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One-pot and catalyst-free amidation of ester: a matter of non-bonding interactions

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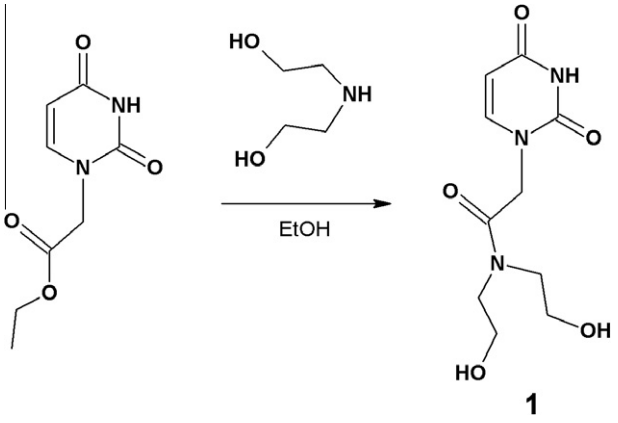
ABSTRACT

This paper describes a one-pot procedure for acetamide synthesis directly from amines and pyrimidine ester, without any catalyst or coupling agents. The inexpensive and simple reaction conditions are the most important features of this amidation. This reaction was performed with various amines, showing that long range stabilizing interactions (H-bonding and π-stacking) are the driving force for chemoselectivity.

C–N bonds are widely present in natural (DNA, peptides, tetrapyrrolic macrocycles, etc.) as well as in synthetic products.[1] Amide bonds exemplified these bonds, being found in many synthetic substances as intermediates or as active pharmaceutical products or prodrugs.[2] However its formation remains a challenging issue of organic synthesis. The process for the formation of amide bonds from esters involves hydrolysis of the ester followed by the conversion of carboxylic acid to a more reactive functional group or in situ activation by using coupling agents (BOP, DCC, NHS, HBTU, HOBt or ByBOP).[3] Both chemical and enzymatic methods for direct amidation of esters were reported in the literature.[4] In most of these methods, complexes of amine derived from strong bases or acids are used,[5] such as Grignard or alkylaluminium reagents.[6] Due to their corrosive nature, expensive reagents, and formation of by-products, these methods are not amenable for large scale reactions.

We recently developed a new and simple method for the amidation of pyrimidine esters in the field of mustard derivatives.[7] Directly from uracil acetate and diethanolamine, by refluxing and without any catalyst, we obtained an acetamide derivative of the nucleic acid. This process appears as an easy and 'green' procedure providing the final product with high yields and selectivity, as no esterification reaction was observed.



Scheme 1. Direct amidation of uracil ester with diethanolamine.

Here we propose to extend this methodology for the amidation of uracil acetate with a series of amine derivatives and to determine the favoring factors.

A preliminary study using uracil ester and diethanolamine has been conducted in ethyl alcohol (Scheme 1).

The influence of the concentration of diethanolamine (from large excess to equimolar ratio) was first investigated (Table 1). Large excess of amine gives the product in high yields and within relatively short time in refluxing ethanol (entry 1). In order to re-

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Table 1
Influence of diethanolamine amount and activation

Entry	Diethanolamine (equiv)	Activation	Reaction time (h)	Isolated yield (%)
1	10	Δ	24	94
2	1.5	Δ	96	80
3	1.2	Δ	96	75
4	1.02	Δ	144	90
5	1.02	Ultrasound	10	70
6	1.02	Microwave	13	55

duce such large quantities of amine (especially when it is not commercial), and because the further purification is awkward with a large reactant concentration, the amidation reaction was tested with lower and more reasonable excesses of amine (entries 2 and 3). These conditions appear as adequate compromises as the reaction also provided the final product in high yields. An equimolar amount of amine (entry 4) also gives product **1** in a similar yield with respect to entry 1. Nonetheless for entries 2, 3, and 4, the reaction time was significantly increased.

The influence of two activation processes was investigated under equimolar conditions. Compared to classical heating, ultrasound activation (entry 5) and microwave irradiations (entry 6) dramatically reduced the reaction times, but also the yields, particularly in the case of microwave activation.

This preliminary study confirms that a stoichiometric amount of diethanolamine (1.02 equiv) is sufficient to afford the final product in high yield and reasonable reaction times in refluxing ethyl alcohol after only recrystallization from ethanol.

To validate this method of catalyst-free amidation in refluxing ethanol, a series of primary and secondary amines were tested under these experimental conditions (Table 2).

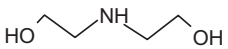
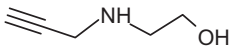
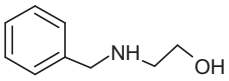
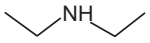
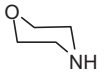
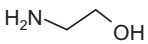
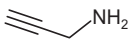
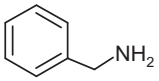
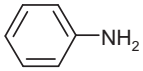
This easy method can be used for a range of amines providing relatively high yields (Table 2, entries 1, 3, 5, 6 and 8). The process surprisingly appears chemoselective. The presence of one to two hydroxyethyl groups on the nitrogen of amine (compounds **1**, **3** and **6**) significantly enhances yields and decreases reaction time with respect to the compounds without this moiety (compounds **4**, **5**, **7**, **8** and **9**).

To rationalize chemoselectivity, 3D conformations of reactants and products, and Gibbs energy of reaction were calculated at the quantum level.[10] The best stability observed with compound **1** is explained by the existence of two H-bonds, giving a stabilizing Gibbs energy of -6.8 kcal mol^{-1}, rationalizing a yield of 90%. The hydroxyl ethyl group can form two H-bonds, a weak H-bond with the uracil carbonyl moiety (2.07 Å) and a stronger bond with the carbonyl group of the amide function (1.83 Å) (Fig. 1a).

For compound **6**, only one H-bond can be formed preferentially between the hydroxyethyl group and the carbonyl group of the amide bond (Fig. 1b), as the H-bond is weaker with the uracil carbonyl moiety (1.83 Å vs 2.06 Å, respectively). This compound is slightly less stable than compound **1**. Nonetheless due to the presence of a strong H-bond it still exhibits high stability ($\Delta G = -6.2$ kcal mol^{-1}). No H-bond can be formed in compound **4** which explains non-product formation ($\Delta G^\circ = -2.4$ kcal mol^{-1}).

Surprisingly the formation of compound **8** is favored (60% yield). In this case no H-bond is expected and may explain stabilization. Nevertheless the compound is stabilized by π-stacking interaction between the aromatic rings (Fig. 1c). The flexibility of the molecule allows an optimized parallel displaced stack between both aromatic rings (Fig. 1c), thus stabilizing the final compound ($\Delta G^\circ = -4.4$ kcal mol^{-1}) by dispersive interactions. Such stabilizing interactions are also observed in compound **3** ($\Delta G^\circ = -6.0$ kcal mol^{-1}), for which the concomitant presence of one H-bond with the carbonyl group of the amide bond (Fig. 1d) explains the efficient 70% yield.[9] For compound **8**, π-stacking is the only driving force for amidation. This influences the reaction time which is signifi-

Table 2
Direct amidation of different amines[8,11]

Entry	Amine	Reaction time (days)	Compound	Isolated yields (%)	ΔG°[10] (kcal mol^{-1})
1		6	**1**	**90**	−6.8
2		22	**2**	**10**	−3.2
3		9	**3**	**70**	−6.0
4		34	**4**	—[a]	−2.4
5		11	**5**	**46**	−3.9
6		6	**6**	**70**	−6.2
7		34	**7**	—[a]	−2.6
8		20	**8**	**60**	−4.4
9		15	**9**	—[a]	2.5

[a] TLC did not show any evolution of reaction.

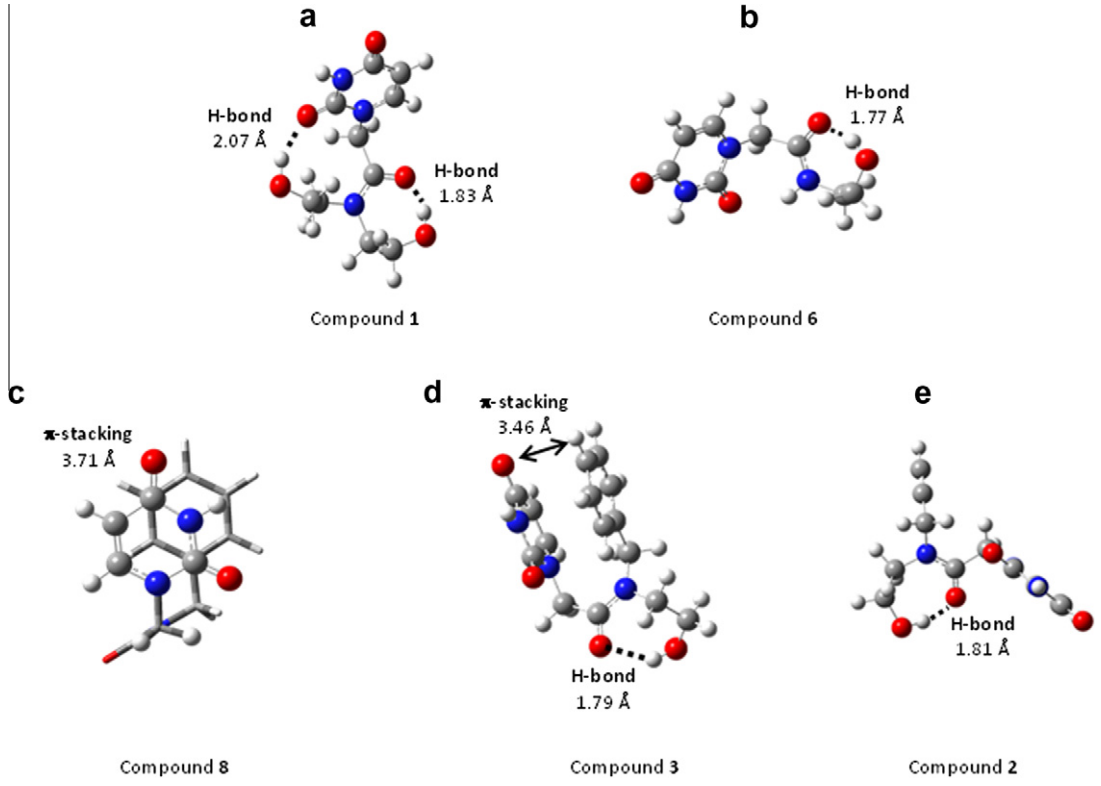


Figure 1. 3D conformation of compounds **1** (a), **6** (b), **8** (c), **3** (d) and **2** (e) exhibiting non-bonding interactions. For compound **8** (c) the view is perpendicular to the plane defined by both aromatic rings, the upper ring (uracil moiety) being drawn in balls & cylinders while the lower ring is in sticks.

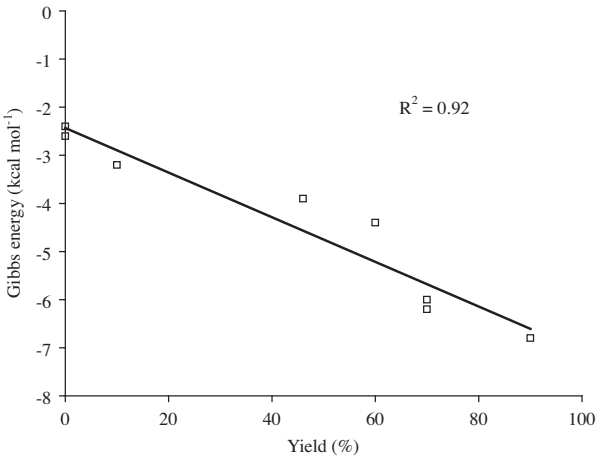


Figure 2. Correlation between Gibbs energies of reaction (ΔG°) and experimental yields. The regression coefficient is obtained without taking compound **9** into account (see footnote 12).

cantly higher than for compounds having also H-bond as a driving force (e.g., 20 vs 9 days for compounds **8** and **3**, respectively).

For compound **9**, three reasons may explain the positive ΔG° (Table 2): (i) the flexibility of the aniline moiety does not allow the formation of π-stacking complexes, (ii) no H-bond can be formed, (iii) the doublet of the amine is delocalized over the aromatic ring, being less available for the reaction.

The amidation reaction with propargylamine did not occur after 34 days of reaction (entry 7); while it is completed with *N*-propargylethanolamine (entry 2) within 22 days, but at a low 10% yield. The absence or non-efficiency of the amidation reaction in these cases is mainly attributed to the dramatic increase of steric hindrance due to the alkyne group, preventing molecular flexibility (Fig. 1e) hence producing less of stable compounds ($\Delta G^\circ = -2.6$ and -3.2 kcal mol^{-1} for both compounds, respectively).

Reaction with the secondary cyclic amine, morpholine (entry 5), exhibited 46% yield. This efficient yield cannot be explained by H-bonding and π-stacking, however the calculations confirm the formation of a relatively stable compound ($\Delta G^\circ = -3.9$ kcal mol^{-1}). In this particular case, nucleophilicity of this cyclic amine is more probably the major descriptor explaining reaction feasibility.

A series of pyrimidine esters have been synthesized by a simple and very convenient amidation in refluxing ethanol. The yields are very promising thus highlighting the relevancy of this method to obtain amides easily and with a variety of amines. The avoidance of corrosive reactants or coupling agents is the main benefit of this procedure. All final products were obtained by a simple recrystallization from ethyl alcohol. A surprising chemoselectivity has been observed, which has been rationalized by the presence of intramolecular stabilizing effects attributed to long range interactions, H-bonding, and π-stacking. We have also shown that the method of calculation must be carefully chosen in order to fit with experimental data, the use of recent functionals including dispersive effects is mandatory.[10] The correlation between the calculated ΔG° and the experimental yields is particularly noteworthy. Taking all nine compounds into account, the regression coefficient between both parameters is around 0.7; excluding compound **9**[12] it is higher than 0.9 (Fig. 2).

Supplementary data

Supplementary data (Gibbs energies of reaction obtained with a series of DFT functionals including more or less HF (Hartree-Fock)

exchanges and non-bonding corrections) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.043.

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8. *General procedure* (Table 2): 1-Ethoxycarbonyluracil (100 mg, 0.5 mmol) in ethanol (3 mL), at 70 °C. Amine (1.02 equiv) was then added after dissolution of the alkylated uracil. Products have been obtained by a simple recrystallization from ethanol.
9. Compound **3**, actually exhibits three conformers with very similar energies having (i) one H-bond between the hydroxyethyl group and the carbonyl group of the amid bond, (ii) π-stacking stabilization as for compound **8** and (iii) combination of both. Disregarding the comparison obtained from calculations which must be very accurate to discriminate relative stabilities, here we believe that the third is the most probable conformer in solution.
10. Calculations were performed at the DFT (density functional theory) level using functionals introducing dispersive corrections. Both wB97XD and B3LYP-D were used and provided the same trend. The classical hybrid functionals do not allow providing accurate results due to the importance of H-bond and non-bonding interaction in this study. Only the results obtained with wB97XD are shown in Table 2. Results obtained with the other functional are given as Supplementary data. The 6–31+G(d,p) basis set was used. The conformational analysis was carefully performed at the DFT level, scanning flexible torsion angles. The lowest energy conformers (ground-state geometries) were confirmed by vibrational frequency analysis that indicated the absence of imaginary frequencies. The solvent effects were implicitly taken into account with the PCM (polarizable continuum model) method, in which the solute is embedded in a shape-adapted cavity surrounding by a dielectric continuum characterized by its dielectric constant. Ethanol is a relatively good HBA (H-bond acceptor) solvent, which probably allows specific non-bonding intermolecular interaction (between solute and solvent). It is known that such solvent effect can influence mainly kinetics of the reactions involving the H-atom engaged in these intermolecular H-bonds (Litwinienko, G.; Ingold, K. U. *Acc. Chem. Res.* **2007**, *40*, 222–230) according to the β_2^H Abraham's coefficient, characteristic of HBA capacities of solvents (around 0.4 for ethanol). In our case, thermodynamics would probably be corrected by specific H-bond interactions with solvent. However the general trend would be the same and taking explicitly the solvent into account would have required a huge computational effort. Geometries, energies, and Gibbs energies (G) at 298 K of the reactants and products were determined at the PCM-wB97XD/6–31+G(d,p) level. The Gibbs energy of reaction under standard conditions ΔG° was obtained as the difference [G(products) − G(reactants)]. All calculations were carried out using Gaussian09 (Frisch, M. J. et al. *Gaussian 09, Revision A.02* Wallingford CT, 2009).
11. Spectroscopic data (400.13 MHz, DMSO-d_6).
Compound ***1***: ^{1}H NMR (δ). *Uracil*: (1H, s, NH), 7.43 (1H, d, J = 7.8 Hz, H_6), 5.55 (1H, d, J = 7.8 Hz, H_5); *Acetamide*: 4.66 (2H, s, –CH_2); *Hydroxyethyl chains*: 4.94 (1H, t, J = 5.2 Hz, OH_α), 4.70 (1H, t, J = 5.4 Hz, OH_β), 3.58 (2H, dt, J = 5.3 Hz, J = 5.2 Hz, CH_2– OH_α), 3.47 (2H, dt, J = 5.4 Hz, J = 5.6 Hz, CH_2– OH_β), 3.43 (2H, t, J = 5.6 Hz, CH_2–N_β), 3.35 (2H, t, J = 5.3 Hz, CH_2–N_α). Pure product as a white solid: mp = 142 °C. *Compound* ***2***: ^{1}H NMR (δ). Major rotamer (70%): *Uracil*: 11.27 (1H, s, NH), 7.47 (1H, d, J = 7.9 Hz, H_6), 5.55 (1H, d, J = 7.9 Hz, H_5); *Acetamide*: 4.70 (2H, s, –CH_2); *Hydroxyethyl*: 4.98 (1H, t, J = 5.3 Hz, OH), 3.63 (2H, dt, J = 5.3 Hz, J = 5.3 Hz, –CH_2–O), 3.49 (2H, t, J = 5.3 Hz, –CH_2–N); *Propargyl*: 4.19 (2H, d, J = 2.3 Hz, –CH_2), 3.20 (1H, t, J = 2.3 Hz, H *alkyne*). Minor rotamer (30%): *Uracil*: 11.27 (1H, s, NH), 7.49 (1H, d, J = 7.7 Hz, H_6), 5.55 (1H, d, J = 7.7 Hz, H_5); *Acetamide*: 4.68 (2H, s, –CH_2); *Hydroxyethyl*: 4.74 (1H, t, J = 5.2 Hz, OH), 3.49 (2H, br dt, –CH_2–O), 3.40 (2H, m, –CH_2–N); *Propargyl*: 4.29 (2H, d, J = 2.4 Hz, –CH_2), 3.40 (1H, m, H *alkyne*). Pure product as a colorless oil. *Compound* ***3***: ^{1}H NMR (δ). Major rotamer (70%): *Uracil*: 11.26 (1H, s, NH), 7.52 (1H, d, J = 7.8 Hz, H_6), 5.57 (1H, d, J = 7.8 Hz, H_5); *Acetamide*: 4.77 (2H, s, –CH_2); *Hydroxyethyl*: 4.96 (1H, t, J = 5.2 Hz, OH), 3.57 (2H, dt, J = 5.2 Hz, J = 5.2 Hz, –CH_2–O), 3.33 (2H, t, J = 5.2 Hz, –CH_2–N); *Benzyl*: 7.41–7.22 (5H, m, H_{Ar}), 4.57 (2H, s, –CH_2). Minor rotamer (30%): *Uracil*: 11.26 (1H, s, NH), 7.54 (1H, d, J = 7.7 Hz, H_6), 5.56 (1H, d, J = 7.7 Hz, H_5); *Acetamide*: 4.67 (2H, s, –CH_2); *Hydroxyethyl*: 4.68 (1H, t, J = 6.0 Hz, OH), 3.45 (2H, dt, J = 6.0 Hz, J = 6.0 Hz, –CH_2–O), 3.28 (2H, t, J = 6.0 Hz, -CH_2-N); *Benzyl*: 7.41–7.22 (5H, m, H_{Ar}), 4.64 (2H, s, –CH_2). Pure product as a white solid: mp = 160 °C. *Compound* ***5***: ^{1}H NMR (δ). *Uracil:* (1H, s, NH), 7.48 (1H, d, J = 7.8 Hz, H_6), 5.57 (1H, d, J = 7.8 Hz, H_5); *Acetamide*: 4.62 (2H, s, –CH_2); *Morpholine*: 3.62 (2H, t, J = 4.7 Hz, –CH_2), 3.57 (2H, t, J = 4.7 Hz, –CH_2), 3.46 (2H, t, J = 4.7 Hz, –CH_2), 3.43 (2H, t, J = 4.7 Hz, –CH_2). Pure product as a white solid: mp = 178 °C. *Compound* ***6***: ^{1}H NMR (δ). *Uracil:* (1H, s, NH), 7.53 (1H, d, J = 7.8 Hz, H_6), 5.54 (1H, d, J = 7.8 Hz, H_5); *Acetamide*: 8.17 (1H, t, J = 5.3 Hz, NH), 4.31 (2H, s, –CH_2); *Hydroxyethyl*: 4.69 (1H, br t, OH), 3.40 (2H, br dt, –CH_2–O), 3.14 (2H, dt, J = 5.8 Hz, J = 5.8 Hz, –CH_2–N). Pure product as a white solid: mp = 238 °C. *Compound* ***8***: ^{1}H NMR (δ). *Uracil:* (1H, s, NH), 7.58 (1H, d, J = 7.8 Hz, H_6), 5.56 (1H, d, J = 7.8 Hz, H_5); *Acetamide*: 8.66 (1H, t, J = 5.8 Hz, NH), 4.38 (2H, s, –CH_2); *Benzyl*: 7.34–7.22 (5H, m, H_{Ar}), 4.30 (2H, d, J = 5.8 Hz, –CH_2). Pure product as a white solid: mp = 236 °C.
12. Compound **9** is significantly less stable than **4** and **7** (Table 2), while the yield is 0 (no yield actually) for the three compounds and therefore cannot be distinguished. Compound **9** is probably much more difficult to be formed with respect to **4** and **7** but this cannot be observed.