, while there was no NOE between the 4-CH_3 and 5-H protons.
13. *Synthesis of* **14a**: A solution of *trans*-**10a** (0.256 g, 1.12 mmol) and TsOH·H_2O (0.067 g, 0.35 mmol) in EtOH (5 mL) was heated at reflux for 33 min with stirring and the solvent was removed under vacuum. To the white solid residue was added a saturated aqueous solution of $NaHCO_3$ (1 mL). Upon cooling to 0 °C, the precipitate was filtered, washed with ice-cold water, light petroleum ether, and dried to give (0.206 g, 87%) of **14a**. Mp 214–215 °C (EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.61 (2H, br s, NH_2), 6.94 (1H, q, $^4J_{5\text{-}H,4\text{-}CH3}$ = 1.2 Hz, 5-H), 4.18 (2H, q, $^3J_{CH2,CH3}$ = 7.1 Hz, OCH_2), 2.62 (3H, s, 2-CH_3), 2.10 (3H, d, $^4J_{4\text{-}CH3,5\text{-}H}$ = 1.2 Hz, 4-CH_3), 1.27 (3H, t, $^3J_{CH3,CH2}$ = 7.1 Hz, CH_3 in OEt). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 164.86 (C=O in COOEt), 152.06 (NH_2–C=O), 137.20 (C(2)), 119.65 (C(4)), 117.81 (C(5)), 114.13 (C(3)), 59.03 (OCH_2), 14.20 (CH_3 in COOEt), 13.27 (2-CH_3), 12.44 (4-CH_3). IR (Nujol) ν, cm^{-1}: 3433 s, 3337 m, 3243 m, 3197 s (ν NH), 1720 s (ν C=O in COOEt), 1672 s (amide-I), 1622 s (amide-II), 1588 m, 1531 m (ν C=C), 1309 s, 1257 s, 1132 c (ν C–O). Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.17; H, 6.61; N, 13.44.
Compound **14b** (0.390 g, 69%) was prepared in the same way as **14a** from **11** (0.618 g, 2.88 mmol) and TsOH·H_2O (0.168 g, 0.88 mmol) in EtOH (31 mL) (reflux, 1 h 20 min). Mp 185–186.5 °C (EtOH). Mp lit.[4b,4c] 186–187 °C (H_2O–EtOH). ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.76 (2H, br s, NH_2), 7.13 (1H, d, $^3J_{5\text{-}H,4\text{-}H}$ = 3.4 Hz, 5-H), 7.13 (1H, d, $^3J_{4\text{-}H,5\text{-}H}$ = 3.4 Hz, 4-H), 4.18 (2H, q, $^3J_{CH2,CH3}$ = 7.1 Hz, OCH_2), 2.66 (3H, s, 2-CH_3), 1.25 (3H, t, $^3J_{CH3,CH2}$ = 7.1 Hz, CH_3 in OEt). ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 164.24 (C=O in COOEt), 152.11 (NH_2–C=O), 136.95 (C(2)), 119.44 (C(5)), 114.38 (C(3)), 109.97 (C(4)), 59.26 (OCH_2), 14.35 (CH_3 in COOEt), 12.97 (2-CH_3). IR (Nujol) ν, cm^{-1}: 3418 s, 3342 m, 3258 m, 3208 s (ν NH), 1741 s (ν C=O in COOEt), 1686 s (amide-I), 1628 s (amide-II), 1574 m, 1519 m (ν C=C), 1309 s, 1205 s (ν C–O). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.10; H, 6.16; N, 14.28. Found: C, 55.21; H, 6.29; N, 14.43.
14. (a) Sopowa, A. S.; Perekalin, V. V.; Bobowitsch, Ya. S. *Zh. Obshch. Khim.* **1961**, *31*, 1528–1531 [*J. Gen. Chem. USSR* (*Engl. Trans.*) **1961**, *31*, 1417–1419]; (b) Sopowa, A. S.; Perekalin, V. V.; Yurchenko, O. I. *Zh. Obshch. Khim* **1964**, *34*, 1188–1189 [*J. Gen. Chem. USSR* (*Engl. Trans.*) **1964**, *34*, 1180–1181]; (c) Gomez-Sanchez, A.; Stiefel, B. M.; Fernandez-Fernandez, R.; Pascual, C.; Bellanato, J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 441–447; (d) Boberg, F.; Garburg, K.-H.; Görlich, K.-J.; Pipereit, E.; Redelfs, E.; Ruhr, M. *J. Heterocycl. Chem.* **1986**, *23*, 1853–1859; (e) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Eur. J. Org. Chem.* **2003**, *14*, 2635–2644; (f) Trukhin, E. V.; Sheremet, E. A.; Masalovich, M. S.; Berestovitskaya, V. M. *Russ. J. Org. Chem.* **2004**, *40*, 1823–1825.
15. (a) Zaugg, H. E. *Synthesis* **1970**, 49–73; (b) Kobayashi, T.; Ishida, N.; Hiraoka, T. *J. Chem. Soc., Chem. Commun.* **1980**, 736–737; (c) Zaugg, H. E. *Synthesis* **1984**, 85–110; (d) Zaugg, H. E. *Synthesis* **1984**, 181–212; (e) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *Tetrahedron* **1992**, *48*, 5163–5178; (f) Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159–186; (g) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 940–947; (h) Mazurkiewicz, R.; Pazdźierniok-Holewa, A.; Orlińska, B.; Stecko, S. *Tetrahedron Lett.* **2009**, *50*, 4606–4609.