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One-Pot Synthesis of α-Branched *N*-Acylamines via Titanium-Mediated Condensation of Amides, Aldehydes, and Organometallics

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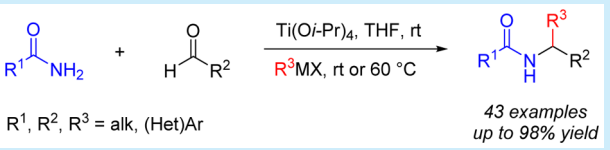
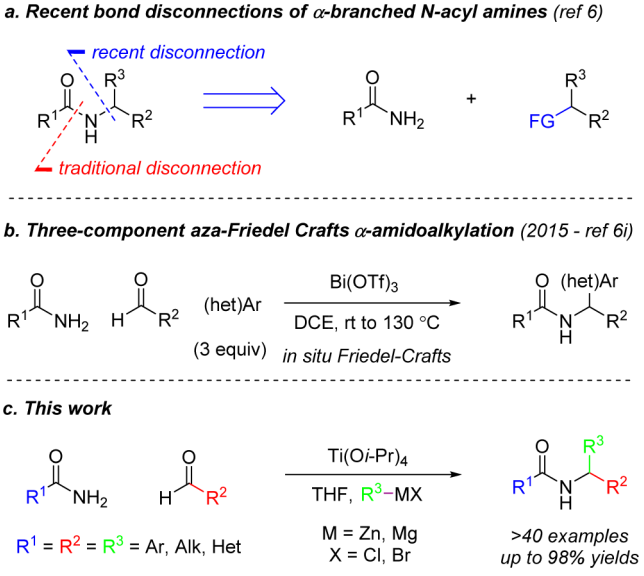
Supporting Information

ABSTRACT: A three-component, titanium-mediated synthesis of α-branched *N*-acylamines from commercial or readily accessible amides, aldehydes, and organometallic reagents is reported. The transformation proceeds under mild reaction conditions and tolerates a variety of functional groups (including nitrile, carbamate, olefin, basic amine, furan, and other sensitive heteroaromatics) to generate a large umbrella of α-branched *N*-acylamine products in high yields. The operationally practical procedure enables the use of this method in parallel chemical synthesis, a valuable feature that can facilitate the screening of bioactive molecules by medicinal chemists.



α-Branched *N*-acylamines are highly prevalent motifs across all areas of organic chemistry.[1,2] Their synthesis has traditionally relied upon the preactivation of carboxylic acids with coupling reagents (including the use of anhydrides, carbodiimides, hydroxybenzotriazole, or thionyl chloride) followed by their condensation with a secondary amine.[3] A standard alternative is the hydrogenation of α-substituted enamides, yet it is limited by the supply of this class of substrates that require preparation.[4] In the past decade, new synthetic methods have emerged, taking advantage of an alternate bond disconnection (Scheme 1a)[5,6] via the coupling of primary amides with a variety of reaction partners such as boronic acids,[6a] alkanes,[6b] alkyl halides,[6c] vinyl arenes,[6d,e] alcohols,[6f,g] or carbonyl compounds (ketones/aldehydes).[6h,i,k] However, most of these new methods suffer from a range of limitations such as harsh reaction conditions (elevated temperatures, use of peroxides), excess reagents, limited substrate scope, and the requirement of preparing the starting building blocks.

Scheme 1. Access to α-Branched *N*-Acylamines



A multicomponent transformation that takes advantage of three readily available coupling partners could both improve efficiency and enable access to a greater and more diverse chemical space. Such chemical diversity is not as readily accessible via traditional methods. For instance, amide bond couplings are restricted by the limited scope of α-branched hereroarylamines available. In addition, a three-component and operationally practical method could allow the screening of bioactive molecules via targeted parallel chemical synthesis, a valuable approach in drug discovery. One such method is the recent $Bi(OTf)_3$-catalyzed aza-Friedel–Crafts of in situ generated *N*-acylimine/*N*-acyliminium (Scheme 1b).[6i] This elegant transformation is, however, restricted to electron-rich arenes used in excess (3 equiv) that typically lead to regioisomeric product mixtures.

Herein, we report the first three-component Ti-mediated synthesis of α-branched *N*-acylamines using a large variety of aliphatic and (hetero)aromatic primary amides, aldehydes, and organometallic reagents such as Grignards and organozincates (Scheme 1c).

A previous report on the Ti-mediated condensation of amides and aldehydes to generate sterically hindered enamides in the presence of triethylamine prompted us to explore these reaction conditions to access α-branched *N*-acylamines.[7] We

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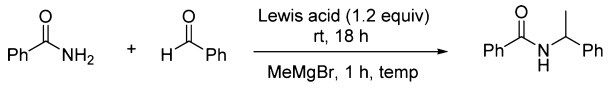
hypothesized that the putative *N*-acylimine or *N*,*O*-hemiaminal enamide precursor could be trapped upon addition of a suitable nucleophile to afford α-branched *N*-acyl amine products.

At the outset of our studies, we selected benzamide (**1**) and benzaldehyde (**2**) as test substrates to optimize the reaction conditions following the reported protocol using methylmagnesium bromide as a source of nucleophile (Table 1). The

Table 1. Optimization of the Ti-Mediated Three-Component Condensation



1 **2** **3**

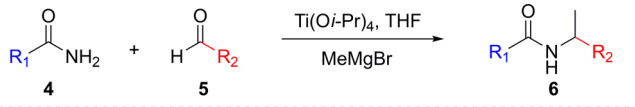
entry	Lewis acid	solvent	base[a]	MeMgBr[a]	temp (°C)	yield[b] (%)
1	$TiCl_4$	DCE	5	5	rt	16
2	$Ti(Oi\text{-}Pr)_4$	THF	0	5	rt	65
3	**$Ti(Oi\text{-}Pr)_4$**	**THF**	**0**	**5**	**60**	**77**
4	$Ti(Oi\text{-}Pr)_4$	THF	0	4	60	72
5	$Ti(Oi\text{-}Pr)_4$	THF	0	3	60	34

[a]Equivalents of reagent. [b]Isolated yield.

conditions operative for the formation of enamides, $TiCl_4$ (1.2 equiv) and NEt_3 (5 equiv) in DCE at room temperature, only afforded α-methyl-*N*-acylamine **3** in 16% isolated yield (entry 1). Several side products were observed under these reaction conditions including the presumed *N*-acylimine and bis-*N*-acyl-*N*,*N*-hemiaminal product resulting from the addition of a second amide molecule as well as cinnamaldehyde well-known to form under these reaction conditions.[8] Further optimization (for more details, see the Supporting Information) showed that the reaction in THF using $Ti(Oi\text{-}Pr)_4$ in place of $TiCl_4$ and in the absence of NEt_3 led to a cleaner reaction profile with 65% isolated yield (entry 2). These results hint to the key role of $Ti(Oi\text{-}Pr)_4$ (versus $TiCl_4$) and the detrimental effect of the base; both points are in sharp contrast with the conditions reported for the formation of enamides.[7] An increased yield (77%) was observed when the reaction mixture was stirred at 60 °C for 1 h after Grignard addition (entry 3). The stoichiometry of Grignard reagent also proved critical to ensure the formation of product in high yields (entries 3−5).

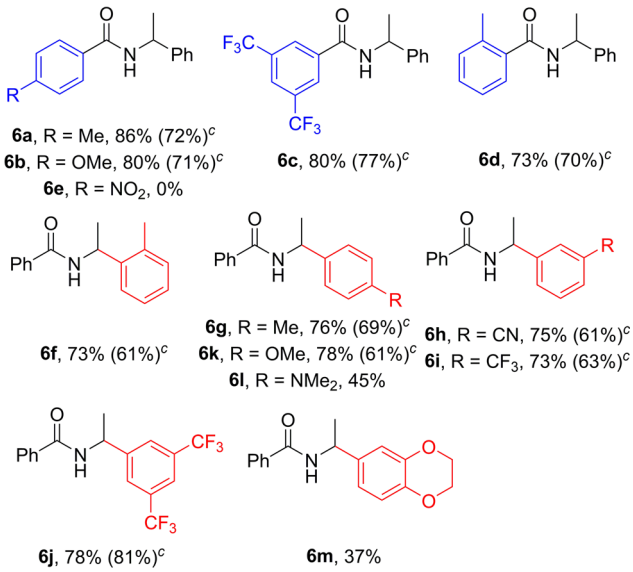
With our optimized conditions in hand, the substrate scope was investigated starting with electronically differentiated aryl amides (Scheme 2a). The electronics of the aryl group did not seem to impact the nucleophilicity of the amido group given that both electron-rich (*p*-methyl, *p*-methoxy) and electron-deficient (*m*-bistrifluoromethyl)benzamides worked equally well to form *N*-acylamines **6a−c** in 86%, 80%, and 80% yields. Increased steric bulk at the *ortho* position (**6d**) did not impact the yields significantly. *p*-Nitrobenzamide failed to give product **6e**. This is consistent with the known propensity of Grignard reagents to react with nitro-aromatics.[9] The benzaldehyde coupling partner appeared more sensitive to the electronics of the ring. *o*- and *p*-methyl benzaldehydes (**6f,g**) worked equally well along with electron-deficient benzaldehydes (**6h−j**), presumably enhancing the electrophilicity of the carbonyl group. However, an electron-rich substituent such as *p*-methoxy (**6k**) did not impact the yield. Increasing aromatic electron-density with the *N*,*N*-dimethylamino and the catechol motifs still generated *N*-acylamines **6l** and **6m**, albeit in lower yields.[10] In agreement with our optimization of conditions, the

Scheme 2. Ti-Mediated Coupling of Aromatic Amides and Aldehydes Followed by MeMgBr Addition[a,b]

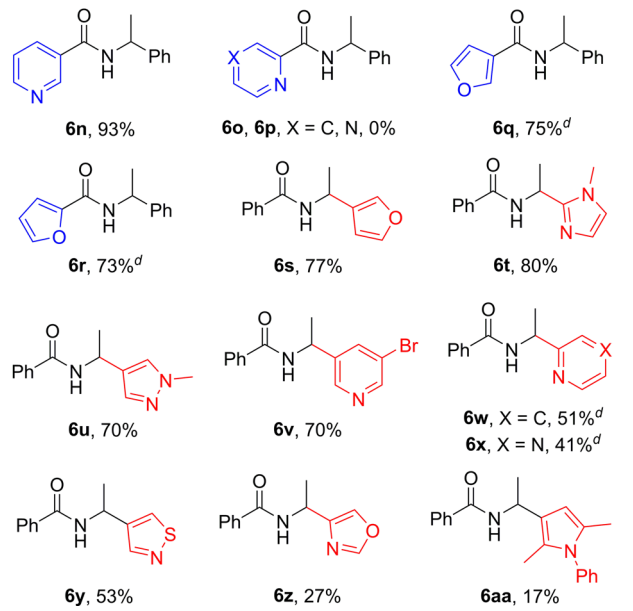


4 **5** **6**

a. Aromatic amides and aldehydes:



b. Heteroaromatic amides and aldehydes:



[a]Conditions: aldehyde (1.0 equiv), amide (1.05 equiv), $Ti(i\text{-}OPr)_4$ (1.2 equiv), THF, 18 h, rt; MeMgBr (5.0 equiv), 60 °C, 1 h. [b]Isolated yields. [c]Reaction carried out at room temperature. [d]The reaction mixture was also stirred at 60 °C for 1−3 h before Grignard addition.

transformation can be run at room temperature with minimal loss of efficiency.

To our delight, a diverse set of heteroaromatics was tolerated under the reaction conditions (Scheme 2b). For instance, reaction of benzaldehyde with nicotinamide provided *N*-acylamine **6n** in 93% isolated yield. However, attempts to

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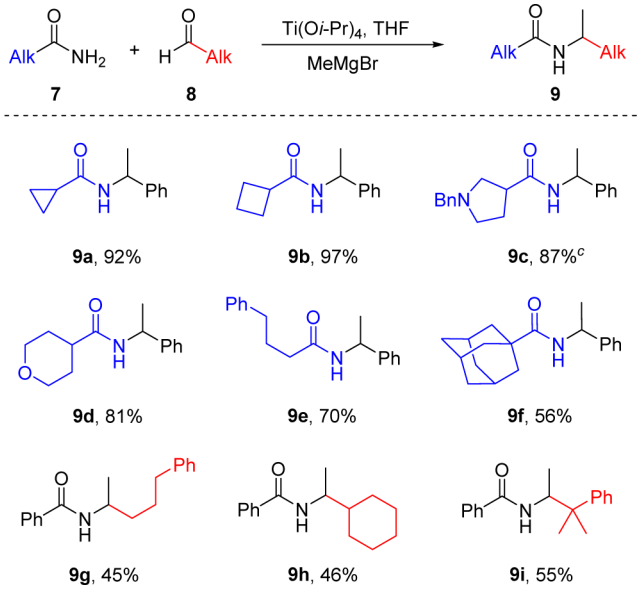
couple either picolinamide or pyrazine-2-carboxamide with benzaldehyde failed to afford **6o** and **6p**, supposedly due to the formation of a stable 5-membered titanacycle precluding any further reaction. In contrast, heterocyclic aldehydes reacted successfully to generate the products in remarkably good yields considering the presence of several chelating atoms (N, O, S). This includes motifs such as furans (**6q−s**), imidazole (**6t**), pyrazole (**6u**), pyridines (**6v,w**), pyrazine (**6x**), isothiazole (**6y**), oxazole (**6z**), and pyrrole (**6aa**). The low yields observed in some instances were either due to the difficult isolation/shelf stability of the prepared starting aldehydes (**6y**) or the increased steric hindrance (**6aa**).[11]

To further demonstrate the substrate scope of this method, we continued our study with aliphatic substrates (Scheme 3).

Scheme 3. Condensation of Aliphatic Amides and Aldehydes[a,b]

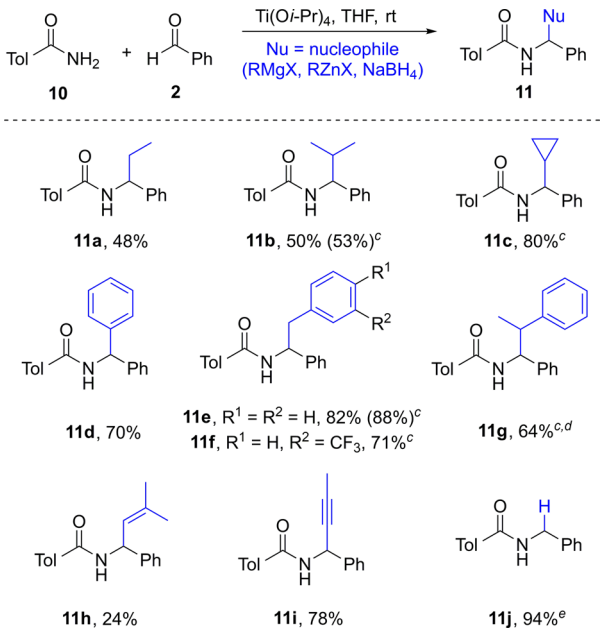


[a]Conditions: aldehyde (1.0 equiv), amide (1.05 equiv), Ti(*i*-OPr)$_4$ (1.2 equiv), THF, 18 h, rt; MeMgBr (5.0 equiv), 60 °C, 1 h. [b]Isolated yields. [c]Isolated as a mixture of two diastereomers.

Aliphatic linear and *α*-branched amides were all suitable substrates that led to a highly efficient coupling (**9a−e**). The bulkier adamantane-1-carboxamide led to slightly diminished yield (**9f**). *α*-Proton-containing aliphatic aldehydes such as linear 4-phenylbutyraldehyde and *α*-branched cyclohexanecarboxaldehyde successfully afforded the desired products (**9g,h**) in spite of the competing enamide formation. It is noteworthy that the hindered 2-methyl-2-phenyl-1-propanal reacted as efficiently as benzaldehyde to form **9i** in 55% yield.[12]

To maximize the potential of this three-component reaction, we finally decided to explore a range of commercially available Grignard and organozinc reagents (Scheme 4). Even though Grignard reagents with *α*-hydrogens can undergo *β*-hydride elimination giving rise to an olefin and a titanohydride complex, ethyl- and isopropylmagnesium bromide both reacted smoothly to form *N*-acylamines **11a** and **11b** in 48% and 50% yields, respectively. The use of an organozinc equivalent (*i*-PrZnCl) to form **11b** did not impact the yield (53%) significantly. Organozincates were demonstrated to be generally efficient under these reaction conditions; for instance, cyclopropylzinc chloride was used to generate *N*-acylamine **11c** in a remarkable

Scheme 4. Grignards and Organozincates Addition[a,b]



[a]Conditions: aldehyde (1.0 equiv), amide (1.05 equiv), Ti(*i*-OPr)$_4$ (1.2 equiv), THF, 16 h, rt, MeMgBr (5.0 equiv), rt, 1 h. [b]Isolated yields. [c]The corresponding organiczinc was used in place of the Grignard reagent. [d]The product was isolated as a mixture of two diastereomers. [e]$NaBH_4$ was used as nucleophile in place of the organometallic reagent.

80% isolated yield. Grignard or organozinc sources of phenyl and benzyl derivatives all proceeded smoothly to form the products in moderate to excellent yields (**11d−g**; 64−88%). Vinyl- and propargylmagnesium bromides reacted as well (**11h,i**) and provided reasonable yields. In addition, *α*-branched *N*-acyl propargylic amines (similar to **11i**) are known to cyclize under mild conditions (catalytic $FeCl_3$, DCE, 80 °C or IPrAuCl, $AgNTf_2$, DCM, rt) to form oxazoles,[13] which makes this method an alternate and highly versatile strategy to access trisubstituted oxazoles. The use of a reductant such as $NaBH_4$ as nucleophile enabled the isolation of *N*-acylamine **11j** in 94% yield.

While the exact reaction mechanism remains under investigation, we presume that the amide adds to the Ti(O*i*-Pr)$_4$−aldehyde complex to initially form a six-membered *N*-acyl *N,O*-acetal titanocycle **12** (Figure 1). At this point, it is possible

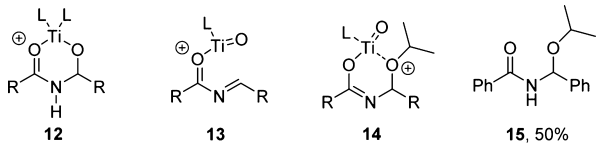


Figure 1. Putative reaction intermediates.

that key imine intermediate **13** is formed via deprotonation of the nitrogen proton by the Grignard reagent. Such an intermediate is likely to undergo a reaction mechanism similar to Ellman's 1,2-addition of Grignard reagents to sulfinimines.[14] It is also possible that chelate **14** is generated in situ given that *N*-acyl-*O*-isopropyl *N,O*-acetal **15** was isolated on several occasions (see the SI). The formation of related *N,O*-acetals under similar reaction conditions is known in the literature.[15]

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When *N*,*O*-acetal **15** was submitted to the reaction conditions with MeMgBr with or without the titanium Lewis acid, full conversion to the desired methylated product was observed.

To conclude, we developed the first three-component condensation of amides, aldehydes, and organometallic reagents to form α-branched *N*-acylamines in good to high yields. The method is highly versatile with a broad substrate scope, and each of the three coupling partners is commercially available or easily prepared. The high level of diversity achievable with this operationally practical one-step protocol is well suited to the fast screening of chemical matter in small library format to progress medicinal chemistry projects efficiently. The use of differentiated nucleophiles to expand the chemical diversity of the products is currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00082.

Reaction optimization details, procedures, and full characterization of the products (PDF)

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Notes

The authors declare no competing financial interest.

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(11) Amide bond cleavage of the heterocyclic products under acidic conditions may also be a cause for the lower yields.

(12) When the amide coupling partner was replaced by urea or carbamate starting materials, no reaction was observed. Similarly, the use of acetophenone provided no reaction.

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