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A stereoselective, multiple-component approach to α–β-substituted-β-amino carbonyl derivatives ☆

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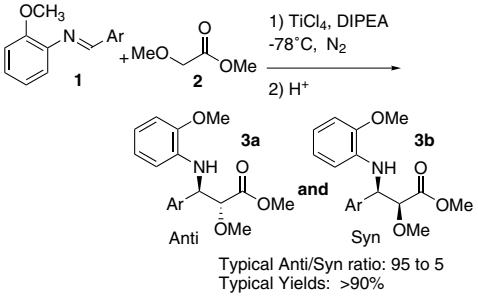
Abstract—A new stereoselective multiple-component condensation is presented. This three-component condensation combines an aldehyde, aniline, and chlorotitanium enolates, to afford α–β-substituted-β-amino carbonyl compounds as its core structure.

1. Introduction

The multiple-component condensation (MCC) strategy has the power to rapidly build molecular complexity and is the recognized workhorse for the preparation of large libraries of compounds based on a common core architecture. Many unique structures can be attained rapidly when three or more reactants are combined in a single step to afford new compounds possessing the combined features of the building blocks.[1]

Recently we have shown that the addition of titanium enolates of methyl methoxyacetate to activated aldimines proceeds in an asymmetric fashion, affording the anti-diastereomer in excellent yields (Scheme 1).[2,3] However this process was indirect, requiring a pre-made imine. Due to the difficulty in isolating imines based on enolizable aldehydes it was limited to aryl imines.

In this paper we report our efforts to expand our previously reported sequential protocol[2] to a multiple-component process. In this way we have been able to expand the scope of this asymmetric addition to include the alkyl imines. This new MCC reaction (Scheme 2) affords yields and diastereoselectivity comparable with that observed for the indirect protocol (Scheme 1).[2] To the best of our knowledge this is the first use of chlorotitanium enolates in a multiple-component Mannich-type reaction system.



Scheme 1.

2. Results and discussion

To determine an effective dehydration method, we confined our initial studies to nonenolizable aldehydes (Table 1). While several dehydrating reagents were effective, 4-Å molecular sieves proved to be ideal. A solution of the aldehyde and aniline derivatives (1:1.05 molar ratio) in CH_2Cl_2 were stirred together at room temperature under a dry nitrogen atmosphere with crushed molecular sieves.

After about 30 min the mixture was cooled to −78 °C and a violet CH_2Cl_2 solution of the titanium enolate of methyl methoxyacetate was added via canula.[4] The reactions were judged complete based on TLC analysis, but were generally complete within 2–24 h.[5] When the

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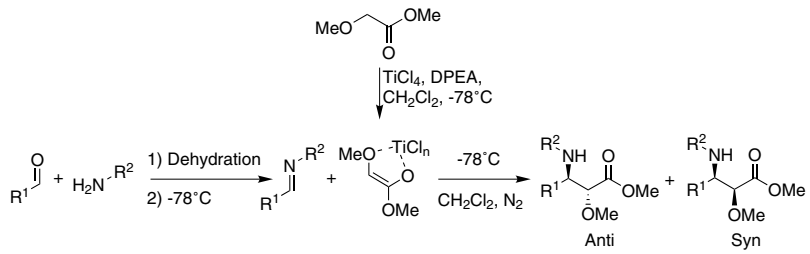


Scheme 2.

Table 1. Results with nonenolizable aldehydes using 4-Å molecular sieves as dehydrating agent

Entry	R^1	R^2	% Conversion[b]	Isolated yield (%)	Dr (A:S)[e]	Prev. yield (%)[f]	Prev. dr (A:S)[f]
1	p-ClPh	OMP[a]	>99	92[c]	92:8	95	95:5
2	p-MePh	OMP	92	88[c]	95:5	95	92:8
3	β-Naphthyl	OMP	>99	94[c]	96:4	87	92:8
4	Ph	PMP	81	71[c]	79:21	77	79:21
5	*tert*-Cinnamyl	OMP	>99	87	99:1	—	—
6	Cyclohexenyl	OMP	94	86	96:4	—	—
7	*t*-Bu	OMP	—	NR[d]	NR	NR	NR

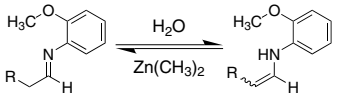
[a] OMP: *ortho*-methoxyphenyl, PMP: *para*-methoxyphenyl.
[b] Percent conversion determined by ^{1}H NMR of the reaction mixture immediately after workup.
[c] All spectroscopic data consistent with those reported in Ref. 2.
[d] No reaction and is consistent with Ref. 2.
[e] Determined using HPLC of the isolated material.
[f] Data from Ref. 2.

reactions were complete the cold reaction mixture was suction-filtered directly into stirring 1 M HCl and allowed to warm to room temperature. The quenched reaction mixtures were then separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organics were washed sequentially with a saturated $NaHCO_3$, saturated NaCl, and then dried with $MgSO_4$, filtered, and concentrated in vacuo.

The results of these experiments are presented in Table 1 and are nearly identical to those observed for reaction between the enolate and pre-made imines (entries 1–4 and 7). Entries 5 and 6 represent two new nonenolizable imines and in both cases the yields and diastereoselectivies of α-oxy-β-amino esters were excellent. In our previously reported indirect sequence we found the presence of an *ortho* substituent, other than hydrogen, on the R^2 group of the imine leads to high anti-selectivity[2] and the same appears to be true for this MCC process. For example, when the R^2 substituent is a PMP group (entry 4) the selectivity slips to 79% anti. These data appear to support the contention that a similar mechanism for selection is operating in both the present direct and previous indirect processes. It is interesting to note that while the steric demands of the R^2 substituent appear to be of importance to the mode of stereoselection, the same does not appear to be so for the R^1 group. Radically changing the steric demand of the R^1 group (entry 3: R^1 = β-naphthyl vs entry 5: R^1 = *tert*-cinnamyl) does not significantly affect the diastereoselection (**a**:**s**, 96:4 vs 99:1, respectively).

We next turned our attention to the enolizable aldehydes. All attempts to optimize the reaction with this class of aldehydes using molecular sieves and other classic drying agents failed. We hypothesized that in the presence of a small amount of water, our enolizable imine solution might be in equilibrium between the imine and enamine forms, likely favoring the later due to the influence of a favorable π–n–π conjugation (Scheme 3).[6] The imine–enamine equilibrium has been shown to be related to the pK_a of the starting aniline derivative with increasing acidity leading to greater percentages of enamine.[6] Based on this, we would expect our mixture to contain, at a minimum, about 20% enamine.[7] To test our hypothesis we used dimethylzinc as an alternative drying agent.[8] Using such a protocol should remove all water generated during imine formation and provide a chelating Lewis acid, thus stabilizing the imine form.

The results of these experiments are presented in Table 2. To our delight the conversions of these reactions are excellent with concomitant isolated yields.[9] As can be seen in these data the reaction still favors the anti-product, however, in three cases (entries 2–4) the selectivity slips to 83% anti. An additional concern when using dimethylzinc as the dehydrating agent is the possible formation of the methyl adduct.[10] While the methyl adduct was detectable, in all cases it comprised less than 1% of the product mixture and was easily removed by column chromatography.[11] It is particularly interesting



Scheme 3.

Table 2. Results with enolizable aldehydes using 2 M dimethylzinc in toluene as dehydrating agent

Entry	R^1	R^2	% Conversion[a]	Isolated yield (%)	Dr (A:S)[b]
1	Hydrocinnamyl	OMP	>99	94	92:8
2	Isobutyryl	OMP	>99	93	83:17
3	Isovaleryl	OMP	>99	93	83:17
4	Cyclohexanyl	OMP	92	81	84:16

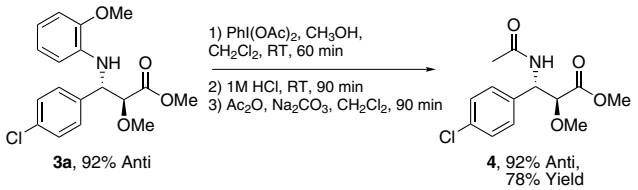
[a] Percent conversion determined by ^{1}H NMR of the reaction mixture immediately after workup.
[b] Determined using HPLC of the isolated material.

to note that the use of dimethylzinc was restricted to reactions with enolizable aldehydes, its application to nonenolizable aldehydes resulted in little or no formation of the β-amino ester products.

Our choice of the *ortho*-methoxyphenyl (OMP) group was prompted by previous observation that an *ortho*-substituent on the imine R^2 group leads to higher anti-selectivity,[2] and our recent experience in the preparation of β-amino esters as the sole products via the addition of (methoxycarbonyl)methyl zinc bromide to aldimines derived from *ortho*-methoxyaniline.[12] In addition, the OMP group, like the PMP group, can be removed by various oxidative methods, such as mild CAN oxidation[13] or $AgNO_3/(NH_4)S_2O_8$.[14] However, we have found that these methods are often plagued with problems such as low yields, expensive reagents and in our hands, poor reproducibility.

Recently Snapper and co-workers have introduced a new deprotection–reprotection protocol that uses iodobenzene diacetate to achieve oxidative removal of the OMP group (Scheme 4).[15] This is then followed by acidic extraction of the resulting free amine, which can be isolated or immediately reprotected as the acetamide by reaction with acetic anhydride in the presence of Na_2CO_3. Typical overall yields are in the 80% range. Importantly, application of this method to the deprotection–reprotection of ester **3a** afforded ester-amide **4** with no apparent loss of relative stereochemistry.[16,17]

We have developed an efficient and stereoselective titanium enolate based three-component condensation reaction that affords α–β-substituted-β-amino carbonyl compounds as its core structure (Fig. 1). These protocols extend our previously reported work[2] to include enolizable imines. In addition, other work in our labs has shown that acetate esters bearing an α-thioether are also reactive and afford the anti-products predominantly, thus adding another dimension to product diversity.[18] With four sites for substitution this new multiple-component reaction has significant potential



3a, 92% Anti

4, 92% Anti, 78% Yield

Scheme 4.

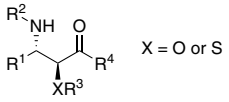


Figure 1. α-Substituted β-amino carbonyl core structure with four sights of diversity.

for preparing α,β-disubstituted-β-amino carbonyl libraries. Efforts to further develop this and other new multi-component condensation reactions are under way and will be reported in due course.

Supplementary material

General experimental information and characterization data for all new β-amino esters including HPLC separation protocols.

Acknowledgements

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(c) Shimizu and Sahara recently reported that the TiI_4 promoted addition of α,α-dialkoxyacetates to premade imines resulted in the formation of α-oxy-β-amino esters and in the cases were diastereoselectivity was observed, the major isomer obtained was that of the anti-configuration Shimizu, M.; Sahara, T. *Chem. Lett.* **2002**, 888–889.

4. *MCC with nonenolizable imines:* To a stirred mixture of crushed 4 Å molecular sieves in 6 mL of CH_2Cl_2 under a nitrogen atmosphere was added the aldehyde followed by *ortho*-anisidine (1:1.05 molar equivalents). The enolate solution was prepared according to the method used in Ref. 2. After 30 m the mixture is cooled to −78 °C and the violet titanium enolate solution (2.0 equiv) was transfered into the imine solution. After the reaction had gone to completion, based on TLC analysis, the cold reaction mixture was suction-filtered directly into a stirring solution of 1 M HCl and allowed to warm to room temperature. The work-up procedure used in Ref. 2 was followed from this point.
5. See Supplementary material.
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10. We did not anticipate significant methyl alkylation since dimethylzinc is an extremly poor nucleophile, for leading references see: (a) Inoue, S.; Imanaka, Y. *J. Organomet. Chem.* **1972**, *35*, 1–7; (b) Knochel, P.; Singer, R. *Chem. Rev.* **1993**, *93*, 2117–2188; (c) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414–4435.
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16. *Deprotection–reprotection*: Methyl 3-*N*-(acetyl)amino-2-methoxy-3-(4-chloro)phenylpropanoate. To a stirred solution of $PhI(OAc)_2$ (364 mg, 1.10 mmol) in methanol (5 mL) at room temperature was added a solution of the beta-amino ester **3a** (99 mg, 0.30 mmol) in CH_2Cl_2 (1 mL) and methanol (1 mL) over 30 min via syringe pump. The syringe was then rinsed with methanol (2×0.5 mL) and the rinses were added to the reaction. After an additional 30 min (60 min total) 1 M HCl (10 mL) was added to the reaction and a white precipitate immediately formed, which slowly dissolved with stirring to afford a yellow solution after 90 min. The organic layer was separated and the aqueous layer subsequently extracted with 2×15 mL portions of CH_2Cl_2. The combined organic layers were then back extracted with 10 mL 0.1 M HCl and added to the previous aqueous layer. To the aqueous layer was added CH_2Cl_2 (10 mL). To this biphasic mixture was added, with vigorous stirring, Ac_2O (134 μL, 1.40 mmol) followed by and Na_2CO_3 portionwise to afford a pH of 10–11. This mixture was stirred for 90 min with occasional addition of Na_2CO_3 to maintain the pH of 10–11. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated in-vacuo to afford 67 mg (78%) of **4**; mp: 96–98 °C; IR (thin film); 3426, 1738, 1651 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.25 (s, 4H), 6.48 (d, 1H, $J = 8.0$ Hz), 5.42 (dd, 1H, $J = 8.0$ Hz, $J = 4.0$ Hz), 4.13 (d, 1H, $J = 4.0$ Hz), 3.60 (s, 3H), 3.49 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 169.9, 169.3, 135.8, 133.9, 129.0, 128.7, 82.0, 59.3, 53.6, 52.0, 23.4. Anal. Calcd for $C_{13}H_{16}ClNO_4$: C, 54.65; H, 5.64; N, 4.90. Found: C, 54.89; H, 5.74; N, 4.54. Minor isomer (syn) is visible in the NMR and the C*H*OCH_3 resonates at δ 4.02 (d, 1H, $J = 2.0$ Hz).
17. The anti:syn ratio was determined by comparative integration of the H^1 NMR of both the starting material and resulting product.
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