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Unprecedented Intermolecular Transamidation Reaction of *N*-Carbamoylmethyl-*N'*-tosylguanidines

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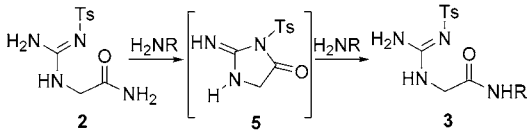
ABSTRACT



a, R = Me; **b**, R = Et, **c**, R = Pr

***N*-Carbamoylmethyl-*N'*-tosyl guanidine 2 reacts easily with primary alkylamines to afford substituted carboxamides 3. The reaction proceeds via a five-membered-ring intermediate 5, which could be isolated, and features a rare example of an intermolecular transamidation reaction under mild conditions.**

Transamidation is a useful tool in synthetic organic chemistry. However, direct transamidation is known to be a difficult reaction and it is restricted to special conditions and requirements such as ring expansion of lactams[1] and oxosultams,[2] lower carboxamides,[3] intramolecular processes,[4] activated amides, [5] catalytic conditions (enzymatic,[6] Lewis acid catalysis[7]), or high temperatures[8] and critical pH.[9] Amide exchange has also been described in solid-phase synthesis.[10]

Herein, we report a novel transamidation of non-activated N-unsubstituted carboxamides with primary alkylamines under mild reaction conditions.

In a previous paper,[11] we have reported that 1,2-dihydro-2-tosyliminopyrimidine **1** undergoes ring cleavage by reaction with methylamine (gas) in acetonitrile to give *N*-tosylguanidine **2** with high yields along with 3-methylaminoprop-2-enal. To extend the scope of this finding, the reaction of

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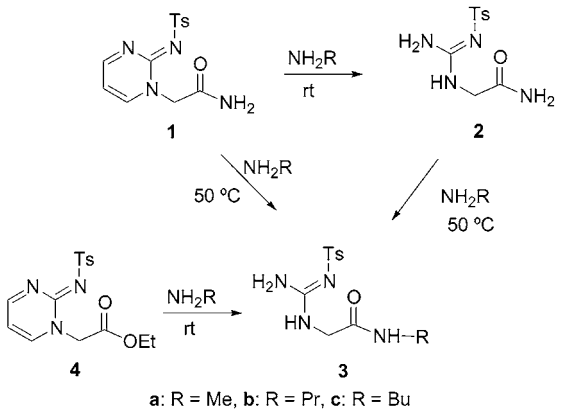
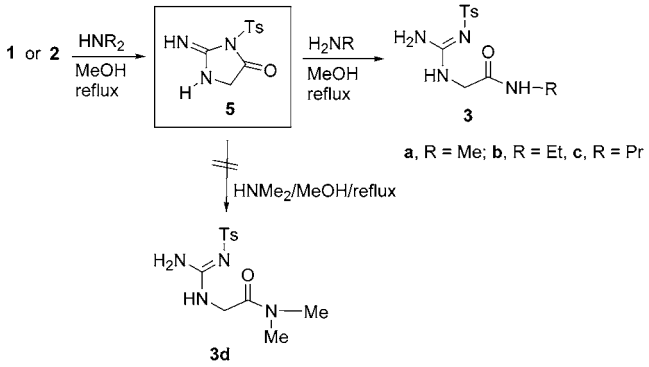
Scheme 1



Scheme 2



dihydropyrimidine **1** with other alkyl primary amines was examined (Scheme 1). Thus, we studied the behavior of dihydropyrimidine **1** with *n*-propyl and *n*-butylamine at room temperature, and the expected guanidine **2** was isolated in good yields (70−75%) along with 3-propylaminoprop-2-enal and 1,3-dibutyliminopropane, respectively.[12] Surprisingly, when the reaction conditions were changed and dihydropyrimidine **1** was treated with the same alkylamines (methylamine in acetonitrile, propyl, and butylamine) under heating (50−60 °C), the unexpected guanidines **3a**−**c**,[13] resulting from a transamidation reaction, were exclusively obtained in moderate to good yield (50−64%). Moreover, treatment of guanidine **2**, derived from dihydropyrimidine **1**, with methylamine (gas) (acetonitrile, 50 °C, sealed tube), propyl, and butylamine (50 °C), afforded the same transamidated products **3a**−**c** with higher yields (80−85%).

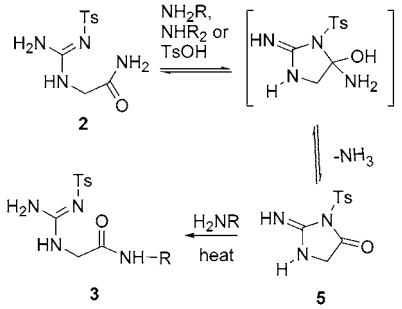
The structure of guanidines **3a**−**c** was elucidated by spectroscopic means. In addition, guanidines **3** were alternatively synthesized in 60−65% yield from the ester **4** by treatment with alkylamine for 12 h at room temperature. This experiment, along with NMR analysis, constitutes unequivocal evidence for the structure of carboxamides **3** and confirms the proposed transamidation reaction.

Actually, to the best of our knowledge, this is the first example of a transamidation reaction of *N*-carbamoylmethyl-*N*′-tosylguanidines under mild conditions. Taking these results into account, the reaction of dihydropyrimidine **1** and guanidine **2** with secondary amines (Me_2NH, Et_2NH, *i*-Pr_2NH) was also studied (Scheme 2), and in this case, no reaction products were observed at room temperature; interestingly, however, when the reaction was carried out at reflux temperature in methanol as a solvent, 2-imino-3-tosylimidazolidin-4-one **5** was obtained. The formation of compound **5** through an intramolecular transamidation reaction agrees with similar results reported in the literature under basic or acidic conditions.[1b,14]

Imidazolidinone **5** was fully characterized by analysis and spectroscopic data. In fact, the observed strong carbonyl absorption at 1749 cm^{-1} agrees with a five-membered imidazolidin-4-one ring. To verify whether the cyclization product **5** could be a key intermediate in the transformation of dihydropyrimidine **1** and guanidine **2** into the transamidation products **3**, we investigated the reaction of **5** with primary alkylamines (methyl, propyl, and butylamine) in methanol at reflux temperature. In all cases, the corresponding guanidines **3a**−**c** were quantitatively obtained. However, in the reaction of **5** with a secondary amine as dimethylamine, under the same conditions, the starting material was recovered even under extended reaction times and no traces of compound **3d** could be detected.

The formation of guanidines **3** could be explained by means of the proposed mechanism outlined in Scheme 3.

Scheme 3



Although imidazolidinone **5**, proposed as an intermediate in the transamidation, was always obtained in the reaction of carboxamides **1** or **2** with secondary amines under heating conditions; the formation of this compound **5** does not

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(13) Physical and spectroscopic data for compound **3a**. Mp: 174−176 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.34 (3H, s); 2.58 (3H, d, J = 4.7 Hz); 3.70 (2H, d, J = 5.25 Hz); 6.83 (2H, br); 6.94 (1H, br); 7.28 (2H, d, J = 8.1 Hz); 7.63 (2H, d, J = 8.1 Hz), 7.88 (1H, br) ppm. ^{13}C NMR (300 MHz, DMSO-d_6) δ: 20.9 (CH_3); 25.4 (CH_3); 43.3 (CH_2NH); 125.6 (CH); 129.0 (CH); 141.1 (C); 141.5 (C); 156.5 (C=N); 168.6 (C=O) ppm. IR (KBr): 1148, 1248, 1533, 1629, 1669, 3305, 3345, 3408 cm^{-1}. HRMS (IE^+): *m*/*z* cald for $C_{11}H_{16}N_4O_3S$, 284.0943; found, 284.0878.

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necessarily require reflux temperatures, but solubility in the reaction mixture is needed. In fact, in the reaction of **1** at room temperature with *n*-propylamine, which solubilizes dihydropyrimidine **1**, the transamidation product **3b** could be detected (6%) after a long reaction period (24 h).

In conclusion a simple, an efficient and practical method for the direct conversion of N-unsubstituted carboxamides to secondary carboxamides carried out by aliphatic primary amines in mild conditions has been developed. Studies are in progress in order to investigate the scope of this useful transformation.

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Supporting Information Available: Experimental procedures and full characterization for compounds **3a**−**c**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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