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Redox-neutral Metal-free Three-component Carbonylative Dearomatization of Pyridine Derivatives with CO_2

Alessandro Cerveri,[a] Stefano Pace,[a] Magda Monari,[a] Marco Lombardo*[a] and Marco Bandini*[a]

Abstract: The TBD (1,3,5-triazabicyclodec-5-ene) assisted three-component carbonylation of pyridine-2-methanamines is documented by means of CO_2 as a benign CO surrogate. The redox-neutral methodology enables the realization of densely functionalized imidazo-pyridinones in high yields (up to 93%) and excellent chemoselectivity. Combined computational and experimental investigations revealed an unprecedented RCOCl/TBD concerted electrophilic activation of carbon dioxide.

The carbonylation reaction of organic compounds is counted among the most useful synthetic methodology in organic as well as organometallic chemistry.[1] In this scenario, the ongoing seek for replacing highly toxic carbon monoxide with more environmentally benign and easy handling chemical entities is noteworthy.

The use of CO_2 as a carbonylative surrogate is becoming a popular synthetic tool being a highly desirable, abundant, nontoxic one-carbon synthon.[2,3] On the other hand, the combined requirements of stoichiometric reducing agents and noble metal catalysis could represent an obstacle to apply this straightforward approach to large scale productions.[4]

Alternatively, the so called "redox-neutral" carbonylation reaction based on CO_2 can be conveniently adopted for the direct carbonylation of bifunctional compounds, also via C-H activation events, in absence of external reductants.[5]

The field was pioneered by Iwasawa on *ortho*-alkenyl(aryl) phenols[6a] and faced a rapid expansion to aniline[6b-e] and ketone derivatives.[6f] However, despite the undoubted efficiency, the requirements of 5d-TMs catalysis, strong inorganic bases (*i.e.* CsF, NaO*t*Bu, LiO*t*Bu) or super-stoichiometric electrophilic co-activators (*i.e.* MeOTf) are crucial issues that predict further developments in the field.[7]

In continuation with our ongoing interests focused in the chemical manipulation[8] and dearomatization[9] of aromatic compounds,[10] we decided to combine the aforementioned carbonylation strategies to tackle an ongoing "synthetic challenge" in the dearomatization reaction realm: the pyridine.[11] It should be emphasized that the use of "electrophilic" CO_2 as a reaction partner in dearomatization processes is almost unknown[12] and this can be conveniently rationalized by considering that both processes, namely CO_2 activation and aromaticity loss are highly energy demanding.

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Final target of the protocol would deal with the realization of a direct synthetic access to an important class of pharmacologically active bicyclic-fused arenes: namely imidazo-pyridinones **A** (Figure 1).[13] As such, a simple deconvolution of the acylated pyridinone scaffold prompted us to verify the potential double role of acyl chlorides (*i.e.* acylating agents and electrophilic co-activators of CO_2) in a three component dearomative process involving pyridine-2-methanamines as the pyridyl reagent.[14]

In this communication, our initial findings in the redox-neutral TBD-assisted three-components one-pot synthesis of imidazo-pyridinone scaffolds, via pyridine dearomatization, is presented. A full mechanistic interpretation is also documented by means of a dedicated and combined experimental, spectroscopic and computational analysis.

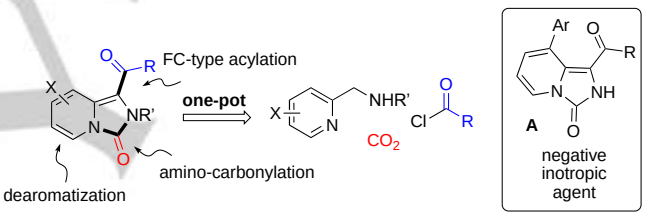

Figure 1. Working plan for the one-pot synthesis of imidazo-pyridinones via redox-neutral CO_2 based carbonylation.

At the outset of the investigation, we addressed our attention to a metal-free methodology in order to positively impact the overall synthetic sustainability. In this direction, the superbase TBD was targeted as an organocatalyst[15] in the condensation of pyridine **1a** and benzoylchloride (**2a**) under CO_2 atmosphere.

Chemoselectivity (*i.e.* formation of the *N*-benzoyl-pyridine methanamide **3aa'**) as well as regioselectivity (*i.e.* site-selective final acylation) emerged as major obstacles to be faced in the titled transformation. However, we were pleased to record that upon an extensive screening of reaction conditions (see SI for a complete list of attempts), the use of **1a**:**2a**/TBD/TEA (1/3/0.5/2.5) in MeCN at 140 °C (reaction time = 0.5 h) led to the pyridinyldene adduct **3aa** in 93% yield with specific acylation at the C(1)-position (Table 1, entry 1).

Variations from optimal conditions resulted in a significant drop in reaction performance as highlighted in the Table 1. In particular, CO_2 proved fundamental for the protocol, as a matter of fact, when the process was run under nitrogen atmosphere the amide **3aa'** was isolated quantitatively (entry 2). Interestingly, by comparing entries 3 and 4 emerged that the electrophilic activation exerted by TBD towards CO_2 was crucial for the carbonylation event. In fact, by adopting pre-formed TBD-CO_2 carbamate[15c] in the titled process (entry 4), **3aa** was isolated in comparable yield to entry 3 (55% *vs* 66%, respectively). Other

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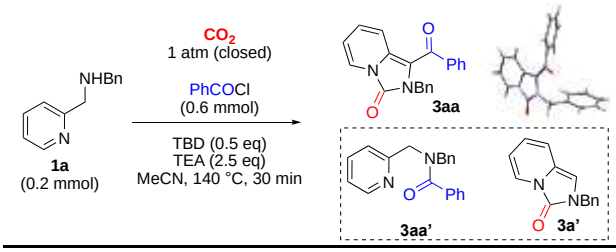
tertiary amines (*i.e.* DABCO) proved less efficient with respect to TBD in the activation of the CO_2 (entry 8) while TEA was selected as acidity scavenger with respect to DIPEA and DABCO (entries 6 and 7) for the highest selectivity furnished.

Table 1. Variations from the optimal conditions in the three-component synthesis of imidazo-pyridinones **3**.

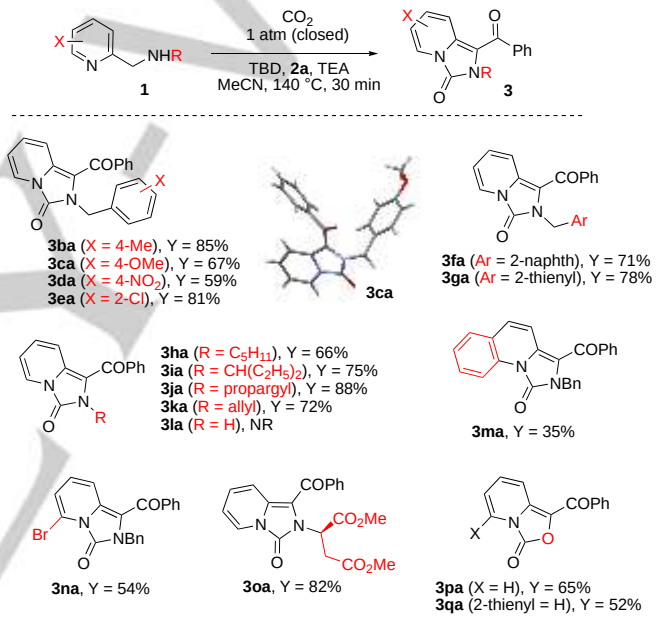


Run[a]	Deviations from optimal	Yield (%) **3aa**[b]	Yield (%) **3aa'**[b]
1	--	93	traces
2	NO CO_2	--	95
3	TBD (3 eq) and no TEA	66	28
4[c]	Preformed TBD-CO_2 (3 eq)	55	40
5	DBU (3 eq) instead of TBD	31	58
6	DIPEA (2.5 eq) instead of TEA	71	15
7	DABCO (2.5 eq) instead of TEA	86	9
8	DABCO (0.5 eq) instead of TBD	68	26
9[d]	No TBD and TEA (3.0 eq)	42	50
10	TBD (0.2 eq)/TEA (2.8 eq)	53	41

[a] All the reactions were carried out with anhydrous solvents, unless otherwise specified. [b] Determined after flash chromatography. [c] Under N_2 atmosphere. [d] Reaction time = 3 h. X-ray structure of **3aa** is also represented (see SI).

Attempts to lower further the TBD loading at 20 mol% (entry 10) caused a marked drop in **3aa** formation (yield = 53%) with the concomitant isolation of the amide **3aa'** in significant amount (41%). Finally, the crucial role of TBD in accelerating the CO_2 fixation was ascertained by running the model annulation with TEA (3 eq) as the only basic additive. The isolation of **3aa** in 42% yield in 3 h suggested that moderate CO_2 activation could also be exerted by the methanamine **1a** itself.[16] It is worthy to mention that in some sporadic cases the formation of **3a'** in traces was observed.

The protocol proved extremely high flexibility in terms of functional group tolerance performing effectively for a large variety of multi-component one-pot dearomative events. Variations on the pyridine amine congeners were operated both at the amine group and pyridyl core (**1b**-**q**). From the data collected in the Scheme 1 emerged that secondary benzylamines worked excellently in the process delivering the corresponding three-component adduct **3** in very good yields (up to 85%) regardless size, electronic features and substitution patterns at the benzylic site (**3ba**-**3fa**). It is worth of mention that, also electron-rich heteroarenes (*i.e.* thiophene) were adequately tolerated, showing high regioselectivity towards the final C(1)-imidazo-FC-acylation (**3ga**, yield = 78%). The replacement of the benzylic groups with other C-sp^3 units (*i.e.* *n*-C_5H_{11}, allyl, propargyl and $CH(C_2H_5)_2$) was also envisioned (**3ha**-**3ka**) and good to excellent yields (up to 88%) were achieved in all cases. On the contrary, the primary pyridine-2-methanamine **1l** proved unsuitable for the titled transformation, delivering the amide **3la'** as the exclusive product.[17] Modifications on the pyridine ring were also assessed by employing the quinoline analogous **1m** and the 6-Br derivative **1n**. In these reactions, moderate to good yields (35-54%) were obtained. Finally, the protocol was not exclusively restricted to nitrogen-based species, but also pyridyl alcohols **1p,q** reacted smoothly under optimal conditions delivering the corresponding 3*H*-oxazolo[3,4-*a*]pyridin-3-ones **3pa** and **3qa** in 65% and 52% yield, respectively.



Scheme 1. Reaction with anhydrous MeCN. **1**/**2a**/TBD/TEA = 1/3/0.5/2.5. NR = no reaction. X-ray structure of **3ca** is also represented (see SI).

Therefore, a survey of acylating agents **2b-j** was undergone and the results collected in Scheme 2. Aromatic carboxylic acid chlorides proved effectiveness regardless the electronic nature of the substituents as well as pattern of functionalization. They can easily accommodate both electrondonating and electronwithdrawing groups delivering the corresponding ketones **3** in up to 81% yield. Aliphatic acylating agents (**2h,i**) were also effectively tested in the titled reaction delivering the three-component adduct in serviceable yields: 84% and 79% respectively. Finally, we surmised that the installation of a trichloroacetyl unit at the C(1)-position would open interesting opportunities to generate carboxylic derivatives. In this regard, we were pleased to verify that trichloroacetyl chloride **2j** worked smoothly in the three-component strategy resulting in **3aj** with 69% yield.

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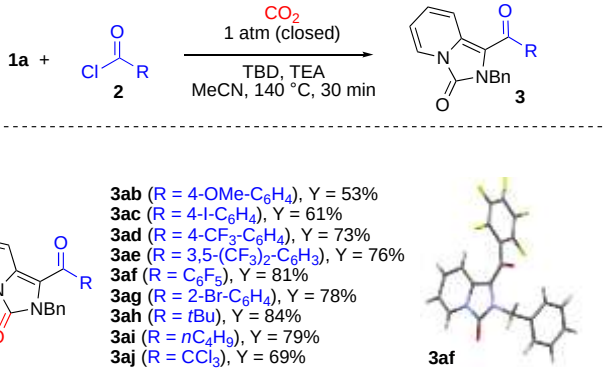

Scheme 2. Reaction with anhydrous MeCN. **1a**/**2**/TBD/TEA = 1/3/0.5/2.5. X-ray structure of **3af** is also represented (see SI).

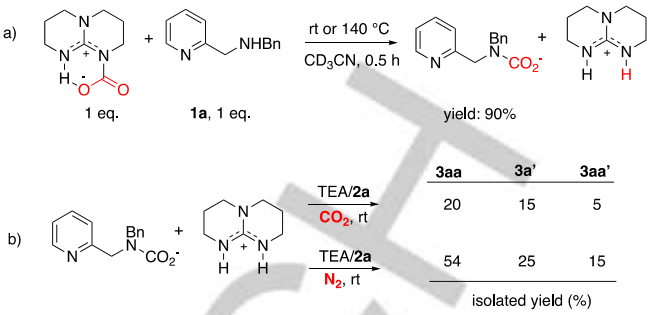

Figure 2. Experiments of a) *trans*-carbonylation between TBD and **1a**; b) proving the poisoning effect of CO_2 towards TBD during the reaction course (**1a**-CO_2/TBD/TEA/**2a**: 1/1/2/3.

We then turned our attention to shed some light on the reaction profile by means of a series of dedicated experimental, spectroscopic and computational investigations.

The carbonylative events involving TBD and benzylamine **1a** was firstly studied. Interestingly, by monitoring the reaction of preformed TBD-CO_2[15b] and **1a** in CD_3CN under nitrogen, (^{1}H-NMR and FT-IR), we discovered that a quantitative CO_2 transfer from TBD-carbamate to **1a**-CO_2 analogous occurred both at rt and 140 °C in 30 min (Figure 2a and *vide infra* for mechanistic hypotheses).[18] Therefore, **1a**-CO_2^-/TBDH$^+$ mixture (1 eq) was allowed to react with TEA (2 eq) and **2a** (3 eq) under two different environmental regimes at rt: CO_2 and N_2. Here, while the cyclization under CO_2 performed poorly, providing a **3aa**/**3a'**/**3aa'** mixture only in 30% overall yield (4/3/1 ratio by ^{1}H-NMR crude), the presence of nitrogen conditions enabled the formation of a **3aa**/**3a'** mixture in 82% overall yield at rt (2.2/1 ratio, Figure 2b). These results clearly prove that i) free TBD is essential during the whole reaction course and specifically in the initial carbonation of **1a** and during the dearomatization event of the pyridine (*vide infra* for computational rationale) and ii) **3a'** is an intermediate of the reaction pathway that could undergo subsequent acylation reaction with the excess of chloride **2** to leave compound **3**.[19]

The structural determinations of three compounds, namely **3aa**, **3ca** and **3af** by SC-XRD studies were carried out. Loss of the aromaticity involving the pyridine unit has been detected in all cases since an alternation of double and single C-C bonds was observed in the pyridine rings (see Table S3).

Additionally, the reaction proved competence also at rt, however higher temperatures enable both better performance and the one-pot addition of all the reaction partners can be operable, concomitantly.[20]

These intriguing mechanistic insights prompted us to further explore the real role of TBD as a catalyst and the possible multiple-role played by the acid chloride. Therefore, a detailed DFT computational investigation of the reaction course relative to the formation of **3a'** was carried out at the ωB97X-D/6-31G(d) level of theory in CH_3CN. From this analysis (see Si for details) the catalytic cycle depicted in the Figure 3 is proposed.

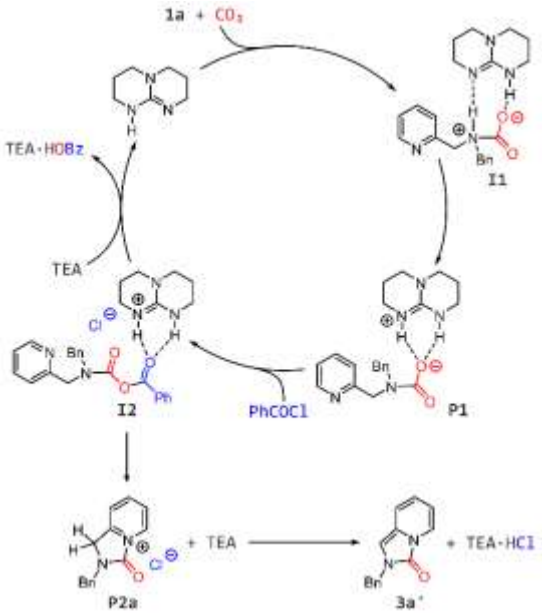

Figure 3. Proposed catalytic cycle for the CO_2-based synthesis of imidazo-pyridinone scaffolds.

Interestingly, no direct transfer between TBD-CO_2 adduct and **1a** was located. Indeed, free TBD acts as a bifunctional activator first templating the approach of **1a** and CO_2 then quickly deprotonating the intermediate **I1** and finally strongly stabilizing the final adduct **P1** through a hydrogen-bonding network with the carbamate moiety.[21]

TBD plays also a crucial role in the subsequent PhCOCl-promoted cyclization of intermediate **P1** to give the annulated zwitterionic intermediate **P2**. It should be emphasized also the

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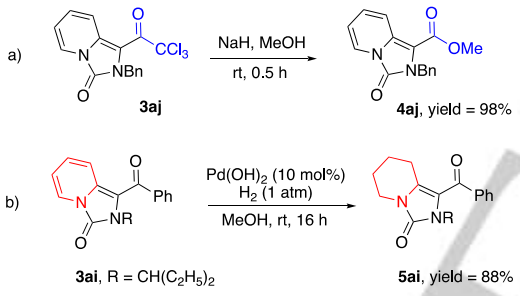
pillar activating role played by the acyl chloride that was found in forming the highly electrophilic mixed anhydride of the carbamic acid **I2**, responsible for the final dearomatization event.

In this process, transition states (**TS3** and **TS4**, see SI) are characterized by a S_N2-like concerted mechanism, where no tetrahedral intermediate is located.[22] Here the role of TBD as a Brønsted acid is again pivotal in making the benzoate unit a much better leaving group, allowing the nucleophilic attack by the pyridyl nitrogen and leading to the formation of the zwitterionic product **P2**. The final deprotonation step of **P2a** to the neutral intermediate **3a'** was modelled using both TEA and TDB as the base (see SI for details) leading to very favourable exergonic reaction paths. Furthermore, the three-component adduct **3** could be easily obtained via Friedel-Crafts type acylation.[23]

Finally, the synthetic manipulation described in Scheme 3 clearly underlined the chemical modulability of the final compounds **3**. In particular, the trichloro derivative **3aj** was effectively subjected to methanolysis in the presence of NaH/MeOH to give the corresponding methyl ester **4aj** in 98% yield (Scheme 3a). Additionally, the partially dearomatized pyridine ring provides an expedient platform that can be conveniently (88% yield) and selectively reduced to a piperidinyl core (*i.e.* **5ai**) by means of mild reducing conditions ($Pd(OH)_2/H_2$/MeOH, Scheme 3b).



Scheme 3. Examples of synthetic manipulation of the **3**.

In conclusion, a redox-neutral metal-free dearomative carbonylation of pyridine derivatives with CO_2 is documented. The three-component one-pot methodology enables the realization of a large library of densely functionalized and synthetically flexible imidazo- and oxazolo-pyridinones in excellent yield and chemo-/regioselective manner. The intriguing role of TBD as a promoter and RCOCl as an electrophilic CO_2 coactivator and acylating agent are proposed and disclosed by means of combined experimental, spectroscopic and computational investigations. Attempts to extend the present CO_2 activation mode to the synthesis of other densely functionalized heterocyclic scaffolds is currently under way in our laboratories.

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Keywords: CO_2 • Carbonylation • Metal-free • Pyridine • Dearomatization reaction

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[19] **3aa** can be obtained (35% yield) by treating **3a'** with TBD and **2a** both at rt and 140 °C.

[20] Among other possible aspects, high T could also favor the partial TBD-CO_2 dissociation during the reaction course even in the presence of a carbon-dioxide regime.

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[23] Subjecting **3a'** to optimal conditions (in absence of **1a**) led to acylated **3aa** in 35% yields.

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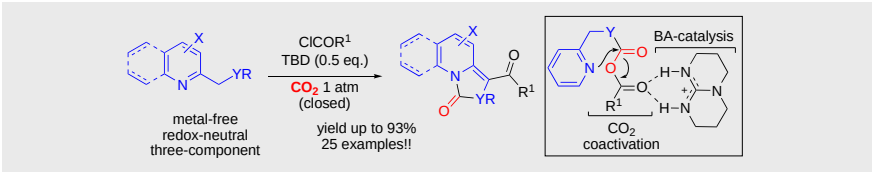

Three is better than two. A three-component metal-free carbonylative dearomatization of pyridine derivatives is documented with CO_2 as CO surrogate. A range of imidazo-pyridinones is obtained in high yield (up to 93%) via an unprecedented RCOCl/TBD concerted electrophilic activation of carbon dioxide (see Scheme).

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