# Catalytic *C*-amidoalkylations: synthesis of β-amido aldehydes by three-component condensations

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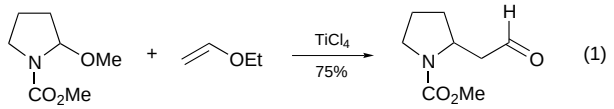
**Primary amides condense with aliphatic aldehydes (2 equiv.) in the presence of trifluoromethanesulfonic acid to give β-amido aldehydes.**

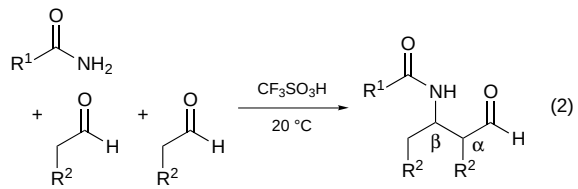
The condensation of aldehydes with primary and secondary amides can lead to valuable products by means of amidoalkylation.[1,2] However, amidoalkylation at carbon has been generally limited to the condensation of an active methylene compound *other than* an aldehyde with an imine substrate usually containing an aromatic substituent.[1,2] In most cases, the amidoalkylating agent must be separately prepared and isolated prior to reaction with the active methylene compound. Whereas amidoalkylation is well-established for cases where either the aldehyde or the amide is aromatic[1,2] (or both are), condensations involving only aliphatic reactants are rare, and appear confined to one example of a cyclic amide [eqn. (1)].[3] Such



(1)

aliphatic amidoalkyations could significantly extend the scope of aliphatic and heterocyclic N–C bond formation, with particular importance for alkaloids and related pharmaceutical products. In this area, the nature of the acid catalyst is known to be crucial; for aromatic reactants, polyphosphoric acid[4] or polyphosphate ester[5] have been shown to effect amidoalkylation followed by cyclization. However, the harshness of these reagents led to decomposition when applied to aliphatic reactants. Accordingly, trifluoromethanesulfonic acid was investigated, since its mildness, and ease of control of reagent concentration result in good yields in acid-catalyzed condensations,[6] notably in the cyclization of β,γ-unsaturated amides to lactams.[7]

Multiple component condensations offer powerful strategies in combinatorial chemistry[8a] and general synthesis.[8b] A new three-component amidoalkylation is here reported that is to the best of our knowledge the first amidoalkylation to deliver acyclic aliphatic aldehydes [eqn. (2)]. Unique features include:



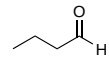
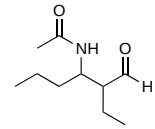
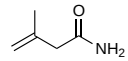
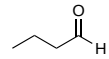
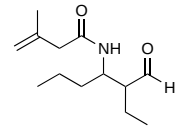
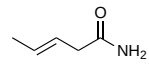
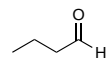
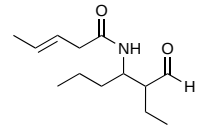
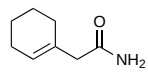
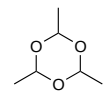
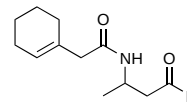
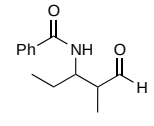
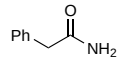
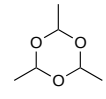
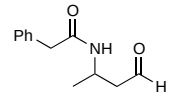
(2)

(a) *in situ* formation[2] of the presumed imine substrate (from an amide and an aldehyde), (b) subsequent amidoalkylation by an aldehyde, in an overall one-pot process to give (c) an isolable β-amido aldehyde as the product, under mild conditions of acid catalysis at 20 °C. β-Amido aldehydes are protected, relatively stable forms of β-amino aldehydes which are generally only isolable with difficulty[9] or accessible *via* indirect synthetic protocol.[10] β-Acetylamino aldehydes are key intermediates in the synthesis of amino cyclitols.[11] Table 1 shows that β-amido aldehydes‡ of the form $R^1CONHCHR^2CHR^2CHO$ can be prepared from an amide $R^1CONH_2$ and an aldehyde $R^2CH_2CHO$ (2 equiv.). For entries 1 and 5, the *syn* : *anti* diastereoisomer ratio is respectively 1 : 2 and 1 : 5,[12] whereas for entries 2 and 3 a 1 : 1 ratio was observed. The diastereoselection found in entries 1 and 5 can be accounted for on the basis of a Zimmerman–Traxler model, leading to preponderance of the *anti*-diastereoisomer.[13]

Notable is the variety of amides (some functionalized) and sensitive aliphatic aldehydes (or their equivalent) that participate under the mild conditions. Attempts to obtain β-amido aldehydes using polyphosphoric acid or polyphosphate ester were unsuccessful in all cases studied, and we have generally observed that simple aliphatic aldehydes and ketals are rapidly decomposed by reagents other than dilute trifluoromethanesulfonic acid. The β,γ-unsaturated amides used in entries 2, 3 and 4 have been shown to cyclize either as the sole reactant[7] or in the presence of an aromatic aldehyde;[4,5] it is noteworthy that in the present reactions the double bond does not participate in a cyclization, but remains intact.

The reaction of amides with aldehydes can give a number of products, depending on the reagent and conditions. Thus, amides have been shown to add reversibly to aldehydes,

**Table 1** Condensation of amides with aldehydes in the presence of 2% v/v trifluoromethanesulfonic acid in dichloromethane at 20 °C

| Entry | Amide | Aldehyde or acetal | *t*/h | β-Amido aldehyde | Yield (%) |
|---|---|---|---|---|---|
| 1 |  |  | 16 |  | 60 |
| 2 |  |  | 12 |  | 50 |
| 3 |  |  | 24 |  | 54 |
| 4 |  |  | 16 |  | 51 |
| 5 |  |  | 48 |  | 69 |
| 6 |  |  | 48 |  | 66 |

particularly formaldehyde, to give *N*-hydroxymethylamides.[2,14] For the latter, basic conditions are usually employed because acidic catalysis is usually either ineffective or affords mixtures. In general (and depending on the stoichiometry), *N*,*N*′-alkylidenebis(amides), $R^1CH(NHCOR^2)_2$, can be prepared by condensing $R^1CHO$ with $R^2CONH_2$.[15]

Preliminary experiments with α,β-unsaturated aldehydes and amides in the presence of $CF_3SO_3H$ did not lead to β-amido aldehydes, and would appear to exclude an initial aldol condensation with dehydration, followed by conjugate addition. More probable is an initial condensation of the amide with one equivalent of aldehyde to give an acyl imine or acyl iminium intermediate which then undergoes attack by an enolic form of a second equivalent of the aldehyde, either in its enolic form, or possibly as an enamide derivative.

In conclusion, a new three-component condensation[8] is disclosed which provides a flexible route to β-amido aldehydes that have been hitherto largely inaccessible. The β-amido aldehydes are of synthetic value in themselves, being relatively stable derivatives of the difficulty isolable β-amino aldehydes.[9] These condensations of amides with aldehydes proceed at 20 °C with acid catalysis, and without the need for protection or derivatisation of the aldehyde function. The new condensation is clearly distinguishable from other related amide–carbonyl condensations; synthetic applications and mechanistic aspects are under investigation.

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## Footnotes and References

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‡ All compounds gave satisfactory spectral data (NMR, IR, mass), and all new compounds gave satisfactory elemental analyses or HRMS. The procedure is described for entry 4 (Table 1). To a solution of cyclohex-1-enylacetamide (1.49 g, 0.01 mol) and paraldehyde (1.32 g, 0.01 mol) in dichloromethane (50 ml) was added trifluoromethanesulfonic acid (1.0 ml). After stirring at 20 °C for 16 h the mixture was poured over ice (50 g), made alkaline with aqueous sodium hydroxide (5%), and extracted with dichloromethane (3 × 50 ml). The combined extracts were dried, evaporated, and the residue purified by column chromatography [silica, 1 : 1 ethyl acetate–light petroleum (40–60 °C)] to give *N*-(4-oxopropan-2-yl)cyclohex-1-enylacetamide (1.1 g, 51%) as an oil; $\delta_H$ 9.77 (1 H, s, C*H*O), 6.00 (1 H, brd s, N*H*), 5.63 (1 H, brd s, =C*H*), 4.42 (1 H, m, NC*H*), 2.86 (2 H, s, $CH_2CO$, 2.65 (2 H, dd, *J* 7 and 2 Hz, $CH_2CHO$), 2.10 (2 H, brd s, allylic *H*), 1.95 (2 H, brd s, allylic *H*), 1.65 (4 H, m, $CH_2CH_2$), 1.25 (3 H, d, *J* 7 Hz, $CH_3$); $\delta_C$ 201.0, 170.6, 132.6, 127.0, 49.7, 46.3, 40.9, 28.3, 25.3, 22.7, 21.9, 20.4. Found: HRMS, $M^+$, 209.1416. $C_{12}H_{19}NO_2$ requires $M^+$, 209.1416.

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12 $^1$H NMR spectra of the separated diastereoisomeric acids obtained by aerial oxidation of the aldehydes in entry 1 exhibit couplings for the vicinal methine hydrogen atoms of 10 and 5 Hz (isolated as the minor diastereoisomer), and 3 and 5 Hz (major diastereoisomer). The former values are consistent with the *syn*-isomer in a preferred conformation in which the amido and aldehyde groups are antiperiplanar, and the methine hydrogen atoms are disposed *trans* ($J$ = 10 Hz). ('*syn*' refers to relation of α-alkyl and β-amido groups, the aldehyde being drawn as part of the 'backbone' of the product.) Such assignments are consistent with those for other β-amido carbonyl compounds: H. Estermann and D. Seebach, *Helv. Chim. Acta*, 1988, **71**, 1824.
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