

CARBON DIOXIDE-CATALYZED STEREOSELECTIVE CYANATION OF COUMARINS

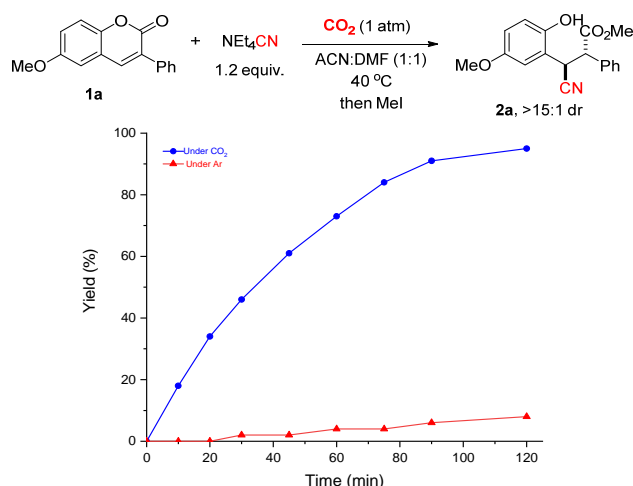
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We report an unprecedented and operationally simple carbon dioxide catalyzed conjugate 1,4-addition of cyanide to coumarins followed by ring-opening/protonation cascade to obtain β -cyano carboxylic acid derivatives. Presently, there is no convenient methods to access the nitrile derivative of coumarins despite their potential as a synthon to a number of amine functionalized building blocks. Carbon dioxide in combination with cyanide spontaneously forms cyanofornate and bicarbonate in presence of water, which controls the delivery of nucleophilic cyanide.^{1,2} Under optimized reaction conditions, CO₂ catalyzed cyanation of a number of 3-substituted coumarins gave the corresponding β -nitrile carbonyls in high chemo- and diastereo- selectivity, whereas poorer reactivities and selectivities were obtained under argon or nitrogen (scheme 1). We performed detailed experimental and computation analysis to suggest the catalytic role of CO₂, bicarbonate and carbonic acid as Lewis- and Brønsted acids to activate the coumarins. The general applicability of the current protocol was validated by large scale (5 g) synthesis of methyl 3-cyano-3-(2-hydroxyphenyl)-2-phenylpropanoate followed by preparation of biologically relevant heterocyclic compounds with ease.



Scheme 1. Hydrocyanation and ring-opening reaction of coumarin 1a and a comparison of reactivities of 1a under CO₂ (blue) and argon (red) as a function of time.

[1] Murphy, L. J.; Robertson, K. N.; Harroun, S. G.; Brosseau, C. L.; Werner-Zwanziger, U.; Moilanen, J.; Tuononen, H. M.; Clyburne, J. A. C., *Science* 2014, 344, 75.

[2] Hering, C.; von Langermann, J.; Schulz, A., *Angew. Chem. Int. Ed.* 2014, 53, 8282-8284.