<u>Cramic</u> LETTERS

N-Heterocyclic Carbene Catalyzed Highly Chemoselective Intermolecular Crossed Acyloin Condensation of Aromatic Aldehydes with Trifluoroacetaldehyde Ethyl Hemiacetal

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Supporting Information

ABSTRACT: A highly chemoselective intermolecular crossed acyloin condensation between aromatic aldehydes and trifluoroacetaldehyde ethyl hemiacetal has been developed under mild reaction conditions using *N*-heterocyclic carbene as a catalyst. A wide range of aromatic aldehydes bearing electron-withdrawing and -donating substituents underwent a smooth transformation to their corresponding trifluoromethyl containing acyloin derivatives in moderate to good yields.

T he distinctive reactivity of *N*-heterocyclic carbenes (NHCs) has been well investigated for the intermolecular homodimerization of aldehydes (Benzoin and acyloin condensation).¹ Nevertheless, the intermolecular cross benzoin or acyloin condensations remain challenging due to a mismatch between the reactivity of aldehyde and the coupling partner (usually another aldehyde). Choosing the right coupling partner is a crucial task in the crossed acyloin reaction; otherwise, the reaction would lead to four different acyloins including two homodimerized products (Scheme 1).



In order to execute the cross-benzoin/acyloin reaction chemoselectively, the coupling partner must be chosen in such a way that it must not react with the NHC, and at the same time its reactivity toward Breslow intermediate² must be more than that of the aldehyde. In line with this concept, many successful reports have appeared in the literature for the asymmetric intramolecular benzoin reaction^{1,3} as well as the inter-/intramolecular Stetter reaction.^{1,4} However, only a handful of reports are available for the intermolecular crossed acyloin type reactions. The first intermolecular crossed acyloin condensation was reported by the Stetter group.⁵ This seminal report was followed by Inoue's contribution, which deals with the cross coupling of aliphatic aldehydes with formaldehyde.⁶



Later, Glorius developed a competent approach for the highly chemoselective hydroxymethylation of aldehydes.⁷ Müller and co-workers reported an enantioselective cross-benzoin reaction through enzymatic cross-coupling of aromatic aldehydes using ThDP-dependent benzaldehyde lyase (BAL).8 Independent reports by Glorius⁹ as well as Zeitler and Connon¹⁰ display that high levels of chemoselectivity could be achieved by introducing a substitution, especially chloro or bromo, at the ortho position of aromatic aldehydes. Yang's group has demonstrated that the choice of NHC is the crucial factor for switching the regioselectivity in crossed acyloin condensation.¹¹ Recently, Gravel reported a highly chemoselective crossbenzoin reaction using morpholinone or piperidinone derived triazolium NHC as a catalyst.¹² The Scheidt group has developed fluoride mediated desilylative coupling of O-silyl thiazolium carbinols with aliphatic aldehydes leading to crossed acyloins.13

In addition, Enders' group has developed an NHC catalyzed chemoselective cross-benzoin reaction of aldehydes with trifluoromethyl ketones.¹⁴ Johnson's group reported a regiospecific cross silyl benzoin reaction using trimethysilyl ketones as donors.¹⁵ Apart from these methods, a few other protocols were also reported for the chemoselective cross-benzoin-type reaction, where α -keto esters¹⁶ or imines¹⁷ were used as acceptors.

While working on NHC catalyzed transformations, we envisioned that the chemoselectivity in the intermolecular crossed acyloin/benzoin reaction could be enhanced if an "aldehyde equivalent" is used as a coupling partner instead of another aldehyde. Herein we report a highly chemoselective intermolecular crossed acyloin reaction of aromatic aldehydes using trifluoroacetaldehyde ethyl hemiacetal $[CF_3CH(OH)-$

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OEt] as an aldehyde equivalent (coupling partner). Although $CF_3CH(OH)OEt$ has been reconnoitered as an aldehyde equivalent in a few other transformations,¹⁸ it has not been explored yet in acyloin condensation. We were particularly interested in $CF_3CH(OH)OEt$ because, unlike other hemiacetals, it is highly stable and commercially available (as 90% aq. solution). Moreover, this hemiacetal introduces the trifluoromethyl group in the acyloin product, which could be easily transformed to pharmaceutically important trifluoromethyl containing heterocycles or drugs.¹⁹

The optimization studies were carried out using *p*-chlorobenzaldehyde (1) and a variety of NHC precursors (7-11) under different reaction conditions (Table 1). Initially,



^{*a*}Reaction conditions: 0.15 M of 1 in solvent. Use of 2 equiv of 2 with respect to 1 was found to be optimal. ^{*b*}Ratio determined by ¹H NMR analysis of the crude mixture after workup. ^{*c*}Isolated yield. rt = 23-26 °C.

we carried out an experiment using 7 as a catalyst (entry 1) and the anticipated crossed acyloin adduct 3 was formed only in 7% yield. Indeed, this result was encouraging because the crossed acyloin product 3 was formed in a chemoselective manner, albeit the yield was quite low. Screening of other NHCs 9 and 10 did not give promising results, as a considerable amount of 4 was obtained and/or the yield of 3 was low (entries 3 and 4). Intriguingly, when the reaction was performed using NHC 11 as a catalyst and DBU as a base, the desired crossed acyloin 3 was obtained in 90% yield with high chemoselectivity (entry 5). Further optimization studies were performed using 11 as a catalyst by altering the base or solvent (entries 6-12). But in all those cases, the yield of the desired product was inferior when compared to entry 5. A noteworthy observation was that the other possible products 5 and 6 were not formed under the reaction conditions. The acyloins 5 and 6 are possible only if trifluoroacetaldehyde is produced during the reaction. To have

a better understanding of this observation, an experiment was carried out in which $CF_3CH(OH)OEt$ was subjected to self-acyloin condensation using 11 as a catalyst followed by esterification with *p*-nitrobenzoyl chloride under basic conditions (Scheme 2). Interestingly, in this case, the acyloin ester

Scheme 2. Control Experiment with CF₃CH(OH)OEt



12 was not observed; instead the acetal ester 13 was isolated in 55% yield. This experiment suggests that $CF_3CH(OH)OEt$ does not decompose to trifluoroacetaldehyde under the reaction conditions, which also explains why 5 and 6 were not observed in any of the reaction conditions tried (Table 1).²⁰

Having optimized conditions in hand (entry 5, Table 1), we shifted our attention in evaluating the substrate scope. As shown in Scheme 3, a wide range of aromatic aldehydes were treated with CF₃CH(OH)OEt under standard reaction conditions. In all cases, the expected crossed acyloin adducts were obtained in moderate to good yields with high levels of chemoselectivity (>95:5). A general observation was that the yields of products in the cases of electron-rich aldehydes (14b-14d) were found to be a bit inferior when compared to those of electron-poor aldehydes (14e-14i). Interestingly, in the cases of halo- and dihalo-substituted aryl aldehydes, the desired acyloin products (14k-14q) were obtained in good yields. Even highly hindered aldehydes such as ortho-bromo substituted aromatic aldehydes underwent smooth conversion to the corresponding products in good yields (14r and 14s). This methodology also worked very well for heteroaromatic aldehydes as well (e.g., 14u-14x). In the case of aliphatic aldehydes such as hydrocinnamaldehyde and phenylacetaldehyde, complex mixtures were obtained. But, cinnamaldehyde was efficiently converted to the acyloin 14t in 66% yield. We also tried to elaborate this methodology to other cyclic hemiacetals (such as lactols and carbohydrate derivatives) as well as acyclic acetals.²¹ Unfortunately, none of them reacted with 1 under standard reaction conditions to give the crossed acyloin products. In all those cases, only benzoin 4 was observed.

It is obvious from the outcome of the reaction that the Breslow intermediate reacts with CF₃CH(OH)OEt chemoselectively to deliver the crossed acyloin product. To understand the reaction in detail, a few experiments were performed. In a typical crossover experiment (Scheme 4), benzoin 15a was treated with an excess of 2 under the standard reaction conditions and the reaction was monitored by ¹H NMR spectroscopy, but the crossed acyloin product 14a was not detected even after 2 days. This experiment clearly indicates that benzoin 15a did not undergo a retro-benzoin reaction under the reaction conditions. This result also suggests that the formation of 15a is irreversible. In another experiment, the standard reaction (Table 1, entry 5) was monitored by ¹H NMR spectroscopy. In this case, the formation of product 3 was observed prior (within 5 min) to the formation of 4. The above experiments clearly show that the chemoselectivity outcome of the reaction is controlled by kinetic factors.





"Yields reported are isolated yields. ^b Ratio determined by ¹H NMR analysis of the crude mixture after workup. rt = 23-26 °C.





To demonstrate the synthetic utility of the products, one of the trifluoromethyl containing crossed acyloin products (3) was refluxed with a small amount of excess of *o*-phenylenediamine (16) in acetic acid and the CF₃-containing quinoxoline 17 was obtained in 65% yield (Scheme 5).²²

In summary, we developed a highly chemoselective crossed acyloin reaction of aromatic aldehydes with CF₃CH(OH)OEt





using NHC as a catalyst. Further elaboration to an enantioselective version will be the focus in the near future. Also, detailed investigation to understand the mechanism is currently underway.

ASSOCIATED CONTENT

S Supporting Information

General experimental procedures and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) Another conceivable explanation for the outcome of the reaction is that even if trifluoroacetaldehyde is present in the solution, the Breslow intermediate derived from it is expected to have a poor nucleophilicity; therefore, it may not react with another molecule of trifluoroacetaldehyde to give 5.

(21) The cross acyloin reaction of *p*-chlorobenzaldehyde (1) with the following hemiacetals/acetals (A-C) was tried under standard conditions.



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