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Selective functional group transformation using guanidine: the conversion of an ester group into an amide in vinylogous ester–aldehydes of imidazole

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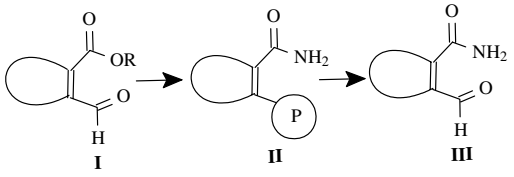
Abstract—An efficient and convenient method has been described for the selective conversion of an ester group into the corresponding carboxamide in vinylogous ester–aldehydes of imidazole. The method uses excess guanidine, which protects the aldehyde function as a diaminodihydro-*s*-triazine moiety. The carboxaldehyde group is regenerated by hydrolysis of the triazine moiety to provide vinylogous amide–aldehydes of imidazole as the final product.

Selective functional group transformation is of pivotal interest in organic synthesis.[1,2] While there are methods available for the protection of an aldehyde group in the presence of an ester functionality,[3,4] not much is known about procedures that allow, in a single-pot reaction, the selective conversion of an ester group into an amide in a vinylogous ester–aldehyde, while simultaneously protecting the aldehyde group with a labile moiety that can be easily removed later (see Scheme 1). We report herein an efficient and convenient method to accomplish this goal.

It is long known that *s*-triazine can be employed as a masked formaldehyde,[5] formimine[6,7] or formamidine.[8]



Scheme 1.

Therefore, *s*-triazine is an excellent candidate for protection of any aldehyde provided that it can be built onto an aldehyde in question using guanidine, and also can be easily removed once the ester has been converted into an amide. Since little is known in this regard, a pilot experiment to try was to react a simple aldehyde such as benzaldehyde with two equivalents of guanidine, which would potentially yield a diaminodihydro-*s*-triazine with concomitant elimination of a molecule of ammonia. However, an extensive search through the literature for the reaction of an aromatic aldehyde with guanidine to form a diaminodihydrotriazine surprisingly revealed that no such product had ever been reported. Instead, we came across a 1972 paper[9] in which the authors report the isolation of a fully aromatic product *s*-triazine (**2**) in low yield from amongst a complex mixture of products by the reaction of excess benzaldehyde (used as a solvent) with guanidine carbonate (Scheme 2). When the authors employed sodium methoxide in methanol for the condensation reaction, they obtained yet another product **3**, which showed that two molecules of aldehyde reacted with one molecule of guanidine. Both **2** and **3** apparently involved an oxidation step that followed the initial product formation. In either case, the authors could not obtain the intended monomeric product, benzylideneguanidine (**1**). Obviously, the authors always used excess benzaldehyde over guanidine instead of vice versa as would be necessary to form **1** or **2**.

Keywords: Selective conversion; Vinylogous ester–aldehyde; Vinylogous amide–aldehyde; Guanidine.
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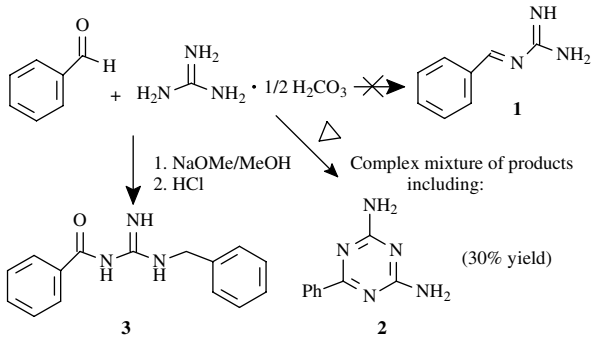
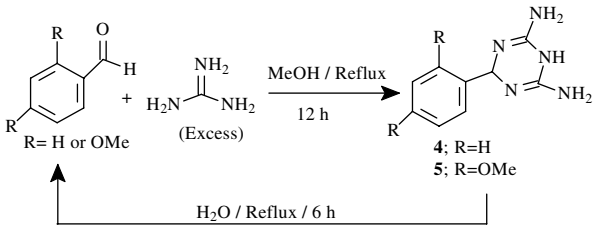


Scheme 2.

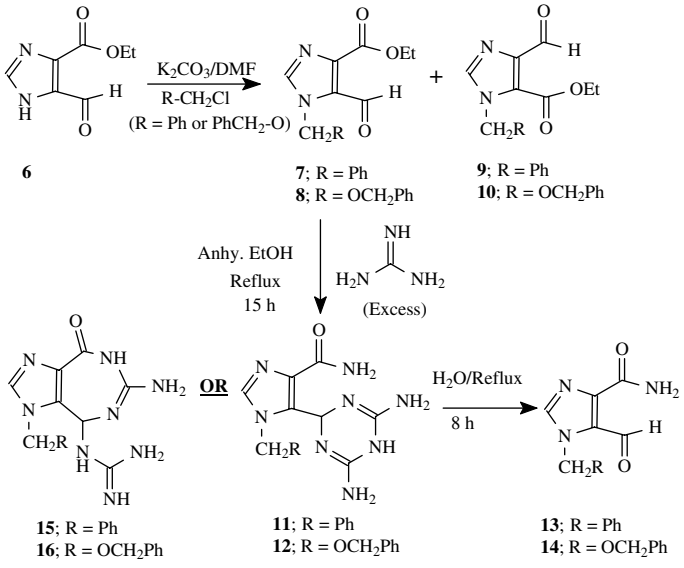


Scheme 3.

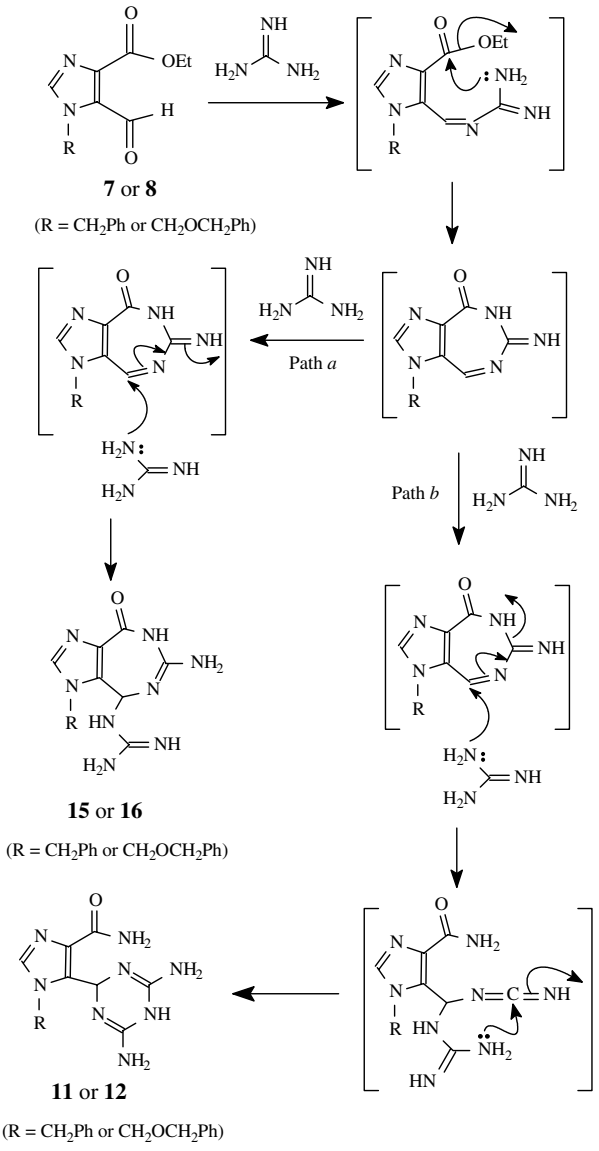
Indeed, when benzaldehyde was reacted with two or more equivalents of guanidine, freshly liberated from the corresponding hydrochloride salt by treatment with sodium methoxide in methanol, 2,6-diamino-3,6-dihydro-6-phenyl-1,3,5-triazine (**4**)[12] was obtained in 61% yield (Scheme 3). The analogous reaction with 2,4-dimethoxybenzaldehyde also gave the corresponding product **5**[12] in 67% yield. Both **4** and **5** exhibited the characteristic triazine methine proton in their respective ^{1}H and ^{13}C NMR spectra at ~5.7 and 60 δ, respectively. Both compounds are stable, colourless, crystalline solids and were fully characterized by spectroscopic (^{1}H and ^{13}C NMR, HMBC and HMQC) and microanalytical (HRMS) data. Both compounds could be readily and cleanly converted back to the starting aldehydes upon heating in water at reflux for 6 h.

The above encouraging results led us to our original objective of one-step conversion of an ester to amide in a vinylogous ester–aldehyde. We were especially interested in exploring this with heterocycles, imidazole in particular, as the stated synthetic goal actually originated while working with two vinylogous ester–aldehydes of imidazole. The necessary starting materials, 4-ethoxycarbonyl-1-benzylimidazole-5-carbaldehyde (**7**)[12] and 4-ethoxycarbonyl-1-benzyloxymethylimidazole-5-carbaldehyde (**8**),[12] along with their respective regioisomers, **9** and **10**, were prepared by alkylation of 4 (5)-ethoxycarbonylimidazole-5(4)-carbaldehyde (**6**)[12] with benzyl- and benzyloxymethyl chlorides, respectively, catalyzed by potassium carbonate in dimethylformamide (Scheme 4). The two regioisomers obtained in each case could be easily separated by flash chromatography, and distinguished from each other by ^{1}H NMR NOESY, which indicated the presence of NOE between the CHO group and the benzyl CH_2 in **7** and **8** but not in **9** and **10**. Compounds **7** and **8** were separately reacted with excess guanidine in anhydrous ethanol at reflux for 15 h, which gave the amide–triazines, **11**[12] (or **15**, *see below*) and **12**[12] (or **16**), respectively. Upon heating in water at reflux for 8 h, **11** and **12** yielded the respective amide–aldehydes **13**[12] and **14**.[12] The structures of all products were confirmed by ^{1}H and ^{13}C NMR spectra as well as mass spectral and microanalytical data.[12]

Finally, a reasonable mechanistic rationalization (see Scheme 5) for the formation of the amide–triazines **11** and **12** from the respective ester–aldehydes **7** and **8**, could not rule out the alternative 5:7-fused ring structures **15** and **16** for **11** and **12**, based on spectral and analytical data alone. The respective pairs of compounds have the same molecular formula, the same characteristic methine signal of either the dihydrotriazine or the dihydrodiazepine ring, and with proper



Scheme 4.

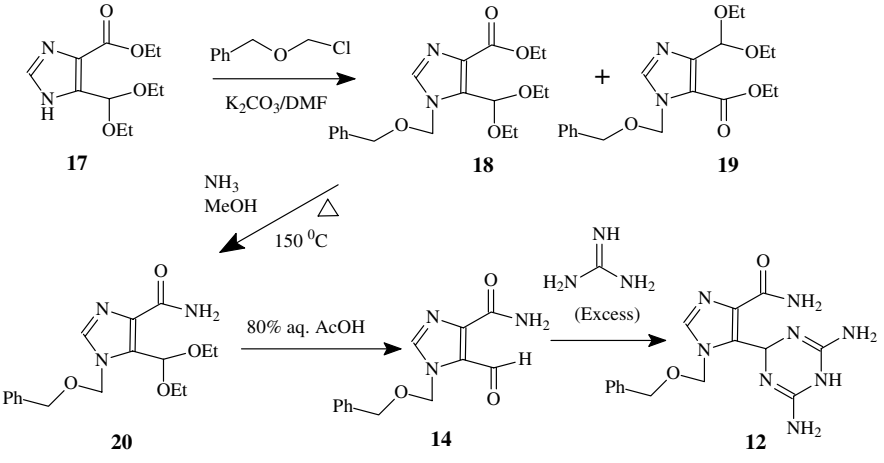


Scheme 5.

tautomerization, the same number of amino/imino groups that are exchangeable with D_2O. In order to resolve this structural ambiguity, we resorted to an unequivocal synthesis of one of the two amide–triazine products (**12**).

The structural ambiguity of **12** lay with compound **16**. In this regard, compound **12** being a simple imidazole derivative seemed easier to synthesize than the 5:7-fused imidazodiazepine ring system **16**. Therefore, compound **12** was chosen over **16** for the purpose of unequivocal synthesis. The synthesis of **12** commenced with the known imidazole derivative, 4-ethoxycarbonylimidazole-5-carbaldehyde diethyl acetal[10,11] (**17**) (Scheme 6). Imidazole ring nitrogen atom of **17** was substituted with the benzyloxymethyl (BOM) group as before by reaction with benzyloxymethyl chloride in dimethylformamide, catalyzed by potassium carbonate, to obtain the two regioisomers **18**[12] and **19**. The isomers were separated by flash chromatography, and distinguished by NOESY NMR as before. The isomer **18** was further reacted with methanolic ammonia in a stainless steel vessel at 150 °C for 48 h to obtain the acetal–amide **20**.[12] The acetal group of **20** was hydrolyzed with 80% acetic acid to obtain the amide–aldehyde **14**. The latter upon reaction with excess guanidine in methanol at reflux provided **12**, which was found to be identical in all respects with the compound obtained by the reaction of **8** with excess guanidine shown in Scheme 4.

The above results, however, raise another mechanistic possibility for the formation of **11** or **12** from **7** or **8**, in which the carboxaldehyde group of the latter would react with excess guanidine to form the triazine ring first. A molecule of ammonia released during the formation of triazine would subsequently react with the ester group to produce the amide product. While this reaction pathway could not be completely ruled out, it appears less likely, however, in view of (a) the harsh reaction conditions that were necessary to convert the ester **18** to amide **20**, and (b) the lack of formation of equally plausible other products such as the ones formed by the



Scheme 6.

reaction of the ester group with guanidine. This is especially true as there is a large molar excess of guanidine in the reaction mixture as compared to the transiently formed ammonia, whose concentration is expected to be further diminished at the reflux temperature of ethanol.

In conclusion, we have discovered a novel functional group transformation involving a selective conversion of an ester group of a vinylogous ester–aldehyde attached to an imidazole ring into the corresponding amide, while simultaneously protecting the aldehyde group as an *s*-triazine. The aldehyde group is deprotected upon simply heating in water at reflux without any acid or base catalysis. The method has distinct advantages over the conventional methods such as the one employed in Scheme 6, in that no prior protection of the aldehyde group would be necessary before conversion of the ester into amide. Furthermore, the aldehyde protecting group can be removed under much milder as well as neutral conditions than would be normally necessary, for example, removal of an acetal group. We are currently exploring the generality of this transformation to other heterocyclic and aromatic systems.

Acknowledgements

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12. Physicochemical data for the key compounds reported are as follows: Compound **4**: Yield 61%; mp 173–175 °C; $R_f = 0.11$ (2:1:0.25 chloroform/methanol/ammonium hydroxide); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40 (m, 6H), 5.77 (s, 1H), 3.47 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.5, 141.2, 129.5, 129.3, 126.5, 62.4; HRMS (FAB) calculated for $C_9H_{12}N_5$, 190.1096 *m/z* (MH^+); observed 190.1093. Compound **5**: Yield 67%; mp 170–172 °C; $R_f = 0.23$ (2:1:0.25 chloroform/methanol: NH_4OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.09 (d, $J = 8.2$ Hz, 1H), 6.57 (s, 1H), 6.45 (d, $J = 8.2$ Hz, 1H), 6.05 (br s, 4H), 5.74 (br s, 1H), 5.73 (s, 1H), 3.72 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.1, 159.1, 157.8, 127.5, 122.9, 104.8, 98.9, 59.7, 56.0, 55.7; HRMS (FAB) calculated for $C_{11}H_{15}N_5O_2$, 250.1304 *m/z* (MH^+); observed 250.1289. Compound **6**: Yield 91%; mp 212 °C; $R_f = 0.41$ (10:1 chloroform/methanol); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 13.74 (s, 1H), 10.16 (s, 1H), 8.01 (s, 1H), 4.28 (q, $J = 7.5$ Hz, 2H), 1.27 (t, $J = 7.5$ Hz, 3H); MS (FAB) *m/z* 169 (MH^+); $C_7H_8N_2O_3$ requires C, 50.00; H, 4.80; N, 16.66. Found: C, 49.88, H, 4.76, N, 16.61. Compound **7**: Yield 64%; mp 69–71 °C; $R_f = 0.24$ (1:1 ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.42 (s, 1H), 7.63 (s, 1H), 7.19 (m, 5H), 5.48 (s, 2H), 4.36 (q, $J = 6.8$ Hz, 2H), 1.35 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.2, 162.1, 142.0, 135.2, 132.1, 129.3, 128.8, 127.8, 61.9, 51.2, 14.5; MS (FAB) *m/z* 259 (MH^+); $C_{14}H_{14}N_2O_3$ requires C, 65.11; H, 5.42; N, 10.85. Found: C, 64.88, H, 5.48, N, 10.81. Compound **8**: Yield 70%; oil; $R_f = 0.27$ (1:1 ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.50 (s, 1H), 7.82 (s, 1H), 7.35 (m, 5H), 5.81 (s, 2H), 4.55 (s, 2H), 4.42 (q, $J = 7.2$ Hz, 2H), 1.41 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.4, 161.2, 141.1, 135.5, 131.3, 128.1, 128.0, 127.8, 127.3, 75.5, 71.1, 61.2, 13.7; MS (FAB) 289 (MH^+); $C_{15}H_{16}N_2O_4$ requires C, 62.49; H, 5.59; N, 9.72. Found: C, 62.57, H, 5.52, N, 9.79. Compound **11**: Yield 66%; mp 184–186 °C; $R_f = 0.24$ (chloroform/methanol/ammonium hydroxide, 2:1:0.25); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.54 (s, 1H), 7.24 (m, 5H), 6.72 (s, 1H), 5.44 (br s, 4H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.6, 159.4, 138.1, 138.0, 132.2, 129.0, 128.4, 128.1, 61.3, 49.2, 40.6; HRMS (FAB) calculated for $C_{14}H_{16}N_8O$, 313.1525 *m/z* (MH^+); observed 313.1536. Compound **12**: Yield 61%; mp 195–197 °C; $R_f = 0.28$ (chloroform/methanol/ammonium hydroxide, 2:1:0.25); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.8 (s, 1H), 7.5 (s, 1H), 7.25 (m, 6H), 6.7 (s, 1H), 5.7 (s, 2H), 4.5 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4, 159.1, 139.1, 137.8, 133.6, 128.8, 128.8, 128.2, 128.1, 75.5, 70.6, 59.5; $C_{15}H_{18}N_8O_2{\cdot}0.5CH_3OH$ requires C, 51.93, H, 5.58, N, 31.27. Found: C, 52.03, H, 5.31, N, 31.35; HRMS (FAB) calculated for $C_{15}H_{18}N_8O_2$, 343.1631 *m/z* (MH^+); observed 343.1583. Compound **13**: Yield 81%; mp 223–225 °C; $R_f = 0.37$ (20:1 chloroform/methanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.38 (s, 1H), 8.23 (s, 1H), 7.82 (s, 1H), 7.63 (s, 1H), 7.21 (m, 5H), 5.50 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.9, 163.0, 143.9, 141.6, 136.1, 129.3, 128.2, 127.4, 126.8, 49.6; $C_{12}H_{11}N_3O_2$ requires C, 62.87; H, 4.84; N, 18.33. Found: C, 63.12, H, 4.93, N, 18.35; HRMS (FAB) calculated for $C_{12}H_{11}N_3O_2$, 230.0929 *m/z* (MH^+); observed 230.0903. Compound **14**: Yield 88%; mp 137–138 °C; $R_f = 0.4$ (20:1 chloroform/methanol); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 8.28 (s, 1H), 7.81 (s, 1H), 7.70 (s, 1H), 7.29 (m, 5H), 5.75 (s, 2H), 4.54 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 183.7, 163.7, 145.1, 143.1, 137.7, 130.1, 128.8, 128.3, 76.2, 70.9; $C_{13}H_{13}N_3O_3$ requires C, 60.10, H, 5.13, N, 15.99. Found, C, 60.22, H, 5.05, N, 16.21; HRMS (FAB) calculated for $C_{13}H_{13}N_3O_3$, 260.1035 *m/z* (MH^+); observed 260.1061. Compound **18**: Yield 33%; oil; $R_f = 0.23$ (2:1 hexanes/ethyl acetate); ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.72 (s, 1H) 7.28 (m, 5H), 6.36 (s, 1H), 5.67 (s, 2H), 4.54 (s, 2H), 4.38 (q, $J = 6.9$ Hz, 2H), 3.81 (q, $J = 7.2$ Hz, 2H), 3.53 (q, $J = 7.2$ Hz, 2H), 1.40 (t, $J = 7.2$ Hz, 3H), 1.19 (t, $J = 7.2$ Hz, 6H); MS (FAB) 363 (MH^+). Compound **20**: Yield 92%; oil; $R_f = 0.29$ (20:1 chloroform/methanol); ^1H NMR (300 MHz, DMSO-d_6): δ 7.63 (s, 1H), 7.31 (m, 5H), 7.15 (s, 2H), 6.53 (s, 1H), 5.68 (s, 2H), 4.57 (s, 2H), 3.86 (q, $J = 7.2$ Hz, 2H), 3.56 (q, $J = 6.9$ Hz, 2H), 1.20 (t, $J = 6.9$ Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.9, 136.4, 132.4, 131.8, 128.0, 127.5, 127.2, 127.2, 95.2, 75.4, 70.7, 63.4, 14.6; MS (FAB) 334 (MH^+).