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Reaction of *N*-(tosylmethyl)ureas with NaCN: Synthetic and Mechanistic Aspects †

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Abstract: Reaction of NaCN with *N*-(tosylmethyl)ureas, prepared by condensation of urea with aldehydes and *p*-toluenesulfinic acid, has been studied. Generally, this reaction afforded the corresponding α-ureido nitriles. Some mechanistic aspects of cyanide-anion amidoalkylation with *N*-(tosylmethyl)ureas were discussed based on DFT calculations.

Keywords: *N*-(tosylmethyl)ureas; sodium cyanide; α-amidoalkylation; α-ureido nitriles

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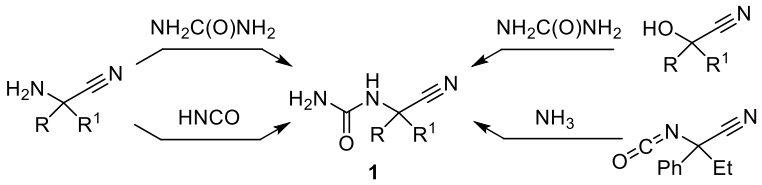
1. Introduction

Nitriles of α-ureidocarboxylic acids are valuable derivatives of α-amino acids. They possess various biological properties, in particular fungicidal [1,2], antitumor [3], antihypertensive [4], and enzyme inhibitory activities [5–9]. These compounds also serve as starting materials for the preparation of hydantoins [10–12], imidazolidin-2-ones [13,14], 2,5-diaminooxazoles [15], 6-carboxydihydrouraciles [16], *N*-(1,2,4-triazol-3-yl)methyl- and *N*-(tetrazol-5-yl)methyl-substituted ureas [17–19], etc.

Nitriles of $N_{(3)}$-substituted α-ureidocarboxylic acids can be readily prepared by reaction of α-aminonitriles with isocyanates [20–22]. In contrast, synthesis of α-ureidonitriles with unsubstituted ureido group (e.g., **1**, Scheme 1) is still a challenge.

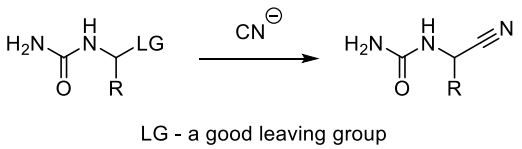


Scheme 1. Described synthesis of α-ureido nitriles with unsubstituted ureido group.

Described syntheses of compounds **1** generally involve formation of different C-N bonds. The most commonly used method is based on the reaction of α-aminonitriles with HNCO generated by the treatment of metal cyanates with acids [10,16,23–28]. Some representatives of these compounds were also prepared by reactions of α-aminonitriles or ketone cyanohydrines with urea [29–31], and 2-isocyanato-2-phenylbutanenitrile with ammonia [11]. However, these methods suffer from various disadvantages such as poor synthetic flexibility, formation of side products, moderate yields of the target products, difficulties in their isolation and purification, etc.

We hypothesized that ureido nitriles could be prepared in a straightforward fashion using C-C bond formation by reaction of appropriate amidoalkylating reagents with a

cyanide source (Scheme 2). To the best of our knowledge, there are no reports on the synthesis of these nitriles according to the proposed method.



Scheme 2. Straightforward approach to ureido nitriles.

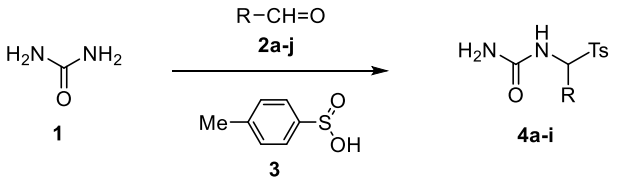
Previously, cyanation of some amidoalkylating reagents based on amides or carbamates has been described using alkali metal cyanides [32–36], $K_4Fe(CN)_6$ [37], ketone cyanohydrins in the presence of a base [38], or TMSCN in the presence of a Lewis acid [39–42] as a cyanide source. It should be noted that additional nucleophilic centers in ureido-based amidoalkylating reagents can affect the outcome of their cyanation. Based on the reported data and our experience [43], we chose NaCN as a cyanide source for our study.

The nature of the leaving group in amidoalkylating reagents plays an important role for successful amidoalkylation of nucleophiles. Previously, we found that the tosyl leaving group is one of choice for the preparation of urea-, thiourea-, and guanidine-based amidoalkylating reagents [44–47]. The reagents with tosyl group are readily available, stable and possess high reactivity.

Herein we report synthesis of *N*-(tosylmethyl)-substituted ureas and their reactions with sodium cyanide to give *α*-ureido nitriles. Some mechanistic aspects of cyanide-anion amidoalkylation with *N*-(tosylmethyl)ureas are suggested based on DFT calculations.

2. Results and Discussion

Starting amidoalkylating reagents, *N*-(tosylmethyl)-substituted ureas were obtained by the method first described by Engberts et al. about 50 years ago [48]. The method involved condensation of amides with aldehydes and *p*-toluenesulfinic acid generated in situ by treatment of its sodium salt with HCOOH. Herein, we applied our convenient modification [44–47] of this method using *p*-toluenesulfinic acid itself. Thus, the three-component condensation of urea (**1**) (5 equiv.) with aromatic **2a-f** or aliphatic aldehydes **2g-i** (1 equiv.) and *p*-toluenesulfinic acid (**3**) (1 equiv.) readily proceeded in water at room temperature to give the corresponding *N*-(tosylmethyl)-substituted ureas **4a-i** in excellent yields (Scheme 3, Table 1).



Scheme 3. Three-component condensation of urea with aldehydes and *p*-toluenesulfinic acid.

In our initial experiments with aliphatic aldehydes **2g-i**, we found that some amount of the corresponding *N*,*N*′-bis(tosylmethyl)-substituted ureas formed along with the target products **4g-i**. For example, use of 3 equivalents of urea in the condensation with butanal (**2g**) or 2-methylpropanal (**2h**) and sulfinic acid **3** afforded mixtures of **4g** or **4h** and the corresponding *N*,*N*′-bis-derivatives in a ratio of 99.5:0.5 and 98.5:1.5, respectively (entries 12 and 15). The amount of these *N*,*N*′-bis-derivatives increased to 17–20 mol% with prolonged reaction times (6.25–7.33 h) (entry 12 vs. entry 11, entry 15 vs. entry 14). Formation of *N*,*N*′-bis-derivatives was completely suppressed when 5 fold excess of urea was used. Under optimized conditions (Table 1, entries 1, 3–5, 10, 13, 16, and 17) with 5 equiv-

alents of urea, the condensation with aliphatic aldehydes completed for 2 h and with aromatic ones for 20 h. The amount of *N,N′*-bis(tosylmethyl)-substituted ureas in the obtained products was less than 1 mol%.

Table 1. Synthesis of *N*-(tosylmethyl)-substituted ureas **4a-i** [a].

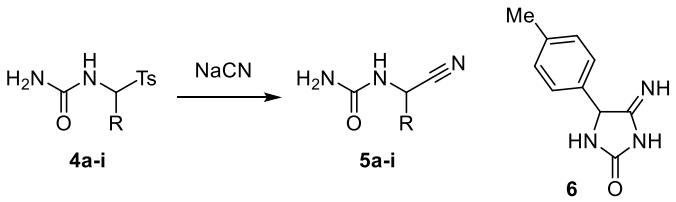
Entry	Aldehyde (R)	1:2:3 Molar Ratio	Solvent	Time (h)	Product	Yield (%) [b]
1	**2a** (Ph)	5:1:1	H_2O	20	**4a**	94
2	**2a** (Ph)	5:1:1	25% aq EtOH	20	**4a**	94
3	**2b** (4-MeC_6H_4)	5:1:1	H_2O	20	**4b**	97
4	**2c** (4-EtC_6H_4)	5:1:1	H_2O	20	**4c**	98
5	**2d** (4-$MeOC_6H_4$)	5:1:1	H_2O	20	**4d**	97
6	**2d** (4-$MeOC_6H_4$)	5:1:1	25% aq EtOH	24	**4d**	96
7	**2e** (3,4-$(MeO)_2C_6H_3$)	5:1:1	H_2O	24	**4e**	97
8	**2e** (3,4-$(MeO)_2C_6H_3$)	5:1:1	25% aq EtOH	24	**4e**	98
9	**2e** (3,4-$(MeO)_2C_6H_3$)	5:1:1	21% aq HCOOH	24	**4e**	99
10	**2f** (fur-2-yl)	5:1:1	H_2O	20	**4f**	96
11	**2g** (Pr)	3:1:1	H_2O	6.25	**4g** [c]	89
12	**2g** (Pr)	3:1:1	H_2O	2	**4g** [d]	94
13	**2g** (Pr)	5:1:1	H_2O	2	**4g**	96
14	**2h** (*i*-Pr)	3:1:1	H_2O	7.33	**4h** [e]	80
15	**2h** (*i*-Pr)	3:1:1	H_2O	2.4	**4h** [f]	88
16	**2h** (*i*-Pr)	5:1:1	H_2O	2	**4h**	90
17	**2i** (Bu)	5:1:1	H_2O	2	**4i**	91

[a] At room temperature. [b] Isolated yield. [c] Product contains 17 mol% of *N,N′*-di(1-tosylbut-1-yl)urea. [d] Product contains 0.5 mol% of *N,N′*-di(1-tosylbut-1-yl)urea. [e] Product contains 20 mol% of *N,N′*-di(2-methyl-1-tosylprop-1-yl)urea. [f] Product contains 1.5 mol% of *N,N′*-di(2-methyl-1-tosylprop-1-yl)urea.

Sulfones **4a-i** precipitated from the reaction mixtures and, after completion the reactions, were isolated by filtration. According to ^{1}H NMR spectroscopic data, the purity of crude products was excellent (>96%), therefore, they were used in the next step without additional purification. Generally, crystallization of sulfones **4a-i**, especially alkyl-substituted ones **4g-i**, from boiling solvents (or mixtures thereof) led to their partial decomposition. These compounds are rather unstable in solutions even at room temperature. For example, the ^{1}H NMR spectrum of sulfone **4b** in DMSO-d_6 (5 min after dissolution) showed its 98% purity. After keeping this solution at room temperature for 70 h, a significant (about 50%) decomposition of **4b** was observed, and among various products formed, 4-methylbenzaldehyde, *p*-toluenesulfinic acid and urea (each about 25 mol%) were identified. Similarly, sulfone **4a** decomposed in DMSO-d_6 solution at room temperature (about 40% after 73.5 h).

It is noteworthy that after addition of sulfinic acid **3** to a solution of an aliphatic aldehyde or an emulsion of aromatic aldehyde in water in all cases (with the exception of **2f**) a coarse suspension formed. The precipitated solid was triturated to obtain a fine suspension followed by the addition of urea, otherwise the purity of isolated sulfone decreased. For large-scale sulfone preparation, the trituration may become laborious. Therefore, with aldehydes **2a,d,e** the procedure was modified by the addition of EtOH (entries 2, 6, and 8) or HCOOH (entry 9) as a co-solvent. In these cases, the corresponding product **4** precipitated from the solution formed after adding all the reagents as a fine solid. Use of co-solvents had a very slight effect on the yield of sulfones **4a,d,e**.

We found that *N*-(tosylmethyl)-substituted ureas **4** smoothly react with sodium cyanide in aprotic solvents to give the expected products of the tosyl group substitution, α-ureido nitriles **5** (Scheme 4).



Scheme 4. Synthesis of *α*-ureido nitriles **5a-i** by the reaction of *N*-(tosylmethyl)ureas **4a-i** with sodium cyanide.

Initially, we studied the reaction of sulfone **4b** with NaCN in DMF with varying reagents ratio, temperature, and reaction time. We found that **4b** reacted with NaCN (1.25 equiv.) at room temperature for 3 h to give cyanide **5b** along with 7 mol% of a side product (Table 2, entry 4). The amount of the latter decreases with decreasing reaction time (entry 4 vs. entry 5), excess of NaCN (entry 6 vs. entry 7), and temperature (entry 5 vs. entry 6). Under the optimized conditions, the reaction of **4b** with 1.1 equivalents of NaCN (DMF, 0 °C, 1 h) followed by precipitation of the product with water afforded cyanide **5b** in 97% yield and >99% purity (entry 7).

Table 2. Reaction *N*-(tosylmethyl)ureas **4a-i** with sodium cyanide.

Entry	4	R	Equiv. of NaCN	Reaction Conditions	Product	Yield (%) [a]
1	**4a**	Ph	1.10	DMF, 0 °C, 1 h	**5a**	83
2	**4a**	Ph	2.00	MeCN, rt, 73 h	**5a**	81
3 [b]	**4a**	Ph	1.51	MeCN, rt, 9.75 h	**5a**	73
4	**4b**	4-MeC_6H_4	1.25	DMF, rt, 3 h	**5b** [c]	85
5	**4b**	4-MeC_6H_4	1.22	DMF, rt, 1 h	**5b** [d]	91
6	**4b**	4-MeC_6H_4	1.21	DMF, 0 °C, 1 h	**5b** [e]	92
7	**4b**	4-MeC_6H_4	1.10	DMF, 0 °C, 1 h	**5b**	97
8	**4b**	4-MeC_6H_4	2.00	MeCN, rt, 113 h	**5b**	97
9	**4c**	4-EtC_6H_4	1.11	DMF, 0 °C, 1 h	**5c**	100
10	**4d**	4-$MeOC_6H_4$	1.11	DMF, 0 °C, 1 h	**5d**	96
11	**4e**	3,4-$(MeO)_2C_6H_3$	1.11	DMF, 0 °C, 1 h	**5e**	95
12	**4f**	fur-2-yl	1.10	DMF, 0 °C, 1 h	**5f**	75
13	**4f**	fur-2-yl	1.12	DMSO, rt, 1 h	**5f**	69
14	**4g**	Pr	1.10	DMF, 0 °C, 1 h	**5g**	69
15 [b]	**4g**	Pr	1.52	MeCN, rt, 8.67 h	**5g**	0 [f]
16	**4h**	*i*-Pr	1.12	DMF, 0 °C, 1 h	**5h**	0 [g]
17	**4i**	Bu	1.10	DMF, 0 °C, 1 h	**5i**	71

[a] Isolated yield. [b] In the presence of 18-crown-6 (0.2 equiv.). [c] Along with 7 mol% of **6**. [d] Along with 3 mol% of **6**. [e] Along with 2 mol% of **6**. [f] An unidentified compound along with some unidentified impurities were isolated. [g] Isobutylidene diurea in 10% yield was isolated.

Based on the experimental data (Table 2), we assume that the side product resulted from conversion of the initially formed cyanide **5b**. Indeed, after keeping of a solution of the crude product containing 7 mol% of the byproduct (entry 4) in DMSO-d_6 at room temperature for 6 days, the amount of the latter increased to 10 mol% (^{1}H NMR data).

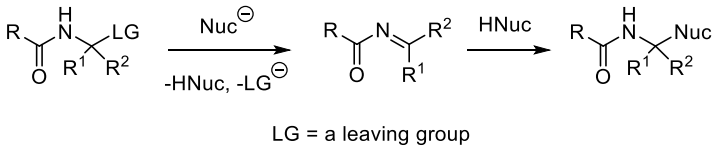
According to ^{1}H NMR spectroscopic data, the structure of the side product was assigned as 4-iminohydantoin **6**. Thus, the ^{1}H NMR spectrum of compound **6** in DMSO-d_6 showed two broad singlet signals at 10.44 and 8.07 ppm corresponding to protons of two NH groups, a multiplet in the range of 7.85–7.90 ppm due to two aromatic protons, and a singlet at 2.37 ppm corresponding to three protons of the methyl group. It is noteworthy that the chemical shifts of NH protons significantly differ ($\Delta\delta$ = 2.37 ppm), which proves very different environments of these protons.

Analogously, under the optimized conditions (DMF, 0 °C, 1 h), sulfones **4a,c-g,i** reacted with NaCN (1.10–1.11 equiv.) to afford the corresponding α-ureido nitriles **5a,c-g,i** in 69–100% yields (entries 1, 9–12, 14, and 17). Decrease in yields of **5f,g,i** are explained by losses during isolation due to their higher solubility in water.

In contrast to **4a-g,i**, the reaction of **4h** with NaCN (1.12 equiv.) in DMF failed to give ureido nitrile **5h**. The only isolated product (yield 10%) after dilution of the reaction mixture with water was isobutylidene diurea (entry 16) [49], whose formation can be explained by relatively low rate of the tosyl group substitution in **4h** caused by steric hindrance of the isopropyl group.

We also studied the effect of solvent on the reaction of sulfones **4** with NaCN. Compound **4f** smoothly reacted with NaCN in DMSO at room temperature to give cyanide **5f** (entry 13). Reaction of **4a,b** with NaCN (2 equiv.) slowly proceeded in MeCN at room temperature (several days), however, the corresponding cyanides **5a,b** were isolated in good yields (entries 2 and 8). The rate of reaction between **4a** and NaCN in MeCN significantly increased in the presence of 18-crown-6 (0.2 equiv.) to give **5a** in 73% yield (entry 3). Interestingly, under similar conditions (MeCN, 18-crown-6), reaction of alkyl substituted sulfone **4g** with NaCN failed to provide cyanide **5g** (entry 15). The isolated product was very poorly soluble in common solvents including DMSO. According to ^{1}H and ^{13}C NMR spectroscopic data, this product mainly contained a heterocyclic compound resulting from the initially formed cyanide **5g**. Unfortunately, we were not able to establish the structure of this compound unambiguously, since its purification failed.

Despite numerous reports on α-amidoalkylation, detailed mechanism of this reaction has not been described [50–59]. It was postulated that amidoalkylating reagents with a good leaving group and derived from primary amides react with sufficiently basic nucleophiles via an elimination-addition mechanism (Scheme 5).



Scheme 5. Postulated mechanism of α-amidoalkylation under basic conditions.

According to this mechanism, the first step of the reaction is transformation of amidoalkylating reagents into acylimines under the action of basic nucleophiles. Next, the acylimines rapidly react with nucleophiles to give the final products. It is noteworthy that in some cases, during the treatment of amidoalkylating reagents with weakly nucleophilic bases (DBU, Cs_2CO_3, etc.), the resulting acylimines were isolated and demonstrated high reactivity towards nucleophiles [60–63].

We performed a computational study of the reaction of sulfones **4a** and **4j** (R = Me in Scheme 3) with cyanide-anion in DMF solution at the DFT B3LYP/6-311++G(d,p) level of theory using the PCM solvation model. Special attention was put on calculations of thermodynamic and activation parameters for the transformation of **4a,j** into the corresponding acylimines.

First, we calculated cartesian coordinates and energies of the optimized geometries for the most stable conformers of compounds **4a,j** (Figure 1, Table 3) considering that, according to ^{1}H NMR spectroscopic data, sulfones **4a-i** in DMSO-d_6 solution exist in a conformation with anti-orientation of the vicinal NH and CH protons (^{3}J = 10.2–10.8 Hz).

Table 3 shows that rotamer **A** is the most stable for both **4a** and **4j**, however, the differences in energy between the rotamers are relatively small (ΔE ≤ 0.90 kcal/mol). The calculations also demonstrate that the energy barriers separating the conformational isomers are very low and do not exceed 3 kcal/mol. It is noteworthy that for all three rotamers of **4a,j**, the C-S bond is significantly longer (1.889–1.926 Å) than that of alkyl sulfones (1.78 Å) [64,65].

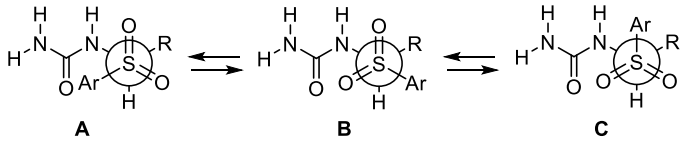


Figure 1. Newman projections of the most stable conformers of compounds **4a** and **4j** along the C-S bond.

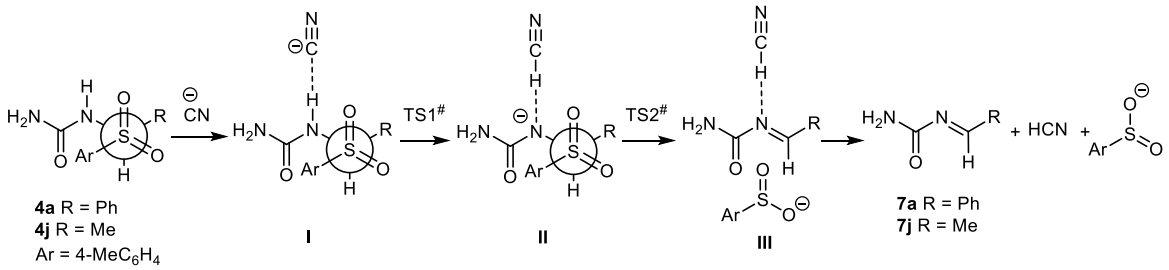
Table 3. Relative electronic energy (ΔE), Gibbs free energy (ΔG), C-S and C-N bond lengths in N-C-S fragment for three rotamers of compounds **4a** and **4j** in DMF solution [a].

Parameter	4a			4j		
	A	**B**	**C**	**A**	**B**	**C**
ΔE, kcal/mol	0.00	0.49	0.90	0.00	0.51	0.70
ΔG, kcal/mol	0.00	0.81	0.36	0.00	0.42	1.35
C-S, Å	1.907	1.915	1.926	1.889	1.903	1.896
C-N, Å	1.425	1.425	1.420	1.424	1.422	1.423

[a] The DFT B3LYP/6-311++G(d,p) calculations were used (298 K, 1 atm).

In contrast to compounds **4a** and **4j**, products of their NH deprotonation, the corresponding conjugated bases, were found to be unstable. According to the DFT calculations, the conjugated bases derived from rotamers **A**, **B**, **C** of **4a** and rotamer **B** of **4j** cannot exist in DMF solution and spontaneously transform into (*E*)-acylimines **7a,j** via the C-S bond cleavage. Although the conjugated bases derived from rotamers **A** and **C** of **4j** lie at energy minima, the energy barriers of their transformation into (*E*)-acylimine **7j** in DMF solution are extremely low ($\Delta E^{\#}$ = 0.10 kcal/mol and $\Delta G^{\#}$ = 0.10 kcal/mol for **A**; $\Delta E^{\#}$ = 0.02 kcal/mol and $\Delta G^{\#}$ = −0.02 kcal/mol for **C**).

Next, we evaluated the role of cyanide-anion in the conversion of conformer **A** of compounds **4a,j** into the corresponding acylimines **7a,j** in DMF solution (Scheme 6).



Scheme 6. Plausible pathway for the transformation of **4a,j** (conformer **A**) into acylimines **7a,j** under the action of cyanide-anion.

The calculations were started from the pre-reaction complexes **I** resulting from attack of cyanide-anion on proton of the NH group in **4a,j**. We found that electronic energy barriers of the proton abstraction (via transition state TS1#) to give complexes of the conjugated bases of **4a,j** with HCN (complexes **II**) are relatively low ($\Delta E^{\#}$ = 12.05 and 12.66 kcal/mol, respectively) (Figures 2 and 3). The next step involves cleavage of the C-S bond in **II** (via transition state TS2#) to afford the post-reaction complexes of acylimines **7a,j** with HCN and *p*-toluenesulfinate anion (complexes **III**). The electronic energy barriers of this step are very low ($\Delta E^{\#}$ = 0.14 and 0.98 kcal/mol, respectively). The IRC analysis demonstrated that the found transition states (TS1# and TS2#) connect the desired minima. Thus, the calculated electronic energy profiles for conversion of **4a,j** into **7a,j** under the action of CN-anion in DMF solution correspond to an E1cB mechanism.

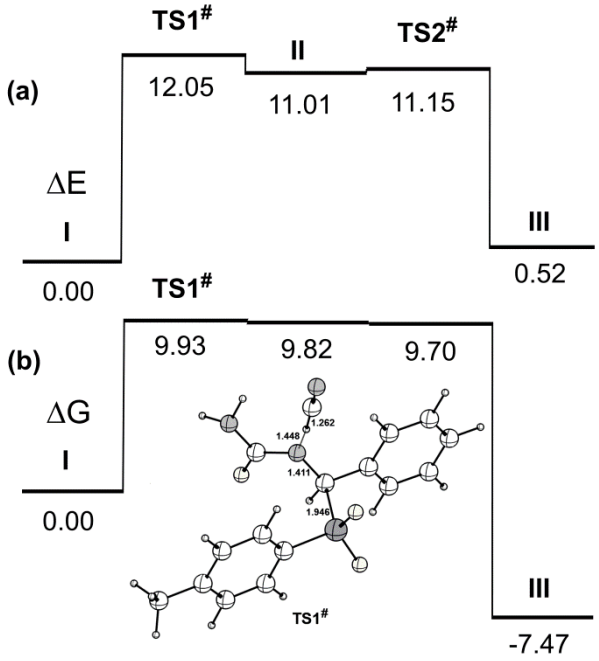


Figure 2. Calculated electronic (**a**) and Gibbs free energy (**b**) profiles for the transformation of **4a** (conformer **A**) into acylimine **7a** under the action of cyanide-anion in DMF solution (1 atm, 298 K). The relative energies are given in kcal/mol. A view of the transition state TS1# with selected bond lengths is presented.

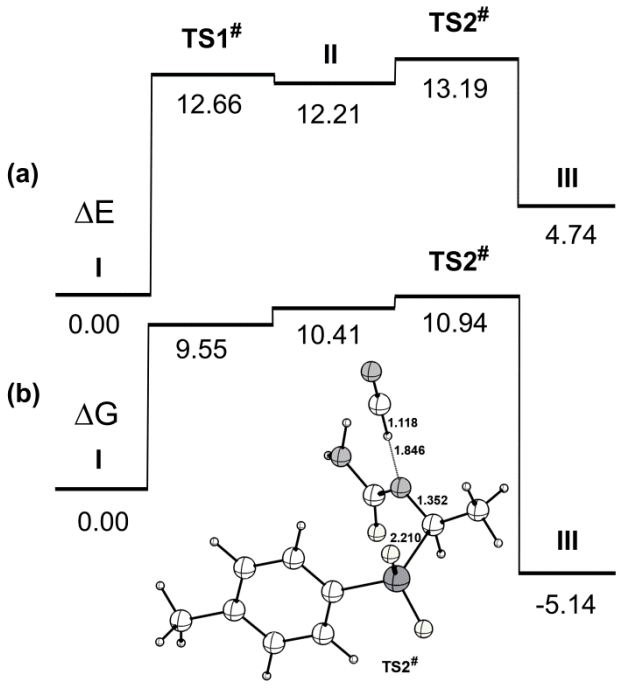


Figure 3. Calculated electronic (**a**) and Gibbs free energy (**b**) profiles for the transformation of **4j** (conformer **A**) into acylimine **7j** under the action of cyanide-anion in DMF solution (1 atm, 298 K). The relative energies are given in kcal/mol. A view of the transition state TS2# with selected bond lengths is presented.

It should be noted that, taking into account zero-point vibrational energies (ZPVE) and thermochemical corrections, the described reaction in DMF has only one transition state (TS1# for **4a** → **7a** and TS2# for **4j** → **7j**) with the Gibbs free energy barrier of 9.93 and 10.94 kcal/mol, respectively. These data prove that intrinsic mechanism of the reaction is

synchronous E2-like pathway but not E1cB. In contrast to classical E2 elimination, the tosyl group and NH hydrogen are in a gauche orientation (the H-N-C-S dihedral angles for conformer **A** of **4a,j** are 71.6 and 77.5°, respectively). The transition states of **4a** → **7a** and **4j** → **7j** transformations are significantly different. In the first case, it is close to the starting complex **I**, and in the second case, it is close to the final complex **III**. The transformation of **4a,j** into **7a,j** under the action of CN-anion is a thermodynamically favorable process with $\Delta G = -7.47$ kcal/mol and $\Delta G = -5.14$ kcal/mol in DMF, respectively (298 K, 1 atm).

We also performed the DFT calculations of the reaction between compound **4j** and CN-anion in DMF via a S_N1 partway involving initial heterolytic cleavage of the C-S bond. However, high activation barrier (>22 kcal/mol) of the heterolysis makes this mechanism unfavorable.

Obviously, the final step of the reaction between **4a,j** and CN-anion involves nucleophilic addition of the nucleophile to acylimines **7a,j** followed by protonation of the resulting conjugated bases of the target products with HCN.

3. Conclusions

In summary, we have shown that the reaction of *N*-(tosylmethyl)-substituted ureas, prepared by condensation of urea with aromatic or aliphatic aldehydes and *p*-toluenesulfinic acid, with sodium cyanide depends on the reaction conditions. Under optimized conditions (DMF, 0 °C, 1 h), *N*-(tosylmethyl)ureas smoothly reacted with NaCN (1.10–1.10 equiv.) to give α-ureido nitriles. According to DFT computational data, the first step of cyanide-anion amidoalkylation with *N*-(tosylmethyl)ureas involves the formation of the corresponding *N*-acylimines under the action of CN-anion via E2-like partway.

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