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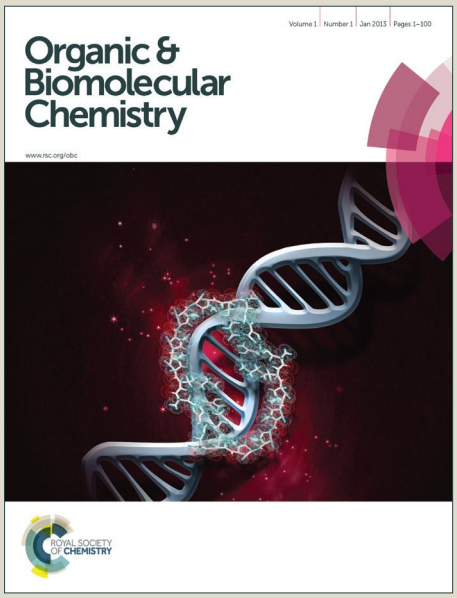

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New enolate-carbodiimide rearrangement in concise synthesis of 6-amino-2,3-dihydro-4-pyridinones from homoallylamines

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Key words: 2,3-dihydro-4-pyridinones, adamantane, homoallylamines, rearrangement, nitrogen heterocycles.

Three-step synthesis of 6-amino-2,3-dihydro-4-pyridinones from homoallylamines involving NBS (or I_2, PhSeCl)-mediated cyclization of *N*-(3-butenyl)ureas to 6-(bromomethyl)-2-iminourethanes, dehydrohalogenation and the novel enolate-carbodiimide rearrangement as a key step has been developed. The scope and limitations of the method as well as the mechanism of the rearrangement supported by kinetic study and isolation of *N*-(1-adamantyl)carbodiimide are discussed. The final products – imino-analogues of well known piperidine-2,4-diones are promising building blocks in synthesis of bio-/pharmacological compounds.

Among heterocycles, composing a variety of natural products and important pharmaceuticals, piperidines occupy one of the privileged places.[1] The various types of biological activity of this particular class of nitrogen heterocycles have stimulated the search for novel syntheses of known molecules as well as the design of new piperidine derivatives. Subset of piperidine - 6-amino-2,3-dihydro-4-pyridinones (ADP) does not only reveal the parent biological activity, but are also valuable building blocks, having multiple sites at the piperidine ring available for functionalization. Several biologically active aminopyridine derivatives are shown in Fig. 1.

† NMR experiments; ‡X-Ray single crystal analysis.

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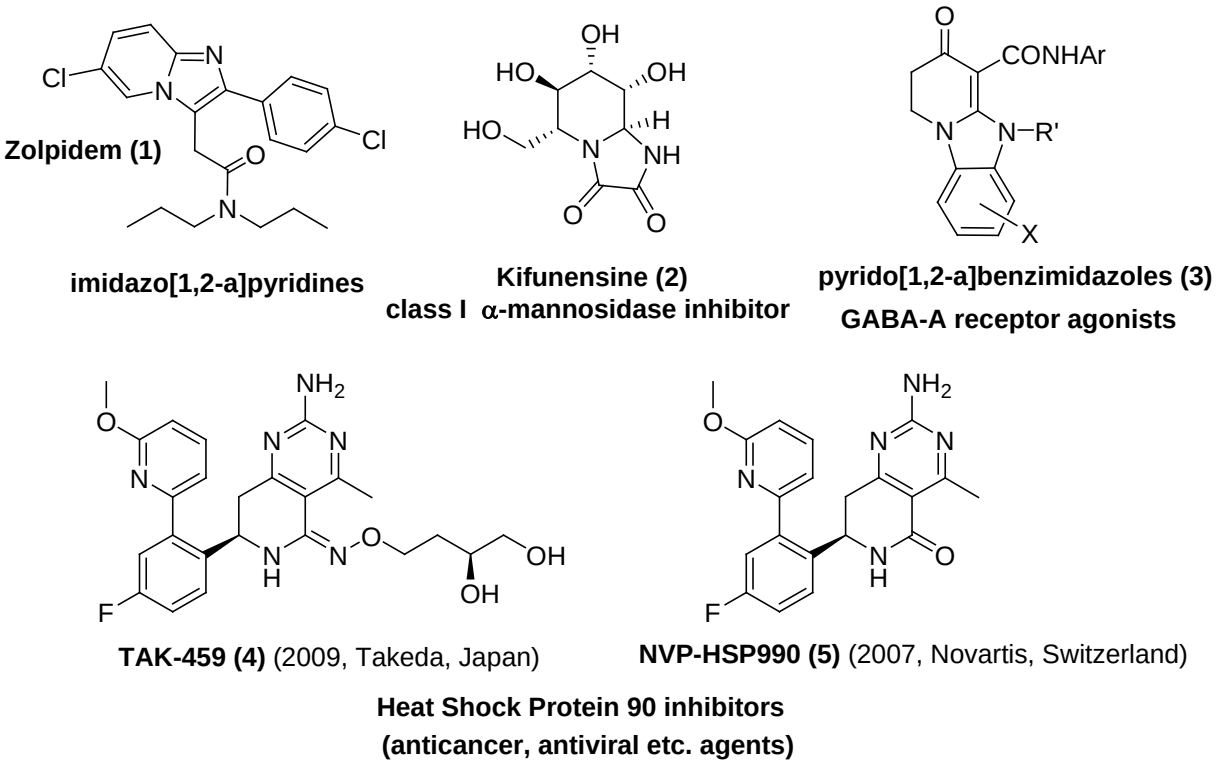

Fig. 1.

Amid these products can be noted Zolpidem (**1**) - blockbuster drug against sleep disorder, a member of numerous imidazo[1,2-a]pyridines, persisting as one of the most favorite groups in the medicinal chemistry[2]. The widespread use of imidazo[1,2-a]pyridines is mainly connected with convenient access to this scaffold from easily available 2-aminopyridines. A saturated derivative of imidazo[1,2-a]pyridine presented by alkaloid kifunensine (**2**) (a natural immunomodulator isolated from actinobacterium *Kitasatosporia kifunensine* no. 9482) relates to potent class I α-mannosidase inhibitor[3] and is perspective for treatment of some genetic diseases, viral infections and cancer metastases. Derivatives of pyrido[1,2-a]benzimidazole (**3**) possess a wide spectrum of biological activity related to GABA-A receptor interaction.[4] Of particular interest is the derivative of 2-aminopyrimidine, built on piperidine-2,4-dione platform, TAK-459 (**4**)[5] which is a hydroxyimino-analogue of Novartis' drug candidate NVP-HSP990 (**5**).[6] Both compounds **4** and **5** are potent inhibitors of heat shock protein 90 (HSP90 – class of chaperone proteins playing a key role in mechanism of cell survival under a number of dangerous diseases including oncological, viral, fungal,[7] parasitic[8] and even tuberculoses[9]) perspective for creation of new generation drugs with variable applications. Synthesis of compounds **4** and **5** is carried out *via* corresponding 6-arylpiperidine-2,4-dione followed by transformation into 2-thioamide under action of Davy methyl reagent and further to final compound **4**.

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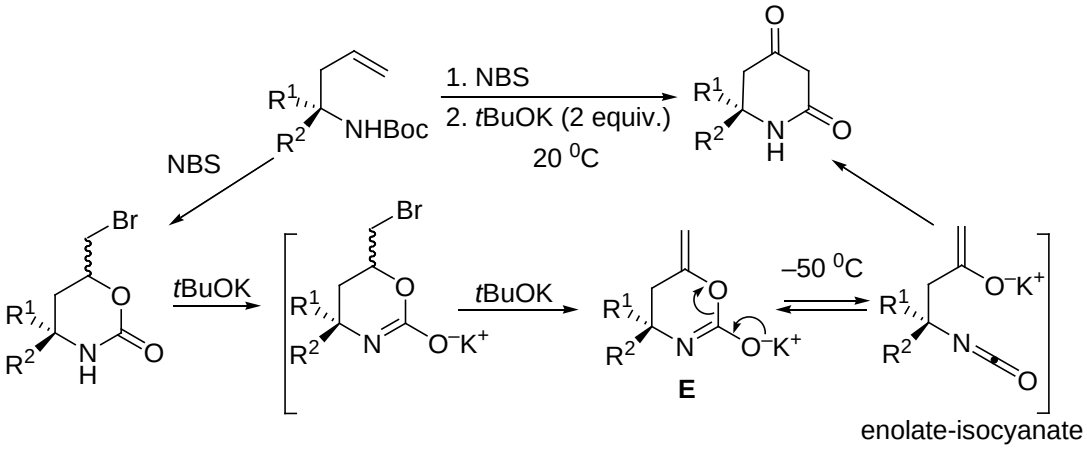
Unlike various methods available for the preparation of imidazo[1,2a]pyridine derivatives, ADP synthesis is limited to two main approaches. The first one is based on Dieckmann's condensation of amidine-esters or its modifications which is actually similar to the classical method for synthesis of piperidine-2,4-diones. This route was realized in synthesis of 3-*C*-analogue of natural antibiotic TAN-1057A/B[10] and GABA-A receptors agonists.[4a] Another approach is based on substitution of thio-groups with amines. It was applied in synthesis of TAK-459 and different ADPs.[11] In the latter case the substitution of α-alkenoyl ketene-(*S,S*)-acetals can be performed stepwise allowing incorporation of different amines residues into the final structure.

Recently, we have elaborated a new convenient method for transformation of *N*-Boc-protected homoallylamines into 6-substituted piperidine-2,4-diones,[12] which are versatile precursors for preparation of different pharmaceutically relevant compounds, and also are a structural motif of many alkaloids,[13] biologically active small synthetic molecules,[14] part of peptidomimetics[15]. An important feature of our method is the application of *N*-Boc-protected homoallylamines as the starting material for the synthesis of diones (Scheme 1).



Scheme 1. Proposed mechanism of the enolate-isocyanate rearrangement

Over this short synthetic chain consisting of cyclobromocarbamation, HBr-eliminaton and a key stage - new enolate-isocyanate rearrangement, a homoallylamine fragment transforms into piperidine ring in an atom-economic manner. The potassium salt of cyclic enolester (**E**) resulting from dehydrobromination undergoes ring-opening reaction, generating, thereby, a highly reactive intermediate enolate-isocyanate which effectively cyclizes to piperidine-2,4-dione even at -50 ^{0}C, though the whole transformation of bromide proceeds at 20 ^{0}C. We considered that 2-imino-1,3-oxazinanes would follow a similar scenario with generation of an enolate-carbodiimide followed by closure into 2-imino-analogues of piperidine-2,4-diones or their tautomers – ADP (Scheme 2).

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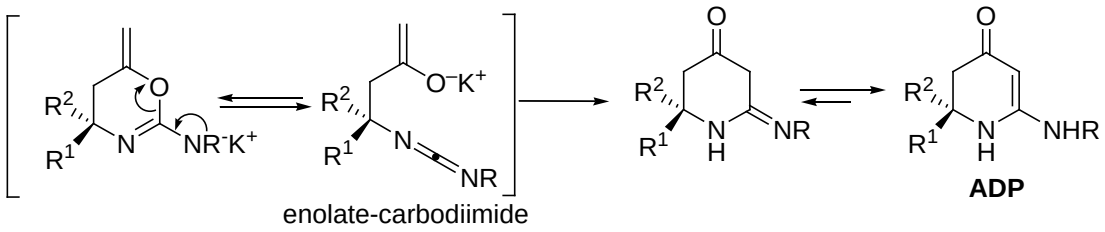
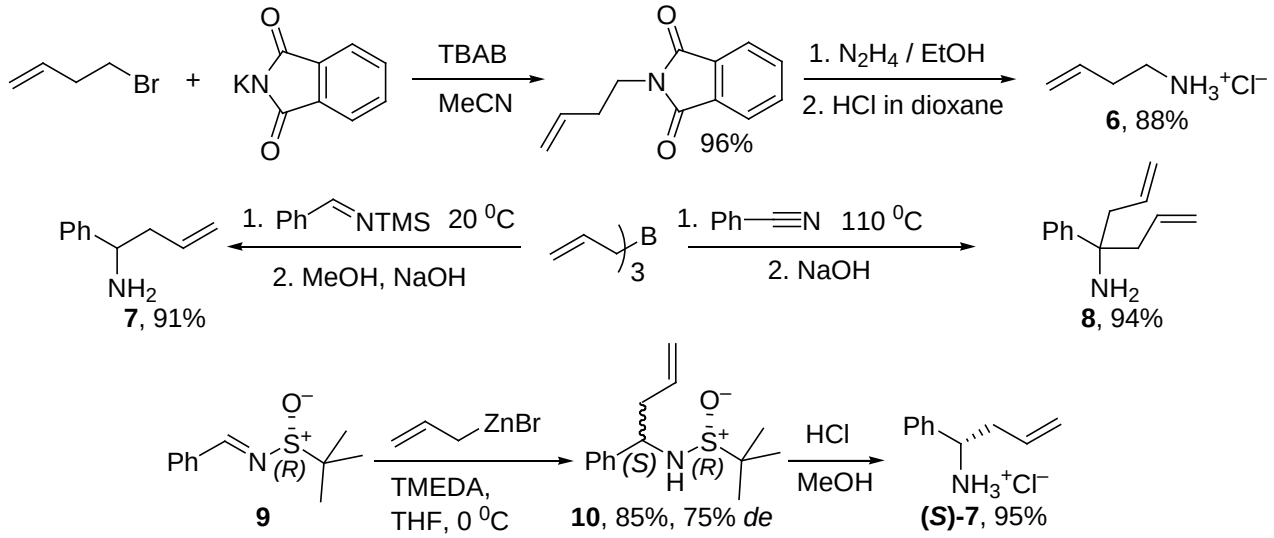


Scheme 2.

Due to the high efficiency of this approach and the significance of the products obtained, we intended to extend our methodology for ADP synthesis starting from *N*-(3-butenyl)ureas.

Results and Discussion

Starting butenylamines were prepared by different methods. Homoallylamine **6** was obtained by the alkylation of potassium phtalimide with 4-bromo-1-butene under phase-transfer catalysis in MeCN followed by hydrazinolysis of *N*-(3-butenyl)phtalimide. This procedure provides clean and high-yielding synthesis of **6** with only filtration and evaporation treatment. α-Phenyl derivatives **7** and **8** were prepared *via* allylboration of 1-phenyl-*N*-trimethylsilylmethanimine or benzonitrile with triallylborane (Scheme 3).[12a] For an asymmetric version of the rearrangement, amine **(*S*)-7** was synthesized in scalemic form. Diastereoselective allylation of (*R*)-phenyl-*N*-*tert*-butanesulfinylimine **9** with allylzinc bromide in the presence of equivalent amount of TMEDA in THF leads to allylated amide **10** with 75% *de*.



Scheme 3.

Deprotection of **10** with HCl in MeOH gave crystalline hydrochloride **(*S*)-7**. We failed to enrich *ee* of **(*S*)-7** by crystallization of its *N*-Boc-derivative similarly to the described procedure,[12a] since the

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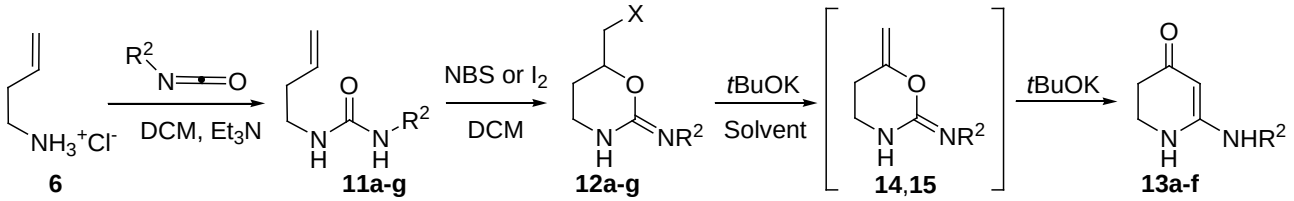
ee of the recrystallized product reached only 84% with much losses of *N*-Boc-amide. Therefore we converted all the amount of *N*-Boc-derivative back to amine **(*S*)-7**.

Amines **6-8** were converted to the corresponding ureas by the reaction with isocyanates bearing substituents with different electronical and sterical nature: aromatic (2-chloro(iodo)phenyl-), aliphatic (methyl-, allyl-), hindered aliphatic (*tert*-butyl-, 1-adamantyl-) and electron deficient (2-methoxyethyloxycarbonyl-, ethyloxycarbonyl-, tosyl-).



Scheme 4.

Table 1.

R^2	Urea, %	RBr, %	Conditions of the rearrangement	ADP, %
$MeO(CH_2)_2OC(O)$-	**11a**, 92	**12a**, 85	DMF, 25 °C, 15 min	**13a**, 96
Cbz-	**11b**, 93	**12b**, 92	THF, 40 °C, 2h THF, 25 °C, 1 min	**13b**, 83 **14**, 96
Ts-	**11c**, 98	**12c**, 95	MeOH, 60 °C, 15 min DMF, 25 °C, 5 min	**13c**,[a] 90 **15**, 92
2-I-Ph-	**11d**, 92	**12d**, 56[b] (RI)	*i*PrOH, 25 °C, 3h	**13d**, 55
2-I-4-Br-Ph-[c]	---	**12e**, 64	*i*PrOH, 40 °C, 1h	**13e**, 98
Me	**11f**, 91	**12f**, 94	THF, 25 °C, 1h	**13f**, 95
*t*Bu	**11g**, 99	**12g**, 99	THF, DMF, *i*PrOH, DMSO	**13g**, NP[d]

a) **13c** exists in the form keto-imine tautomer according to ^1H and ^{13}C NMR spectra; b) reaction with I_2 at 0 °C, 25% of **11d** was recovered; c) R^2 corresponds the structures **12e** and **13e**; d) no product

The reactions of amine hydrochloride **6** with isocyanates in the presence of Et_3N at room temperature gave rise to the corresponding ureas **11a-g** which smoothly undergo cyclization to (bromomethyl)iminourethanes **12a-c** and **12f,g** on treatment with NBS at ambient temperature (Scheme 4, Table 1). However, the cyclization of iodophenyl-urea **11d** under similar conditions is complicated by mono- and dibromination of the aromatic ring; while 2-iodo-4-bromophenyl-derivative **12e** (64%) was obtained when the reaction was run at -20 °C. Alternatively to keep the 2-

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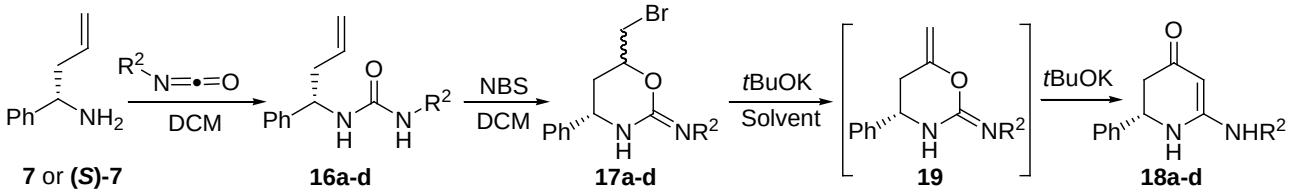
iodophenyl group intact, iodination of **11d** at 0 °C was carried out to give 6-(iodomethyl)urethane **12d** (56%) along with **11d** (25%) recovered. Under the more forced conditions (20 °C or addition of K_2CO_3 to neutralize HI), the reaction is also complicated by iodination of the aromatic ring.

Previously discovered transformation of 6-(bromomethyl)urethanes to piperidine-2,4-diones has been achieved by treatment with *t*BuOK in THF as a solvent (Scheme 1).[12a] As we expected, 6-(bromomethyl)-2-iminourethanes **12a-f** were transformed to 6-amino-2,3-dihydro-4-pyridinones **13** in the presence of *t*BuOK, however, an optimal solvent has to be selected experimentally for each compound **12**. The most convenient solvents were found to be DMF, THF and *i*PrOH (see Table 1). Among the synthesized cyclic bromides, compounds with electron-withdrawing groups R^2 (**12a-c**) are the most reactive ones. Thus ADP **13a** is formed almoust quantitatively (96%) in 15 min at 25 °C. We have found that treatment of bromides **12b** and **12c** with *t*BuOK in THF for very short time (1-5 min) gave rise to enolesters **14** and **15**, which are intermediates in the transformation (Scheme 4, Table 1). When the reaction with **12b** was carried out at 40 ^{0}C for 2 h, enolester **14** formed initially is smoothly transformed to ADP **13b** (83%). Bromide **12c** reacts similarly, however **15** forms potassium salt which is precipitated from THF and DMF, but is readily soluble in MeOH. Therefore, conducting the reaction of **12c** in MeOH (at 60 ^{0}C) leads to expected rearrangement product **13c** (90%). As we previously found iodides are not proper substrates for carring out the rearrangement[16] because of formation of side products. Nevertheless, ADP **13d** (55%) was obtained from 2-iodophenyl-derivative **12d** which is in contrast to with transformation of bromide **12e** into ADP **13e** (98%). Urea **11f** (Table 1) reacts smoothly with NBS and bromide **12f** thus obtained transforms cleanly into ADP **13f** (95%). On the other hand, bulky *t*Bu-group in bromourethane **12g** completely suppress the rearrangement. Different conditions and solvents were used, but ADP **13g** was not obtained or detected.

Having the promising results with ureas **11a-f** derived from **6**, we studied the reactions with monosubstituted phenylamine **7** as well as with **(*S*)-7** to establish the absence of racemization of the α-chiral center during the rearrangement (Scheme 5, Table 2).



7 or **(*S*)-7** **16a-d** **17a-d** **19** **18a-d**

Scheme 5.

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Table 2.

R^2	Urea, %	RBr, %	*cis/trans*	Conditions of the rearrangement	ADP, %
EtOC(O)-	**16a**, 90	**17a**, 99	2.6/1	DMF, 25 ^{0}C, 15 min	**18a**, 94
Cbz-	**16b**, 88	**17b**, 99	2.4/1	THF, 40 ^{0}C, 40 min THF, 0 ^{0}C, 1 min	**18b**, 98 **19**, 97
*t*Bu	**16c**, 99	**17c**, 95	3/1	THF, DMF, iPrOH, DMSO	**18c**, NP[a]
Me-	**16d**, 96	**17d**, 90	2.3/1	THF, 25 ^{0}C, 30 min DMSO, 25 ^{0}C, <1 min	**18d**, 96 **18d**, >95[b]
Me-	**(*S*)-16d**, 43[c]	**(*S*)-17d**, 92	2.3/1	THF, 25 ^{0}C, 30 min	**(*S*)-18d**, 95[d]

a) no product; b)^{1}H NMR yield; c) first crystallization -61%, *ee* 94.7 %, second crystallization – 43%, *ee* 98.6%, HPLC Chiralcel OD-H, hexane:*i*PrOH=9:1, 219nm, flow rate 1 ml/min; retention time **(*R*)-16d** 11.23 min; **(*S*)-16d** 13.40 min; d) *ee* 99%, HPLC Chiralcel OD-H, hexane:*i*PrOH:Et_2NH:Et_3N=80:20:0.1:0.1, 219nm, flow rate 1 ml/min; retention time **(*S*)-16d** 19.24 min; **(*R*)-16d** 22.12 min;

Ureas **16a-d** were synthesized by mixing amines **7** with isocyanates in DCM. Urea **(*S*)-16d** prepared from scalemic amine **(*S*)-7** (*ee* 75%) (see Scheme 3 and text above), was recrystallized twice from *n*-C_6H_{14}:EtOAc = 4:1 mixture to produce **(*S*)-16d** with *ee* 98.6% (see Table 2, footnote c). The cyclization of **16** with NBS proceeds cleanly to produce (bromomethyl)urethanes **17a-d** as a mixture of *cis/trans*-isomers in 2.1-3/1 ratio (^{1}H NMR), their configurations were assigned by analogy with previously studied isomeric (bromomethyl)urethanes.[12a] *cis/trans*-Isomers of **17b** were separated by chromatography and isolated in individual form. All the bromides **17** (except for **17c**) are readily transformed to ADPs **18** in the presence of *t*BuOK, but the compounds **17a** and **17b** are the most reactive ones. As in the case of **12b** (Scheme 4) a short treatment of urethane **17b** with *t*BuOK (0 ^{0}C, 1 min) produced unsaturated enolester **19** (97%) which undergoes the clean rearrangement to **18b** (98%) upon further stirring with gentle heating (40 ^{0}C, 40 min) of the reaction mixture. *t*Bu-Substituted bromourethane **17c** gave a complex mixture of products instead of expected ADP **18c** independently of the solvent or conditions used. At the same time, methyl-analogue **17d** reacts smoothly in THF for 40 min or immediately in DMSO, producing **18d** (>95% by ^{1}H NMR, for less then 1 min). Bromocyclization of enantiomerically pure urea **(*S*)-16d** gave urethane **(*S*)-17d** as a mixture of isomers which were treated with *t*BuOK in THF that affords expected product **(*S*)-18d**.

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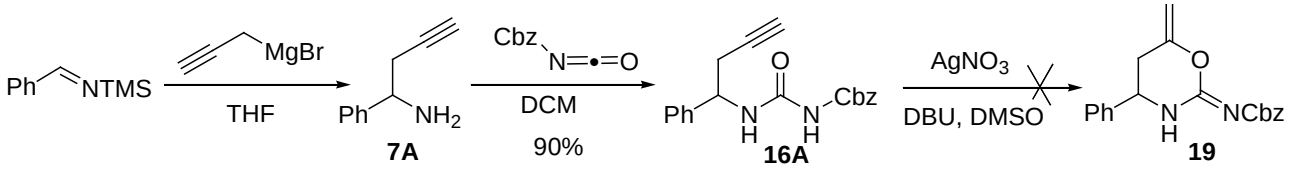
Formation of **(*S*)-18d** (*ee* 99%) from **(*S*)-16d** (*ee* 98.6%) evidently demonstrates the absence of racemization during the whole reaction sequence.

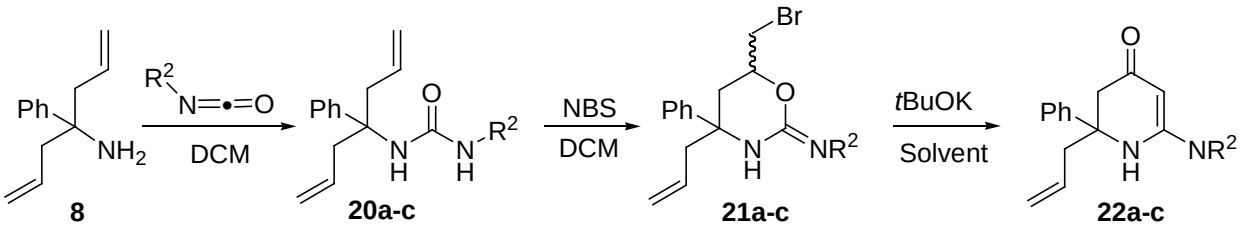
Actually enolester **19** could be obtained through the silver-catalyzed homopropargylamine cyclization. Yamada and co-workers[17] have shown that intramolecular nucleophilic addition of carbamate anion to silver-activated triple bond gave rise to enolesters of benzoxazine-2-one series. That would be an advantageous to avoid the stage of dehydrobromination by metal-catalyzed cyclization.



Scheme 6.

Urea **16A** was prepared from propargyl amine **7A**. We tried similar condition using silver nitrate as a catalyst, however, enolester **19** was not formed (Scheme 6). Probably, the carbonyl group is insufficiently nucleophilic for such cyclization or *vice versa* for such triple bond.

Then, the preparation of 2,2-disubstituted ADP derived from amine **8** was studied (Scheme 7, Table 3). Generally all the reactions of diallylated ureas **20a-d** with NBS procced faster than with ureas **11** and **16**. In the case of **20a**, the reaction became more selective towards double bond in comparison with **11d** where the bromination of the aromatic ring takes place. Decreasing the reaction temperature up to -15 ^{0}C allowed the synthesis of only the product of bromocyclization reaction **21a** (85%). Treatment of ureas **20a-d** with NBS furnished cyclic bromoiminourethanes **21a-d** with different ratios of *cis/trans*-isomers (1:8-1:20).



Scheme 7.

Table 3.

R^2	Urea, %	RBr, %	*cis/trans*[a]	Conditions of the rearrangement	ADP, %
2-Cl-Ph-	**20a**, 99	**21a**, 85	1:20[b]	THF (25 ^{0}C, 2h) DMF (25 ^{0}C, 6h)	**22a**, 47 **22a**, 71

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				iPrOH (45 ^{0}C, 4h)	**22a**, 89
MeO$(CH_2)_2$OC(O)-	**20b**, 90	**21b**, 98	1:15	various	**22b**, NP[c]
*t*Bu-	**20c**, 70	**21c**, 89	1:19	various	**22c**, NP[c]
Allyl-	**20d**, 85	**21d**, 72	1:10	THF (25 ^{0}C, 2h) DMF (25 ^{0}C, 6h) iPrOH (45 ^{0}C, 24h)	**22d,** 45 **22d,** 52 **22d,** 15
Me-	**20e**, 98	**21e**,	1:8	THF (0 ^{0}C, 2h) DMF (25 ^{0}C, 2h)	**22e**, 48 **22e**, 45

a) calculated from NMR spectra; b) the isomer ratio was obtained at -15 ^{0}C; c) no product

Pure *trans*-isomer **21a** was isolated by crystallization of the isomeric mixture (*cis/trans* = 1:20) from *n*-C_6H_{14}/EtOAc mixture and its structure was established by X-Ray single crystal analysis (Fig. 2). It should be noted that similar *trans*-selectivity was observed previously in the cyclization of oxygen analogue of **20a** into 4-allyl-6-(bromomethyl)-4-phenyl-1,3-oxazinan-2-one.[12a]

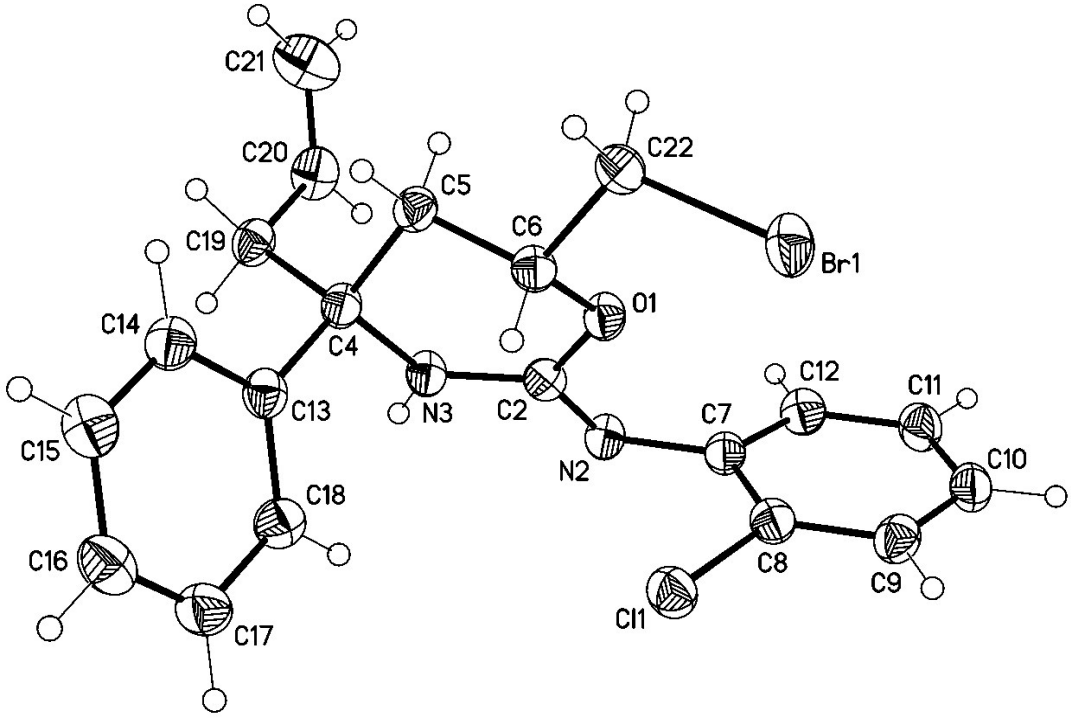

Fig. 2. Molecular structure of *trans*-isomer **21a** (one of the two crystallographically independent molecules is presented only).

Further rearrangement **21a→22a** is strongly solvent dependent (Table 3); only gentle heating in isopropanol provides high yield of ADP **22a** (89%). The structure of **22a** was also supported by X-Ray single crystal analysis (Fig. 3).

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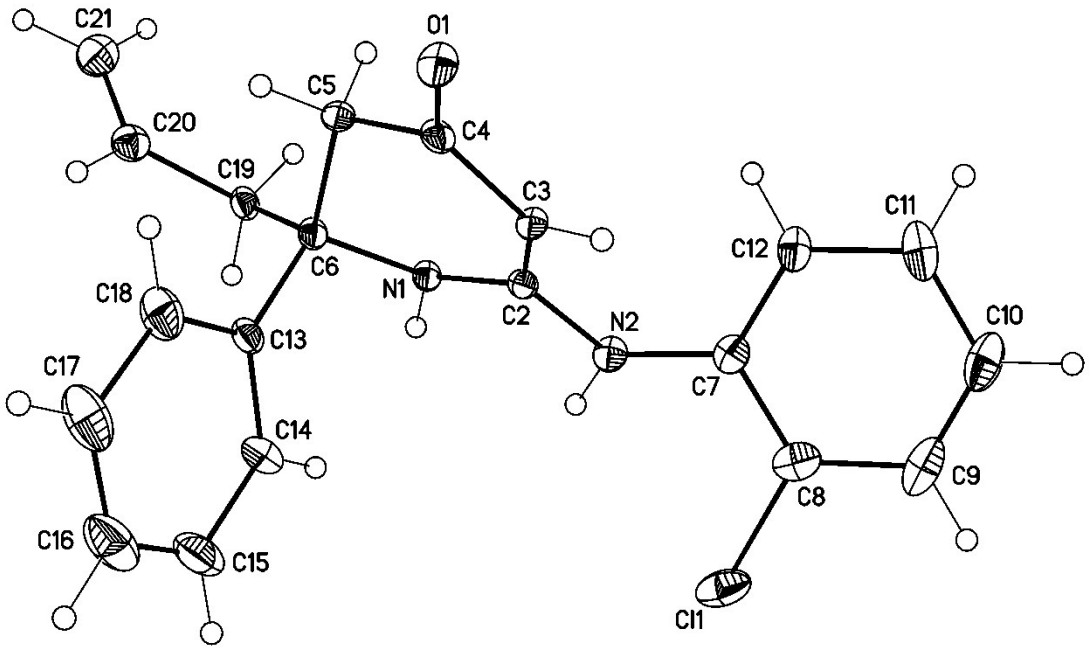

Fig. 3. The structure of ADP **22a**.

Urea with the electron-withdrawing group **20b** (R^2 = $MeO(CH)_2OC(O)$-) and corresponding bromide **21b** are formed cleanly. However, the following rearrangement step gave only traces of product **22b** (TLC-detection), which completely decomposed during workup and chromatography.

Urea **20c** (70%) containing two bulky fragments (two tertiary carbons) in the molecule was prepared by heating of amine **8** and *tert*-butyl isocyanate under reflux in DCM for 4h. Following reaction of **20c** with NBS gave rise mainly to *trans*-isomer **21c** (89%), but the latter does not produce ADP **22c** upon the treatment with *t*BuOK (see also Table 1 and 2), a complex mixture of products was formed. In the case of *N*-allyl compound, the same transformations gave urea **20d** and bromide **21d** in good yields, but the last transformation to ADP was not so efficient. The yield of ADP **22d** in DMF was higher (52%) then in THF (45%) and *i*PrOH (15%). The reasons for moderate yield of **22d** as well as decomposition of *tert*-butyl derivatives (**12g**, **17c**, **21c**) under the treatment with *t*BuOK are unclear.

Actually if one compares the syntheses of piperidine-2,4-diones[12a] and ADPs from (bromomethyl)urethanes, the last transformations (**21a-d** → **22a-d**) take longer time (up to 6 hs) and are more capricious (**21b,c**). There are two key steps which can complicate the reaction. First step is the dehydrobromination and second – rearrangement where enolate anion would add to carbodiimide's moiety (see Scheme 2). We decided to separate the processes of dehydrobromination and rearrangement to understand the efficiency of the elimination step. Thus, two *N*-PMB-protected ureas **24a,b** were prepared by reductive amination of *p*-anisaldehyde with amine **8** followed by the

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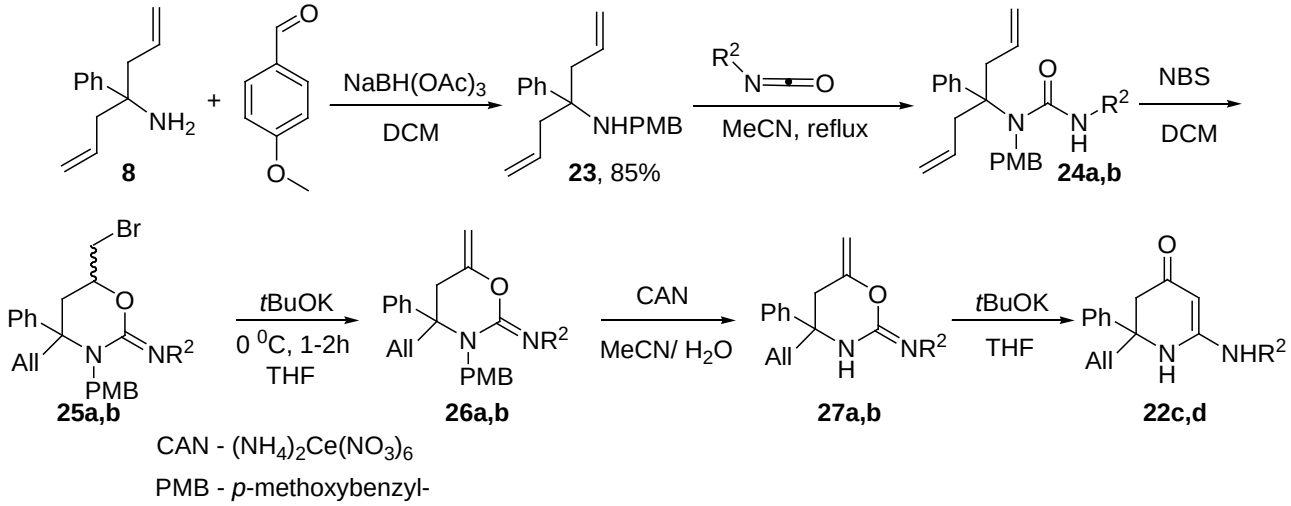
reaction of amine **23** with isocyanates in refluxing MeCN with *t*BuOH as an additive (Scheme 8). It should be pointed out that the reaction of **23** even after two days of reflux with excess of *t*BuNCO did not run to completion, giving urea **24a** in 70% yield. Similarly urea **24b** was obtained in 88% yield.



Scheme 8.

Table 4.

R^2	Urea, %	RBr, %	*cis/trans*[a]	PMB Enol , %	Enol, %	ADP, %
*t*Bu-	**24a**, 70	**25a**, 77	1:12	**26a**, 82	**27a**, 84	**22c**, 72
Allyl-	**24b**, 88	**25b**, 72	1:10	**26b**, 94	**27b**, 68	**22d,** 85[b]

a) calculated from NMR spectra; the isomer ratio was obtained at 0 ^{0}C; b) reaction in *i*PrOH at 50 ^{0}C gave 52% of **22d.**

NBS mediated cyclization of ureas **24a** and **24b** gave rise to cyclic bromides **25a** (77%) and **25b** (72%) as a mixture of *cis*- and *trans*-isomers (*ca* 1:12). Dehydrobromination of bromourethanes **25a,b** under the action of *t*BuOK in THF proved to be a slow process. Both of the reactions are completed at 0 °C within 1-2 hours, producing the corresponding enolesters **26a** (82%) and **26b** (94%). Increasing the reaction temperature to 25 °C for acceleration of elimination stage provocates the partial *exo*-*endo*-migration of the double bond (up to 25-30% by ^{1}H NMR). Such reactivity is in sharp contrast to the previously observed very fast HBr elimination (takes seconds at -20 °C) in similar tertiary 1,3-oxazin-2-ones.[18,12a] This means the elimination of NH-urethanes **21a-d** occuring at room temperature (Scheme 7, Table 3) would be even more difficult process, growing up the chance of any side reactions. Next PMB-deprotection of **26a,b** has been carried out by the oxidation with cerium(IV) ammonium nitrate (CAN) at 0 °C for 5h with portionwise addition of water

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solution of sodium acetate to neutralize nitric acid formed. It should be emphasized that in CAN oxidation mainly the aromatic system is involved. Enolesters **27a** (84%) and **27b** (68%) thus obtained were purified by flash chromatography on silica gel and subjected to rearrangement upon the treatment of *t*BuOK at -30 °C. Notably, only under these conditions the expected product **22c** (R^2 = *t*Bu) was obtained in 72% (see Table 3 and 4). Rearrangement of **27b** in THF gave smoothly **22d** (85%). The same transformation in *i*PrOH at 50 °C was completed in 10 minutes, giving **22d** (52%); while at 0 °C it does not proceed at all. We also tried to use the same PMB-approach for the synthesis of **18c** (Scheme 5, Table 2), but observed mainly the bromination of *p*-methoxyphenyl ring.

Having in hand a new method for construction of ADP with bulky *t*Bu-group, we decided to extend the method for adamantane derivatives. The lipophilic adamantane is an important pharmacophore group composing many well proven drugs such as amantadine and memantine (neurodegenerative deseases), tromantadine and remantadine (antiviral) *etc.*[19] Moreover several adamantane containing piperidine and pyrrolidine derivatives possess high antiviral activity towards influenza virus A (A_2/Japan/305/1957 (H_2N_2)).[20] In order to overcome the problem of side bromination of PMB-group, we envisaged an alternative route towards cyclic enolesters by using the *syn*-elimination of selenoxides[21]. Homoallylamine **28** was prepared by the reaction of dibutyl allylboronate, ammonia and acetone according to the modified procedure[22] (Scheme 10). Reactions of amines **6** and **28** with 1-adamantyl isocyanate gave ureas **29a,b** in good yield. Further phenylselenocyclocarbamation of these ureas with phenylselenyl chloride was carried out in DCM solution similarly to the procedure described previously.[23] In the case of urea **16c**, selenide **30c** is formed as a mixture of *cis/trans* = 1.9:1 isomers. Phenylselenides **30a-c** were oxidized to selenoxides under optimized conditions in a two-phase mixture $NaIO_4$ (3 equiv.) in aqueous MeOH at 0 °C for 20 minutes and were used further without purification. We found that heating selenoxides in dioxane solution at 70 °C provides elimination products **31a-c** in low yields (13-32%). The conducting the elimination stage of selenoxide derived from **30c** in the presence of diisopropylamine and vinyl acetate at higher temperature[24] gave enolester **31c** in the lower yield.

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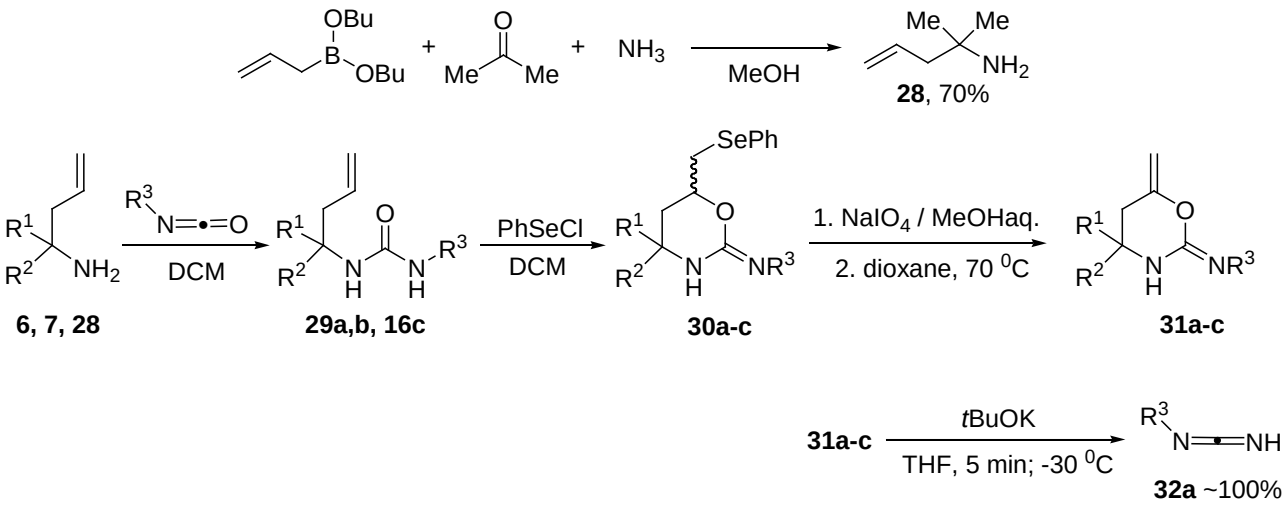

Amine	R^1	R^2	R^3	Urea, %	RSePh, %	Enol , %	Imid, %
6	H-	H-	Ad-	**29a**, 98	**30a**, 73	**31a**, 13	**32a**, ~100
28	Me-	Me-	Ad-	**29b**, 85	**30b**, 81	**31b**, 32	**32a**, ~100
7	Ph-	H-	*t*Bu-	**16c**, 99[a]	**30c**, 85[b]	**31c**, 18	**32b**, NP[c]

a) see Table 2; b) *cis/trans* = 1.9:1; c) no product detected

Scheme 10.

When enolesters **31a,b** were treated with *t*BuOK in THF at -30 ^{0}C, *N*-(1-adamantyl)carbodiimide (**32a**) was quantitatively obtained instead of the expected rearranged ADP products (Scheme 10). In the case of enolester **31c**, we failed to identify the expected *N*-(*tert*-butyl)carbodiimide. The structure of **32a** was confirmed by NMR and HRMS spectra. The reactions in other solvents (*i*PrOH, DMF), in the presence of additives (BF_3-etherate, Ti(O*i*Pr)$_4$) and at different temperatures (-78 , -40 and 0 ^{0}C) do not change the result: the only isolated product was carbodiimide **32a**. Evidently, we have succeeded in isolation of the compound derived from decay of the anticipated intermediate enolate-carbodiimide (Schemes 2 and 11). The mechanism of carbodiimide **32a** formation can be described as E1cb elimination process (retro Michael decay) occurring in the enolate-carbodiimide molecule that supports the analogous mechanistic pathway of the enolate-isocyanate rearrangement discovered earlier.[12a] This result gives an insight into possible side processes accompanying the reaction and explains our failures upon synthesis of sterically hindered ADPs. Apparently, the less active (more crowded) the carbodiimide group in the intermediate, the greater possibility of such type of its decay.

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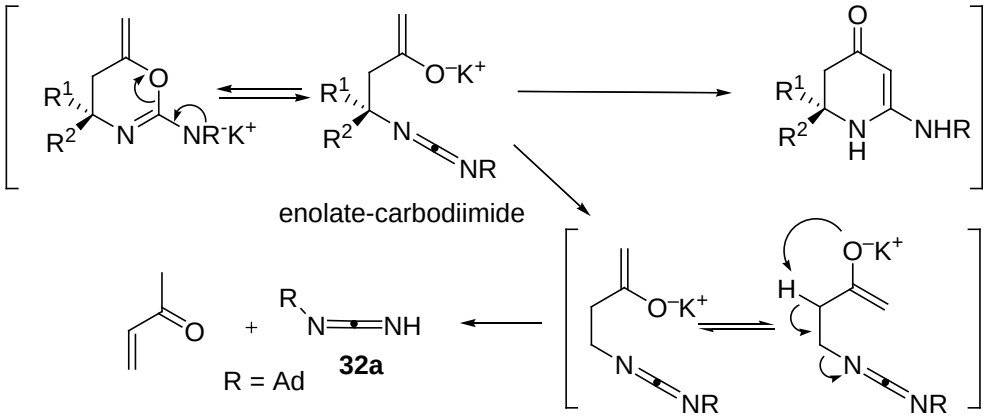

Scheme 11. Mechanism of enolate-carbodiimide rearrangement and formation of **32a**.

We also carried out kinetic study of the rearrangement of enolester **19** to ADP **18b** (Scheme 5) which was monitored by proton NMR. The reaction was run in anhydrous DMSO-D_6 at 20.5 °C. The recorded data were used to draw a kinetic curve (Fig. 4) which revealed the first-order of the reaction with a rate constant $k = 4.3\text{x}10^{-3}$ s^{-1} at 20.5 °C, confirming the monomolecular character of the rearrangement. The rate constant was considerably lower than that of the enolate-isocyanate rearrangement ($k = 2.85\text{x}10^{-2}$ s^{-1} at –48 °C)[12a] implying lower reactivity of the carbodiimide reactive center.

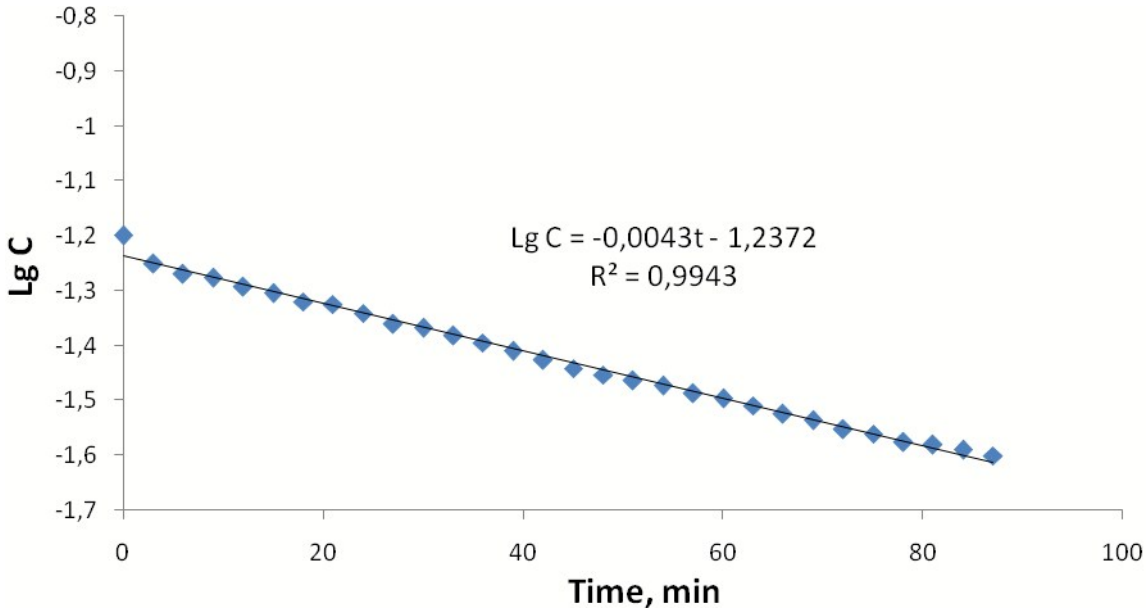

Fig. 4. Kinetic curve of rearrangement enolester **19** to ADP **18b**.

Conclusions

In summary, we have developed a new convenient strategy for the creation of 6-amino-2,3-dihydro-4-pyridinones (ADP). A series of 2,6-substituted ADP were synthesized. The strategy is based on

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rapid, facile and efficient transformation of *N*-(3-butenyl)ureas through the three-step sequence involving NBS (or I_2, PhSeCl)-mediated cyclization to 6-(bromomethyl)-2-iminourethanes, dehydrohalogenation and the novel anionic enolate-carbodiimide rearrangement as a key step. This rearrangement is similiar to the enolate-isocyanate rearrangement previously discovered in our group; however, it has some differences associated with the lower reactivity of carbodiimide intermediate and nature of the substituent at the 6-amino-group. The more electron-withdrawing character of *N*-substituent in (bromomethyl)urethanes, the easier their transformations to ADP proceed. As a limitation of the process, difficulties in synthesis of ADPs with bulky 6-*tert*-butylamino- and 6-(1-adamantyl)amino-groups should be noted. The mechanism of the rearrangement was supported by the kinetic data and isolation of *N*-(1-adamantyl)carbodiimide – a product of enolate-carbodiimide decay. The final piperidinone heterocycles are promising precursors for the synthesis and design of drugs.

Experimental Section

General. The manipulations with sensitive to air compounds were carried out under inert atmosphere of dry Ar. Triallylborane was prepared according to described procedure.[20] NMR spectra were recorded on Bruker Avance-300, 400 and 600 MHz instruments. Mass spectra were recorded on Finnigan Polaris Q Ion Trap spectrometer. Monoisotopic mass spectra (HRMS) were obtained from Bruker microTOF, Maxis. Optical rotation was measured on Perkin Elmer 341 instrument. Column chromatography was carried out using silica gel 60–230 mesh (Merck). Thin layer chromatography was run on Alugram Sil G/UV_{254} (Macherey-Nagel). Melting points were measured on a Suart SMP10 capillary melting point apparatus. Compounds **7**,[12a] **8**,[25] **9**,[26] **7A**[27] were synthesized as described.

General procedure of synthesis of ureas 11a-d, **16a-d**, **20a-c**, **16A**, **29a,b**.

To the hydrochloride homoallylamine **6** (0.86 g, 8.0 mmol) solution in $CHCl_3$ (15 ml) (or DCM for free amines **7, 8, 7A, 28** and without Et_3N addition) was added corresponding isocyanate (8.0 mmol) and Et_3N (1.0 g, 1.39 ml, 10.0 mmol) dropwise with stirring. The mixture was stirred at ambient temperature for 30 min to ensure completion of the reaction. The progress of the reaction was monitored by TLC. After then the mixture was washed consequently with 0.6N HCl and water. Organic phase was dried with Na_2SO_4 and evaporated to dryness. The residue was recrystallized or purified by FC for elemental analysis.

***N*-methyl-*N*'-(1-phenyl-3-butenyl)urea (16d)**

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Yield: 96%, as crystalline solid, m.p. 79-80 °C (*n*-C_6H_{14}/EtOAc). R_f 0.25 (*n*-C_6H_{14}/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.32-7.21 (m, 5H, Ph); 5.74-5.63 (m, 2H, NH and CH=); 5.28 (br.s, 1H, NH); 5.08-5.03 (m, 2H, CH_2=); 4.78 (br.m, 1H, CHPh); 2.62 (s, 3H, Me); 2.51-2.40 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 158.94; 143.00; 134.26; 128.41 2C; 126.96; 126.17 2C; 117.84; 53.77; 41.71; 26.79. $C_{12}H_{16}N_2O$ (204.3): calcd. C 70.56, H 7.90, N 13.71; found C 70.61, H 8.15, N 13.71.

(*1S*)-*N*-methyl-*N*'-(1-phenyl-3-butenyl)urea ((*S*)-16d).

A crude urea **(*S*)-16d** obtained through the general procedure from **(*S*)-7** (*ee* 74%) was crystallized from the *n*-C_6H_{14}:EtOAc = 4:1 mixture to give of **(*S*)-16d**, yield: 61%, *ee* 94.7%; second crystallization furnishes **(*S*)-16d**, yield: 43% (calculated on crude urea), *ee* 98.6% as crystalline solid, m.p. 86-87 °C (*n*-C_6H_{14}/EtOAc, 4:1). $[\alpha]_D^{25}$ -29.7 (C 1, $CHCl_3$). HPLC Chiralcel OD-H, *n*-hexane:*i*PrOH=9:1, 219 nm, flow rate 1 ml/min; retention time **(*R*)-16d** 11.23 min; **(*S*)-16d** 13.40 min.

***N*-(1-Allyl-1-phenyl-3-butenyl)-*N*'-(*tert*-butyl)-*N*-(4-methoxybenzyl)urea (24a).**

PMB-amine **23** (0.50 g, 1.62 mmol) and *tert*-butyl isocyanate (0.32 g, 3.25 mmol) in a mixture of MeCN (1 ml)/*t*BuOH (0.12 ml) were heated at reflux for 2 days. The mixture was concentrated under reduced pressure followed by chromatography separation on silica gel (*n*-C_6H_{14}/EtOAc, 6:1) that gave target urea **24a** (0.46 g, 70%) as crystalline solid, m.p. 98-99 °C (*n*-C_6H_{14}). R_f 0.28 (*n*-C_6H_{14}/EtOAc, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 7.40 (d, *J* = 8.6 Hz, 2H, Ar); 7.36-7.29 (m, 5H, Ph); 6.95 (d, *J* = 8.6 Hz, 2H, Ar); 5.53-5.39 (m, 2H, 2CH=); 5.15-5.10 (m, 2H, $2CH_2$=); 4.81 (s, 2H, CH_2Ar); 4.20 (s, 1H, NH); 3.86 (s, 3H, OMe); 3.12 (dd, *J* = 7.6, 12.8 Hz, 2H, CH_2); 2.69 (dd, *J* = 6.7, 12.8 Hz, 2H, CH_2); 1.05 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 158.13; 157.92; 145.78; 134.04; 133.34 2C; 128.81 2C; 128.74 2C; 127.23; 126.31 2C; 119.20 2C; 113.69 2C; 64.97; 55.12; 50.48; 47.36; 40.73 2C; 28.87 3C. $C_{26}H_{34}N_2O_2$ (406.6): calcd. C 76.81, H 8.43, N 6.89; found C 76.77, H 8.44, N 6.97.

***N*-(1-Allyl-1-phenyl-3-butenyl)-*N*'-(allyl)-*N*-(4-methoxybenzyl)urea (24b)**

A solution of PMB-amine **23** (1.17 g, 3.79 mmol) and AllNCO (0.47 g, 5.7 mmol, 1.5 eq.) in a mixture of MeCN (8 ml) / *t*BuOH (1 ml) were heated under reflux for 18 h with stirring, then more AllNCO (0.31 g, 3.7 mmol) was added and the heating was continued for another 24 h. The progress of the reaction was monitored by TLC (*n*-C_6H_{14}/EtOAc, 6:1), R_f (**24b**) = 0.2. The volatiles were removed under reduced pressure and the residue was subjected to FC on silica gel that affords urea **24b** (1.15 g, 88%) as white solid, m.p. 75-76 °C (*n*-C_6H_{14}). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm):

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7.39 (d, *J* = 8.6 Hz, 2H, Ar); 7.36-7.22 (m, 5H, Ph); 6.93 (d, *J* = 8.6 Hz, 2H, Ar); 5.59 (ddt, *J* = 5.3, 10.4, 17.2 Hz, 1H, CH=, NAllyl); 5.50-5.35 (m, 2H, 2CH=); 5.13-5.08 (m, 4H, $2CH_2$=); 4.88 (d, *J* = 10.4 Hz, 1H, $C\underline{H}_AH_B$=, NAllyl); 4.80 (s, 2H, CH_2Ar); 4.73 (d, *J* = 17.2 Hz, 1H, $CH_A\underline{H}_B$= NAllyl); 4.28 (t, *J* = 5.3 Hz, 1H, NH); 3.84 (s, 3H, OMe); 3.63 (t, *J* = 5.3 Hz, 2H, $HNC\underline{H}_2$); 3.14 (dd, *J* = 7.5, 13.0 Hz, 2H, $C\underline{H}_AH_B$ Allyl); 2.70 (dd, *J* = 6.8, 13.0 Hz, 2H, $CH_A\underline{H}_B$ Allyl). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 158.90; 158.47; 145.59; 135.16; 133.40 2C; 130.92; 128.86 2C; 128.83 2C; 127.30; 126.19 2C; 119.33 2C; 114.67; 113.95 2C; 65.39; 55.26; 48.37; 43.31; 40.80 2C. $C_{25}H_{30}N_2O_2$ (390.5): calcd. C 76.89, H 7.74, N 7.17; found C 76.94, H 7.69, N 7.20.

***N*-(1-adamantyl)-*N*'-(3-butenyl)urea (29a)**.

Yield: 98%, as white solid, m.p. 163-164 °C (EtOH/H_2O). R_f 0.6 (*n*-C_6H_{14}/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 5.75 (ddt, *J* = 6.8, 10.1, 17.2 Hz, 1H, CH=); 5.07 (d, *J* = 17.2 Hz, 1H, $C\underline{H}_AH_B$=); 5.03 (d, *J* = 10.2 Hz, 1H, $CH_A\underline{H}_B$=); 4.68 (br.s, 1H, NH); 4.44 (br.s, 1H, NH); 3.18 (d, *J* = 6.7 Hz, 1H, CH_2N); 2.21 (dt, *J* = 6.4, 6.7 Hz, 2H, CH_2CH=); 2.03 (br.s, 3H, Ad); 1.93 (br.s, 6H, Ad); 1.63 (br.s, 6H, Ad). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 157.39; 135.74; 116.76; 50.66; 42.46 3C; 39.22; 36.38 3C; 34.43; 29.49 3C. $C_{15}H_{24}N_2O$ (248.4): calcd. C 72.54, H 9.74, N 11.28; found C 72.40, H 9.91, N 10.98.

***N*-(1-adamantyl)-*N*'-(2-methylpent-4-en-2-yl)urea (29b).**

Yield: 85%, as white solid, sublimation point 245 °C (DCM). R_f 0.15 (*n*-C_6H_{14}/EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 5.78 (ddt, *J* = 7.5, 9.2, 17.7 Hz, 1H, CH=); 5.07-5.02 (m, 2H, CH_2=); 2.37 (d, *J* = 7.5 Hz, 2H, $C\underline{H}_2CH$=); 2.30 (br.s, 2H, 2NH); 2.01 (br.s, 3H, Ad); 1.89 (m, 6H, Ad); 1.62 (br.s, 6H, Ad); 1.24 (s, 6H, 2Me). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 156.78; 134.66; 117.96; 52.15; 50.54; 45.26; 42.40 3C; 36.36 3C; 29.47 3C; 27.49 2C. $C_{17}H_{28}N_2O$ (276.4): calcd. C 73.87, H 10.21, N 10.13; found C 73.69, H 10.33, N 10.27.

General procedure for NBS mediated cyclobromocarbamation, synthesis of bromides 12a-g, 17a-d, 21a-d, 25a,b.

2-Methoxyethyl *N*-[6-(bromomethyl)-1,3-oxazinan-2-yliden]carbamate (12a).

To a solution of urea **11a** (0.37 g, 1.7 mmol) in DCM (4 ml) NBS (0.36 g, 2.04 mmol) was added with stirring at ambient temperature. The solution was stirred for 40 min. until disappearance of starting urea **11a**. After evaporation of DCM the residue was dissolved in a mixture of Et_2O/EtOAc (4:1, 15 ml) and 10% solution of NaOH (5 ml) was added. The mixture was vigorously stirred for 10 min, the organic layer was separated, dried with K_2CO_3, evaporated and purified through a column of silica gel (EtOAc/MeOH, 10:1) to furnish **12a** (0.43 g, 85%) as oil. R_f 0.20 (MeOH/EtOAc,10:1).

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^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 9.42 (br.s, 1H, NH); 4.44-4.37 (m, 1H, CHO); 4.06-4.03 (m, 2H, $CH_2OC(O)$); 3.51-3.36 (m, 6H, CH_2Br, CH_2N, CH_2OMe); 3.22 (s, 3H, OMe); 2.20-2.12 (m, 1H, $C\underline{H}_AH_BCHO$); 1.94-1.80 (m, 1H, $CH_A\underline{H}_BCHO$). ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 163.88; 161.77; 74.89; 70.26; 63.76; 58.55; 37.33; 32.00; 24.05. $C_9H_{15}BrN_2O_4$ (295.1): calcd. C 36.63, H 5.12, N 9.49; found C 36.72, H 5.16, N 9.37.

Benzyl *N*-[6-(bromomethyl)-1,3-oxazinan-2-yliden]carbamate (12b).

Yield: 92% as a white solid, m.p. 82–84 °C. R_f 0.12 (*n*-C_6H_{14}/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.98 (br.s, 1H, NH); 7.44–7.23 (m, 5H, Ph); 5.12 (s, 2H, $C\underline{H}_2Ph$); 4.52–4.44 (m, 1H, CHO); 3.58 (dd, *J* = 4.4, 10.8 Hz, 1H, $C\underline{H}_AH_BBr$); 3.53–3.37 (m, 3H, $CH_A\underline{H}_BBr$, CH_2N); 2.31–2.21 (m, 1H, $C\underline{H}_AH_BCHO$); 2.03–1.90 (m, 1H, $CH_A\underline{H}_BCHO$). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 164.08; 162.03; 136.80; 128.20 2C; 127.60; 127.49 2C; 75.22; 66.72; 37.53; 31.75; 24.29. $C_{13}H_{17}BrN_2O_3$ (329.2): calcd. C, 47.72; H, 4.62; N, 8.56; found C, 47.72; H, 4.86; N, 8.46.

***N*-[6-(Bromomethyl)-1,3-oxazinan-2-yliden]-4-methylbenzenesulfonamide (12c)**.

Bromo-derivative **12c** is precipitated during the reaction from DCM solution. After evaporation of DCM, the precipitate was suspended in water/Et_2O mixture then filtered and dried on air. Yield: 95% as a white solid, m.p. 199–201 °C (dec.). R_f 0.14 (*n*-C_6H_{14}/EtOAc, 1:1). ^{1}H NMR (400 MHz, DMSO-D_6) (δ, ppm): 8.66 (s, 1H, NH); 7.70 (d, *J* = 7.6 Hz, 2H, Ar); 7.29 (d, *J* = 7.6 Hz, 2H, Ar); 4.57 (br.s, 1H, CHO); 3.67 (br.dd, *J* = 3.2, 11.1 Hz, 1H, $C\underline{H}_AH_BBr$); 3.57 (br.dd, *J* = 5.1, 11.1 Hz, 1H, $CH_A\underline{H}_BBr$); 3.27 (br.s, 2H, CH_2N); 3.34 (s, 3H, Me); 2.02 (br.d, *J* = 12.7, 1H, $C\underline{H}_AH_BCHO$); 2.02 (m, 1H, $CH_A\underline{H}_BCHO$). ^{13}C NMR (100 MHz, DMSO-D_6) (δ, ppm): 156.15; 141.83; 141.54; 129.41 2C; 126.86 2C; 77.27; 37.65; 34.37; 24.20; 21.40. $C_{12}H_{15}BrN_2O_3S$ (347.2): calcd. C, 41.51; H, 4.35; N, 8.07; found C, 41.57; H, 4.28; N, 8.08.

***N*-[6-(Iodomethyl)-1,3-oxazinan-2-yliden]-*N*-(2-iodophenyl)amine (12d)**.

Iodine (0.93 g, 3.65 mmol) and K_2CO_3 powder (5.0 g, 36.18 mmol) were added to a solution of **11d** (1.1 g, 3.48 mmol) in DCM (25 ml). The reaction mixture was stirred for 2 h (TLC control), $Na_2S_2O_3$ solution was added and two-phase system was vigorously stirred for 20 min. Organic layer was separated, dried with Na_2SO_4 and evaporated under reduced pressure. Recrystallization from EtOAc gives **12d** (0.72, 51%) as a yellow powder, m.p. 106–108 °C. Filtrate was evaporated and passed through a short column of silica gel (EtOAc/DCM, 1:3) to give additional **12d** (0.06 g, 5%) and unreacted **11d** (0.28 g, 25%). R_f 0.32 (EtOAc/DCM, 1:3). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.74 (d, *J* = 7.9 Hz, 1H, Ar); 7.50 (d, *J* = 8.0 Hz, 1H, Ar); 7.26 (t, *J* = 7.8 Hz, 1H, Ar); 6.71 (t, *J* = 7.6 Hz, 1H, Ar); 6.45 (s, 1H, NH); 4.26–4.20 (m, 1H, CHO); 3.47–3.34 (m, 2H, CH_2N); 3.33

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(dd, *J* = 5.3, 10.5 Hz, 1H, C$\underline{H}_A$H$_B$Br); 3.26 (dd, *J* = 6.8, 10.5 Hz, 1H, CH$_A\underline{H}_B$Br); 2.18–2.12 (m, 1H, C$\underline{H}_A$H$_B$CHO); 1.89–1.79 (m, 1H, CH$_A\underline{H}_B$CHO). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 149.11; 144.75; 138.59; 128.67; 123.57; 122.41; 92.87; 75.22; 39.26; 27.00; 6.18. $C_{11}H_{12}I_2N_2O$ (442.0): calcd. C, 29.89; H, 2.74; N, 6.34; found C, 29.81; H, 2.67; N, 6.24.

***N*-(4-Bromo-2-iodophenyl)-*N*-[6-(bromomethyl)-1,3-oxazinan-2-yliden]amine (12e)**.

A solution of NBS (4.38 g, 24.6 mmol) in MeCN (40 ml) was added by syringe pump for 1h to a solution of urea **11d** (3.89 g, 12.3 mmol) in a mixture of DCM (30 ml) / THF (40 ml) at -15 °C, after then the stirring was continued at this temperature for another hour. The reaction was quenched by careful addition of $Na_2S_2O_3$ solution in water (50 ml). The mixture was diluted with water (50 ml), organic layer was separated and aqueous one exctracted with DCM (20 ml x 3). The combined extracts were dried with K_2CO_3 and evaporated. The residue was purified by FC (EtOAc/MeOH, 15:1) that gave **12e** (3.70 g, 64%) as beige solid, m.p. 124-125 °C. R_f 0.55 (EtOAc/MeOH, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 7.85 (d, *J* = 2.0 Hz, 1H, Ar); 7.32 (dd, *J* = 2.0, 8.5 Hz, 1H, Ar); 7.25 (br.d, *J* = 8.5, 1H. Ar); 6.49 (br.s, 1H, NH); 4.43-4.35 (m, 1H, CHO); 3.51-3.31 (m, 4H, CH_2Br, CH_2N); 2.15-2.07 (m, 1H, C$\underline{H}_A$H$_B$CHO); 1.97-1.84 (m, 1H, CH$_A\underline{H}_B$CHO). ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 149.3; 145.52; 140.17; 131.49; 123.70; 114.43; 94.01; 75.09; 38.75; 32.73; 25.37. $C_{11}H_{11}Br_2IN_2O$ (473.9): calcd. C, 27.88; H, 2.34; N, 5.91; found C, 27.83; H, 2.27; N, 5.88.

***N*-[6-(bromomethyl)-1,3-oxazinan-2-yliden]-*N*-methylamine (12f)**

Yield: 94% as a viscous oil, R_f 0.43 (EtOAc:MeOH, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 4.61 (br.s, 1H, NH); 4.34-4.28 (m, 1H, CHO); 3.49-3.43 (m, 1H, C$\underline{H}_A$H$_B$N); 3.44 (d, *J* = 5.7 Hz, 2H, CH_2Br); 3.36 (ddd, J = 4.8, 10.5, 14.9 Hz, 1H, CH$_A\underline{H}_B$N); 2.71 (s, 3H, NMe); 1.98 (dm, *J* = 13.6 Hz, 1H, C$\underline{H}_A$H$_B$CHO); 1.74 (dtd, *J* = 5.7, 10.5, 13.7 Hz, 1H, CH$_A\underline{H}_B$CHO). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 152.73; 74.65; 40.59; 33.56; 27.98; 26.12. $C_6H_{11}BrN_2O$ (207.0): calcd. C, 34.80; H, 5.35; N, 13.53; found C, 34.86; H, 5.32; N, 13.47.

General procedure for phenylselenocyclocarbamation. Synthesis of selenides 30a-c.

2-Methyl-*N*-{4-phenyl-6-[(phenylselanyl)methyl]-1,3-oxazinan-2-yliden}-2-propanamine (30c).

Urea **16c** (0.368 g, 1.5 mmol) was added to a stirred solution of phenylselenyl chloride (0.383 g, 2.0 mmol, 30% excess) in DCM (10 mL)/MeCN (1 ml). The reaction mixture was stirred for 10 min. *i*Pr$_2$EtN (0.258 g, 0.33 mL, 2.0 mmol) was added and the mixture was stirred for additional 2 h (TLC control) and then washed with NaOAc solution, dried with Na_2SO_4 and passed through the short pad of silica gel, washed with EtOAc/MeOH (9:1) and evaporated under reduced pressure to gave **30c** (0.51 g, 85%) as slowly solidifying oil, mixture of *cis/trans*-isomers (1.9:1),[28] R_f 0.5

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(EtOAc/MeOH, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.55-7.53 (m, 0.66x2H, Ph, cis); 7.45-7.42 (m, 0.33x2H, Ph, trans); 7.35-7.19 (m, 8H, 2Ph, cis and trans); 4.65 (t, *J* = 6.4 Hz, 0.33x1H, CHN, trans); 4.52 (dd, *J* = 4.4, 11.4 Hz, 0.66x1H, CHN, cis); 4.39 (dddd, *J* = 2.2, 6.0, 11.4, 6.7 Hz, 0.66x1H, CHO, cis); 4.12 (dtd, *J* = 4.8, 8.6, 12.1 Hz, 0.33x1H, CHO, trans); 3.82 (br.s, 1H, NH); 3.13 (dd, *J* = 8.8, 16.7 Hz, 0.33x1H, C$\underline{H}_A H_B$SePh, trans); 3.11 (dd, *J* = 6.8, 12.8 Hz, 0.66x1H, C$\underline{H}_A H_B$SePh, cis); 3.00 (dd, *J* = 5.8, 12.8 Hz, 0.66x1H, $CH_A\underline{H}_B$SePh, cis); 2.96 (dd, *J* = 8.8, 17.0 Hz, 0.33x1H, $CH_A\underline{H}_B$SePh, trans); 2.33 (ddd, *J* = 2.3, 4.6, 13.4 Hz, 0.66x1H, C$\underline{H}_A H_B$CHO, cis); 2.08 (ddd, *J* = 7.5, 11.7, 17.8 Hz, 0.33x1H, C$\underline{H}_A H_B$CHO, trans); 1.97 (dt, *J* = 4.8, 17.8 Hz, 0.33x1H, $CH_A\underline{H}_B$CHO, trans); 1.45 (dt, *J* = 11.4, 13.4 Hz, 0.66x1H, $CH_A\underline{H}_B$CHO, cis); 1.36 (s, 0.33x9H, *t*Bu trans); 1.35 (s, 0.66x9H, *t*Bu cis). MS (70 eV, EI): m/z (%) = 402/400 (M^+, 1.8/0.9); 314(15); 265(15); 189(21); 157(22); 155(15); 154(43); 147(12); 146(100); 145(18); 132(16); 129(25); 128(16); 117(29); 115(18); 106(70); 105(36); 104(41); 91(18); 79(22); 78(13); 77(49); 58(32); 51(14). HRMS (ESI): calcd. for $C_{21}H_{26}N_2OSe$ (M+H) 403.1283, found: 403.1284.

***N*-{6-[(Phenylselanyl)methyl]-1,3-oxazinan-2-yliden}-1-adamantanamine (30a)**.

Yield: 73% as a colorless solid, m.p. 95-97 °C. R_f 0.15 (EtOAc/*i*PrOH/Et_3N, 14:7:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.56-7.50 (m, 2H, Ph); 7.32-7.22 (m, 3H, Ph); 4.28-4.19 (m, 1H, CHO); 3.38 (ddd, *J* = 3.0, 5.9, 14.9 Hz, 1H, C$\underline{H}_A H_B$N); 3.30 (ddd, *J* = 5.1, 10.5, 14.9 Hz, 1H, $CH_A\underline{H}_B$N); 3.16 (dd, *J* = 7.0, 12.7 Hz, 1H, C$\underline{H}_A H_B$SePh); 3.03 (dd, *J* = 5.9, 12.7 Hz, 1H, $CH_A\underline{H}_B$SePh); 2.07 (narrow m, 3H, 3CH Ad); 2.01-1.95 (m, 1H, C$\underline{H}_A H_B$CHO); 1.93-1.92 (m, 6H, $3CH_2$ Ad); 1.71-1.61 (m, 7H, $CH_A\underline{H}_B$CHO and $3CH_2$ Ad). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 151.27; 132.87 2C; 129.76; 129.11 2C; 127.18; 74.66; 50.77; 42.46 3C; 41.41; 36.34 3C; 32.31; 29.15 3C; 27.73. ^{77}Se NMR (95 MHz, $CDCl_3$) (δ, ppm): 264.44. HRMS Calcd for $C_{21}H_{28}N_2OSe$: 405.1440(M+H). Found: 405.1430 (MH^+).

***N*-{4,4-Dimethyl-6-[(phenylselanyl)methyl]-1,3-oxazinan-2-yliden}-1-adamantanamine (30b)**.

Yield: 81% as a colorless solid, m.p. 176-177 °C. R_f 0.54 (EtOAc/*i*PrOH, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.88 (br.s, 1H, NH); 7.48-7.46 (m, 2H, Ph); 7.26-7.25 (m, 3H, Ph); 4.49-4.43 (m, 1H, CHO); 3.16 (dd, *J* = 7.2, 13.0 Hz, 1H, C$\underline{H}_A H_B$SePh); 3.07 (dd, *J* = 5.1, 13.0 Hz, 1H, $CH_A\underline{H}_B$SePh); 2.03-2.01 (m, 4H, 11H, C$\underline{H}_A H_B$CHO and 3CH Ad); 1.97-1.88 (m, 6H, $3CH_2$ Ad); 1.69 (dd, *J* = 12.2, 13.6 Hz, 1H, $CH_A\underline{H}_B$CHO); 1.58 (narrow m, 6H, $3CH_2$ Ad); 1.36 (s, 3H, Me); 1.25 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 156.81; 133.34 2C; 129.43 2C; 128.11; 128.00; 76.11; 54.23; 50.46; 41.54 3C; 39.63; 35.67 3C; 30.80; 29.75; 29.16 3C; 28.97. ^{77}Se NMR

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(95 MHz, $CDCl_3$): δ 269.35. HRMS Calcd for $C_{23}H_{32}N_2OSe$: 433.1754 (M+H). Found: 433.1739 (MH^+).

General procedure of selenides 30a-c oxidation to selenoxides and their thermal elimination with formation of enolesters 31a-c.

***N*-(Adamantan-1-yl)-6-methylene-1,3-oxazinan-2-imine (31a).**

A solution of $NaIO_4$ (0.44 g, 2.28 mmol) in water (5 mL) was added to a mixture of **30a** (0.31 g, 0.76 mmol) in MeOH/DCM (3:2, 10 mL) at 0 °C. The reaction mixture was stirred for 20 min (TLC control). The mixture was diluted with DCM (20 ml) and saturated solution of NH_4Cl (20 ml). The organic phase was separated and aqueous phase extracted with DCM (2x10 mL). The combined extracts were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The selenoxide was dissolved in dioxane (10 mL) and heated with stirring for 1h at 70 °C. The solvent was evaporated and the residue was purified by FC on silica gel in EtOAc/*n*-C_6H_{14}/Et_3N (10:10:1) to give **31a** (0.025 g, 13%) as a beige solid, m.p. 114-116 °C. R_f 0.63 (EtOAc/*n*-C_6H_{14}//Et_3N, 10:10:1). ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 4.42 (s, 1H, $C\underline{H}_AH_B$=); 4.09 (s, 1H, $CH_A\underline{H}_B$=); 3.32 (t, *J* = 6.0 Hz, 2H, CH_2N); 2.36 (t, *J* = 6.0 Hz, 2H, CH_2CHO); 2.04 (narrow m, 3H, 3CH Ad); 1.92 (narrow m, 6H, $3CH_2$ Ad); 1.63 (narrow m, 6H, $3CH_2$ Ad). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 154.08; 148.76; 89.43; 51.11; 42.23 3C; 41.29; 36.34 3C; 29.43 3C; 26.16. $C_{15}H_{22}N_2O$ (246.4): calcd. C, 73.13; H, 9.00; N, 11.37; found C, 73.19; H, 9.12; N, 11.26.

***N*-(Adamantan-1-yl)-4,4-dimethyl-6-methylene-1,3-oxazinan-2-imine (31b)**.

Yield: 32% as a white solid, m.p. 95-97 °C. R_f 0.66 (EtOAc/*n*-C_6H_{14}/Et_3N, 10:10:1). ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 4.50 (s, 1H, $C\underline{H}_AH_B$=); 4.09 (narrow m, 1H, $CH_A\underline{H}_B$=); 2.18 (s, 2H, $C\underline{H}_2CHO$); 2.03 (narrow m, 3H, 3CH Ad); 1.90 (narrow m, 6H, $3CH_2$ Ad); 1.63 (narrow m, 6H, $3CH_2$ Ad); 1.11 (s, 6H, 2Me).^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 153.11; 147.92; 90.47; 51.11; 49.46; 42.49 3C; 39.00; 36.40 3C; 29.80 2C; 29.56 3C. $C_{17}H_{26}N_2O$ (274.4): calcd. C, 74.41; H, 9.55; N, 10.21; found C, 74.25; H, 9.62; N, 10.27.

***N*-(*tert*-Butyl)-*N*-(6-methylene-4-phenyl-1,3-oxazinan-2-yliden)amine (31c)**.

Yield: 18% as oil. R_f 0.66 (EtOAc/MeOH, 9:1). ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.34-7.33 (m, 4H, Ph); 7.27-7.21 (m, 1H, Ph); 4.57 (dd, *J* = 4.5, 9.2 Hz, 1H, CHN); 4.49 (s, 1H, $C\underline{H}_AH_B$=); 4.19 (br. s, 1H, NH); 4.09 (s, 1H, $CH_A\underline{H}_B$=); 2.74 (dd, *J* = 4.5, 14.2 Hz, 1H, $C\underline{H}_AH_BCHO$); 2.26 (dd, *J* = 9.2, 14.2 Hz, 1H, $CH_A\underline{H}_BCHO$); 1.40 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 153.02 C; 148.47 C; 144.47 C; 128.24 2CH; 126.69 CH; 126.26 2CH; 90.28 C; 54.80 CH; 50.75 C; 35.03 CH_2; 29.23 $3CH_3$. MS (70 eV, EI): m/z (%) = 244 (M^+, 11); 202(6); 189(11); 188(33);

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146(20); 145(18); 105(15); 104(100); 103(17); 78(28); 77(22); 32(13). $C_{15}H_{20}N_2O$ (244.3): calcd. C, 73.74; H, 8.25; N, 11.47; found C, 73.81; H, 8.17; N, 11.37.

***N*-(1-Adamantyl)carbodiimide (32a)**.

*t*BuOK (0.168 g, 1.5 mmol) was added to a solution of **31b** (0.274 g, 1.0 mmol) in THF (10 mL) at -30 °C and stirred for 10 min, TLC shows immediate disappearance of the starting **31b**. The reaction mixture was quenched with AcOH (0.108 ml, 1.8 mmol), filtered through a pad of silica gel, washed with EtOAc/*n*-C_6H_{14} (3 x 20 mL), evaporated and subjected to FC on silica gel to yield **32a** (177 mg, 100%) as a white solid, m.p. 136-138 °C. R_f 0.7 (EtOAc/*n*-C_6H_{14}/Et_3N, 10:10:1).^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 3.40 (1H, s), 2.22-2.12 (3H, m), 1.84-1.78 (6H, m), 1.68 (6H, m). ^{13}CNMR (100 MHz, $CDCl_3$) (δ, ppm): 114.17; 52.97; 42.37 3C; 35.64 3C; 29.43 3C. MS (70 eV, EI): m/z (%) = 177 (30, MH^+); 176(1, M^+); 136(11); 135(100); 108(12); 107(37); 93(79); 92(11); 91(41); 81(24); 80(87); 77(43); 67(24); 51(11); 44(14); 39(15); 28(11). HRMS Calcd for $C_{11}H_{16}N_2$: 177.1386(M+H). Found: 177.1394(MH^+).

General procedure of ADPs synthesis from bromourethanes.

2-Methoxyethyl *N*-(4-oxo-1,4,5,6-tetrahydro-2-pyridinyl)carbamate (13a).

A solution of bromide **12a** (0.30 g, 1.0 mmol) in dry DMF (2 ml) was treated with *t*BuOK (0.34 g, 3.0 mmol) at 25 °C and the mixture was stirred for 15 min, when TLC control shows no more starting material, then AcOH (0.15 ml, 2.5 mmol) was added to acidify the potassium salt of **13a**. The mixture was passed through the pad of Super Cel, volitiles were evaporated in vacuum and the residue was subjected to FC on silica gel (EtOAc/MeOH, 9:1) that furnished **13a** (0.206 g, 96%) as crystalline solid, m.p. 145-146 °C. R_f 0.52 (EtOAc/MeOH, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 9.84 (br.s, 1H, NH); 7.89 (s, 1H, NH); 4.88 (d, *J* = 1.4 Hz, 1H, CH=); 4.27-4.24 (m, 2H, CH_2OC=O); 3.60-3.57 (m, 2H, CH_2OMe); 3.51 (td, *J* = 2.2, 7.5 Hz, 2H, CH_2N); 3.33 (s, 3H, OMe); 2.37 (t, *J* = 7.6 Hz, 2H, CH_2C=O). ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 191.24; 158.31; 154.17; 86.00; 70.10; 64.41; 58.63; 40.39; 34.56. $C_9H_{14}N_2O_4$ (214.2): calcd. C, 50.46; H, 6.59; N, 13.08; found C, 50.44; H, 6.58; N, 13.14.

6-(2-Iodoanilino)-2,3-dihydro-4(1H)-pyridinone (13d).

Transformation of iodide **12d** was carried out in *i*PrOH at 25 °C for 3h. Yield **13d**: 55%, as light-yellow solid, m.p. 213-214 °C (EtOAc). R_f 0.19 (EtOAc/MeOH, 6:1). ^{1}H NMR (400 MHz, DMSO-D_6) (δ, ppm): 8.18 (s, 1H, NH); 7.90 (d, *J* = 7.9 Hz, 1H, Ar); 7.40 (t, *J* = 7.0 Hz, 1H, Ar); 7.26 (d, *J* = 7.8 Hz, 1H, Ar); 7.00 (t, *J* = 7.0 Hz, 1H, Ar); 6.62 (s, 1H, NH); 4.13 (s, 1H, CH=); 3.37–3.28 (m, 2H, CH_2N); 2.09 (t, *J* = 7.0 Hz, 2H, CH_2C=O). ^{13}C NMR (100 MHz, DMSO-D_6) (δ, ppm): 187.80,

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160.39, 139.78, 139.33, 129.11, 127.77, 127.75, 98.33, 82.10, 39.73, 35.45. $C_{11}H_{11}IN_2O$ (314.1): calcd. C, 42.06; H, 3.53; N, 8.92; found C, 42.05; H, 3.60; N, 8.85.

6-(4-Bromo-2-iodoanilino)-2,3-dihydro-4(1H)-pyridinone (13e).

The reaction was carried out in *i*PrOH at 40 °C for 1h. Yield: 98%, as brown powder, m.p. 197-200 °C (dec.) (EtOAc/DCM). R_f 0.36 (EtOAc/MeOH, 9:1). ^{1}H NMR (600 MHz, DMSO-D_6) (δ, ppm): 8.24 (s, 1H, NH); 8.07 (s, 1H, Ar); 7.57 (d, *J* = 7.8 Hz, 1H, Ar); 7.19 (d, *J* = 8.2 Hz, 1H, Ar); 6.67 (s, 1H, NH); 4.18 (s, 1H, CH=); 3.32-3.30 (m, 2H, CH_2N); 2.10-2.08 (m, 2H, CH_2C=O). ^{13}C NMR (150 MHz, DMSO-D_6) (δ, ppm): 187.98 C; 160.07 C; 140.76 CH; 139.56 C; 131.99 CH; 128.90 CH; 118.80 C; 99.58 C; 82.41 CH; 39.66 CH_2; 35.43 CH_2. $C_{11}H_{10}BrIN_2O$ (393.0): calcd. C, 33.62; H, 2.56; N, 7.13; found C, 33.59; H, 2.70; N, 7.16.

6-(Methylamino)-2,3-dihydro-4(1H)-pyridinone (13f).

The reaction was carried out in THF at 25 °C for 1h. Yield: 95%, as white solid, m.p. 218-219 °C (EtOAc/MeCN). R_f 0.24 (EtOAc/MeOH, 2:1). ^{1}H NMR (500 MHz, DMSO-D_6) (δ, ppm): 6.75 (br.s, 1H, NH); 6.72 (br.s, 1H, NH); 4.23 (s, 1H, CH=); 3.23 (t, *J* = 7.1 Hz, 2H, CH_2N); 2.61 (d, *J* = 4.9 Hz, 3H, CH_3N); 2.03 (t, *J* = 7.2 Hz, 2H, CH_2C=O). ^{13}C NMR (125 MHz, DMSO-D_6) (δ, ppm): 186.71; 163.52; 80.54; 40.29; 35.76; 28.19. HRMS Calcd for $C_6H_{10}N_2O$: 127.0866 (M+H). Found: 127.0863 (MH^+).

Ethyl (4-oxo-6-phenyl-1,4,5,6-tetrahydropyridin-2-yl)carbamate (18a).

The reaction was carried out in THF at 25 °C for 1h. Yield: 95%, as white powder, m.p. 188-189 °C (dec.). R_f 0.13 (EtOAc). ^{1}H NMR (400 MHz, DMSO-D_6) (δ, ppm): 10.28 (s, 1H, NH); 7.86 (s, 1H, NH); 7.40-7.31 (m, 5H, Ph); 4.81-4.77 (m, 2H, CHPh and CH= cycle); 4.14 (q, *J* = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$); 2.46-2.38 (m, 2H, CH_2C=O); 1.23 (t, *J* = 7.0 Hz, 2H, $OCH_2C\underline{H}_3$). ^{13}C NMR (100 MHz, DMSO-D_6) (δ, ppm): 188.78; 157.14; 154.17; 141.39; 129.12 2C; 128.20; 126.80 2C; 85.85; 62.02; 55.26; 43.24; 14.61. $C_{14}H_{16}N_2O_3$ (260.3): calcd. C, 64.60; H, 6.20; N, 10.76; found C, 64.58; H, 6.27; N, 10.78.

Benzyl (4-oxo-6-phenyl-1,4,5,6-tetrahydropyridin-2-yl)carbamate (18b).

The reaction was carried out in THF at 40 °C for 40 min. Yield: 98%, as white powder, m.p. 82-83 °C. R_f 0.2 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 10.11 (br.s, 1H, NH); 8.24 (s, 1H, NH); 7.40-7.28 (m, 10H, 2Ph); 5.17 (d, *J* = 12.3 Hz, 1H, $C\underline{H}_AH_BPh$); 5.13 (d, *J* = 12.3 Hz, 1H, $CH_A\underline{H}_BPh$); 5.05 (s, 1H, CH= cycle); 4.71 (dd, *J* = 4.8, 14.1 Hz, 1H, $C\underline{H}Ph$); 2.65 (dd, *J* = 14.1, 16.4 Hz, 1H, $C\underline{H}_AH_BC$=O); 2.48 (dd, *J* = 4.8, 16.4 Hz, 1H, $CH_A\underline{H}_BC$=O). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 190.26; 158.64; 154.30; 139.70; 135.01; 128.98 2C; 128.53 2C; 128.46; 128.36;

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128.03 2C; 126.44 2C; 86.18; 67.63; 56.79; 42.95. $C_{19}H_{18}N_2O_3$ (322.4): calcd. C, 70.79; H, 5.63; N, 8.69; found C, 70.77; H, 5.49; N, 8.59.

***rac*- and (*S*)-6-(Methylamino)-2-phenyl-2,3-dihydro-4(1H)-pyridinone (18d) and ((*S*)-18d)**.

The reaction was carried out in THF at 25 °C for 30 min. Yield: 96%, as white powder, **18d**: m.p. 205-206 °C; **(*S*)-18d**: m.p. 222-223 °C; $[\alpha]_D^{25}$ –32.2 (C 0.5, MeOH). R_f 0.30 (EtOAc/MeOH, 4:1). ^{1}H NMR (400 MHz, DMSO-D_6) (δ, ppm): 7.36-7.30 (m, 4H, Ph); 7.26-7.23 (m, 1H, Ph); 6.71 (br.s, 1H, NH); 6.35 (br.s, 1H, NH); 4.57 (dd, *J* = 7.2, 8.2 Hz, 1H, CHPh); 4.26 (s, 1H, CH=); 2.63 (d, *J* = 4.8 Hz, 3H, NMe); 2.28 – 2.18 (m, 2H, CH_2C=O). ^{13}C NMR (100 MHz, DMSO-D_6) (δ, ppm): 185.36 br.; 162.97; 142.33; 128.40 2C; 127.36; 126.51 2C; 79.67 br.; 55.17; 43.77; 28.05. $C_{12}H_{14}N_2O$ (202.3): calcd. C, 71.26; H, 6.98; N, 13.85; found C, 71.37; H, 7.11; N, 13.74.

6-(2-Chlorophenylamino)-2-allyl-2,3-dihydro-2-phenylpyridin-4(1H)-one (22a).

The reaction was carried out in *i*PrOH at 45 °C for 4h. Yield: 89%, as white solid, m.p. 208-209 °C. R_f 0.23 (EtOAc/MeOH, 10:1). ^{1}H NMR (600 MHz, DMSO-D_6) (δ, ppm): 8.33 (s, 1H, NH); 7.59 (d, *J* = 7.7 Hz, 1H, Ar); 7.45-7.37 (m, 6H, Ph, Ar); 7.29 (t, *J* = 6.8 Hz, 1H, Ar); 7.25 (t, *J* = 6.9 Hz, 1H, Ar); 7.10 (s, 1H, NH); 5.56-5.49 (m, 1H, CH=, allyl); 5.18-5.14 (m, 2H, CH_2= allyl); 4.18 (s, 1H, CH=); 2.72-2.63 (m, 4H, CH_2 allyl and CH_2C=O). ^{13}C NMR (100 MHz, DMSO-D_6) (δ, ppm): 187.51, 159.46, 144.33, 135.66, 133.16, 130.45, 128.62 2C, 128.27, 128.25, 127.28, 127.27, 126.93, 125.85 2C, 120.10, 82.46, 60.59, 47.06, 46.36. $C_{20}H_{19}ClN_2O$ (338.8): calcd. C, 70.90; H, 5.65; N, 8.27; found C, 70.74; H, 5.66; N, 8.19.

6-(*tert*-Butylamino)-2-phenyl-2-prop-2-en-1-yl-2,3-dihydropyridin-4(1H)-one (22c).

To a solution of enolester **27a** (0.284 g, 1.0 mmol) in THF (4 ml) was added *t*BuOK (0.168 g, 1.5 mmol) at -30 °C and the mixture was stirred for 1h at this temperature. Then AcOH (0.108 ml, 1.8 mmol) was added for neutralization, the mixture was filtered through the pad of Super Cel, evaporated and the solid residue was recrystallized from *n*-C_6H_{14}/Et_2O to give **22c** (0.204 g, 72%) as white powder, m.p. 121-122 °C (*n*-C_6H_{14}/Et_2O). R_f 0.12 (EtOAc/MeOH, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.58 (br.s, 1H, NH); 7.31-7.23 (br.m, 6H, Ph and NH); 5.47 (br.s, 1H, CH= allyl); 4.97 (br. s, 2H, CH_2= allyl); 4.80 (br.s, 1H, CH=); 2.74 (br.s, 2H, CH_2 cycle); 2.55 (br.s, 2H, CH_2 allyl); 1.27 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 184.69 br.; 161.73; 143.78; 132.23; 128.28 2C; 126.81; 125.27 2C; 119.58; 84.08; 59.74; 51.39; 46.85; 44.41 br.; 29.88 3C. $C_{18}H_{24}N_2O$ (284.4): calcd. C, 76.02; H, 8.51; N, 9.85; found C, 75.98; H, 8.55; N, 9.82.

2-Phenyl-2-prop-2-en-1-yl-6-(prop-2-en-1-ylamino)-2,3-dihydropyridin-4(1H)-one (22d).

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Yield: 85% as oil. R_f 0.25 (EtOAc/MeOH, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.76 (br.s, 1H, NH); 7.66 (br.s, 1H, NH); 7.30-7.18 (m, 5H, Ph); 5.75-5.66 (m, 1H, CH= Nallyl); 5.50-5.40 (m, 1H, CH= allyl); 5.13 (d, *J* = 17.0 Hz, 1H, C$\underline{H}_A H_B$= Nallyl); 5.07 (d, *J* = 10.2 Hz, 1H, $CH_A\underline{H}_B$= Nallyl); 5.01-4.97 (m, 2H, CH_2= allyl); 4.60 (br.s, 1H, CH= cycle); 3.59 (br.s, 2H, CH_2N); 2.74 (s, 2H, CH_2C=O); 2.59-2.49 (m, 2H, CH_2 allyl). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 185.45; 162.82; 143.82; 132.24; 132.08; 128.26 2C; 126.93; 125.19 2C; 119.61; 116.58; 81.42; 59.84; 46.50; 44.38; 44.28. $C_{17}H_{20}N_2O$ (268.4): calcd. C, 76.09; H, 7.51; N, 10.44; found C, 76.14; H, 7.48; N, 10.42.

2-Allyl-6-(methylamino)-2-phenyl-2,3-dihydropyridin-4(1H)-one (22e).

Yield: 48% as yellow solid, m.p. 83-84 °C. R_f 0.2 (EtOAc/MeOH, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.28-7.15 (m, 7H, 2NH and Ph); 5.50-5.39 (m, 1H, CH= Nallyl); 5.01-4.96 (m, 2H, CH_2= allyl); 4.54 (br.s, 1H, CH= cycle); 2.75 (d, *J* = 16.6 Hz, 1H, C$\underline{H}_A H_B$C=O); 2.70 (d, *J* = 16.6 Hz, 1H, $CH_A\underline{H}_B$C=O); 2.63 (s, 3H, NMe); 2.56 (dd, *J* = 6.7, 14.0 Hz, 1H, C$\underline{H}_A H_B$ allyl); 2.51 (dd, *J* = 8.3, 14.0 Hz, 1H, $CH_A\underline{H}_B$ allyl). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 186.27; 163.30; 143.84; 132.31; 128.33 2C; 126.96; 125.29 2C; 119.61; 80.85; 59.93; 46.52; 45.38; 28.53. $C_{15}H_{18}N_2O$ (242.3): calcd. C, 74.35; H, 7.49; N, 11.56; found C, 74.27; H, 7.53; N, 11.48.

Kinetic experiment of rate constant determination of rearrangement 19 to 18b.

*t*BuOK (7.8 mg, 0.0694mmol) was added to a solution of **19** (11.2 mg, 0.0347) in dry DMSO-D_6 (0.55 mL) in a NMR tube. Reaction mixture was analyzed by ^{1}H NMR (20 scans per hour) at 20.5 °C. The integration was performed for the peaks at δ = 2.75 ppm (for **19**) and δ = 7.16 ppm (for t-BuPh (internal standard)).

X-ray structures determination.

The X-ray crystal structure analyses were made on Bruker SMART APEX2 CCD (**21a** and **22a**; MoK_α radiation, graphite monochromator, φ and ω scan mode). The data sets were corrected for absorption with SADABS[29] and crystal structures were solved with the ShelXT[30] structure solution program using Direct Methods and refined with the ShelXL[30,31] refinement package using Least Squares minimization. Non-hydrogen atoms were refined anisotropically. The absolute structures were defined by the refinement of the Flack parameters. The hydrogen atoms of the amino groups were localized in the difference-Fourier maps and refined isotropically with displacement parameters [U_{iso}(H) = 1.2U_{eq}(N)]. The other hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.2U_{eq}(C)].

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	21a	**22a**
Empirical formula	$C_{20}H_{20}N_2OClBr$	$C_{20}H_{19}N_2OCl$
Formula weight	419.74	338.82
T, K	100	100
Crystal system	triclinic	orthorhombic
Space group	P-1	$P2_12_12_1$
Z	4	4
a, Å	10.5960(8)	6.684(2)
b, Å	13.0323(10)	11.847(4)
c, Å	15.0398(11)	22.594(7)
α, °	89.548(2)	66.112(2)
β, °	69.846(2)	84.616(2)
γ, °	82.380(2)	83.113(2)
V, $Å^3$	1930.9(3)	1789.1(9)
d_{calc}, г/см^3	1.444	1.258
μ, см$^{-1}$	2.277	0.222
F(000)	856	712
$2\theta_{max}$, °	60.0	52.2
Reflections collected	25436	17046
Independent reflections	11212	3541
Reflections wth I>2σ(I)	7918	1680
Parameters	185	211
R1	0.049	0.061
wR2	0.125	0.150
GOF	1.001	1.000
Flack	-	0.10(14)

*Parsons`s quotient[32]

Crystallographic data for the investigated compounds have been deposited with the Cambridge Crystallographic Data Center, CCDC 1440015 (**21a**) and CCDC 1440016 (**22a**). Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

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Supporting Information (see footnote on the first page of this article): Experimental details, copies of the ^{1}H and ^{13}C NMR spectra, HPLC traces, and selected crystallographic data.

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