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Catalytic Decarboxylation of 2-Alkynoic Acids

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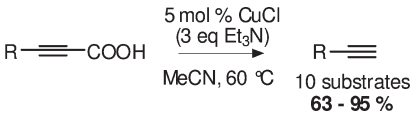


A very efficient protocol enabling catalytic decarboxylation of a wide range of 2-alkynoic acids is described. The reaction conditions and the scope of the process are examined. The method is further utilized in a model decarboxylative coupling.

Over the past years much attention has been paid to the chemistry of alkynes,[1] originating in the richness of the unique chemical transformations and geometric/electronic properties of alkynes. A relatively high reactivity of the terminal C−H bond frequently requires utilization of protecting groups, among which 2-hydroxypropyl **1** and trimethylsilyl **2** have a privileged position (Figure 1).

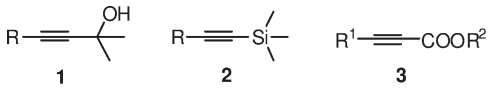
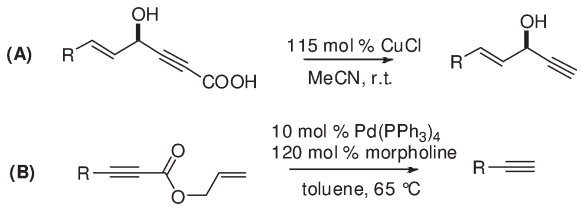


FIGURE 1. Protection for terminal alkynes.

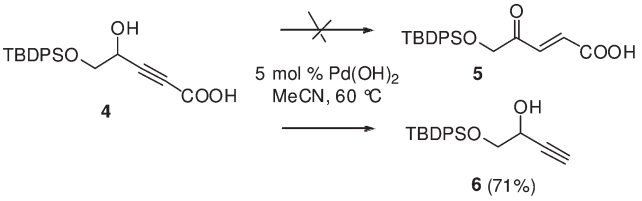
Alkoxycarbonyl group **3** is employed much less frequently; however, its presence might be necessary to achieve a high stereoselectivity.[2a] As well, after hydrolysis to the related carboxylic acid, one can take advatage of a classic resolution as an alternative. So far the most convenient methods of decarboxylation of 2-alkynoic acids and related esters involve decarboxylation with a stochiometric amount of CuCl (**A**)[2] and Pd-catalyzed deallylation−decarboxylation (**B**) (Scheme 1).[3a] In the first case, use of an excess of the transition metal reagent might be considered to be problematic, whereas method **B** relies on a relatively high loading of the costly catalyst. Additionally, the presence of morpholine is incompatible with sensitive substrates.

SCHEME 1. Methods of Decarboxylation of 2-Alkynoic Acids



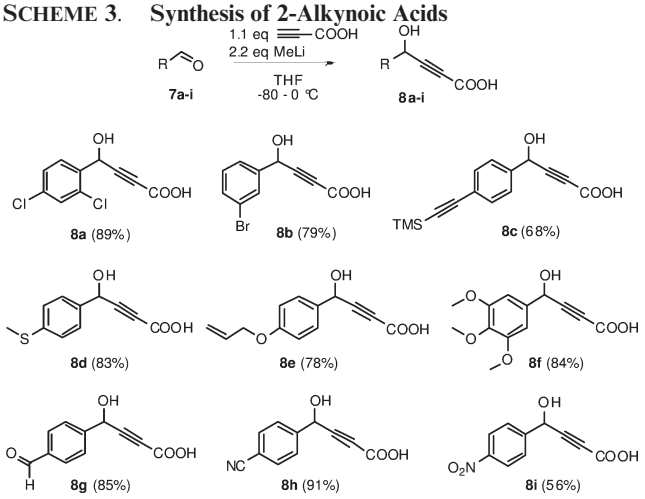
Our initial aim was to find a simple but general catalytic system allowing a redox rearrangement of propargylic alcohols.[4] During screening of selected catalysts, we found out that $Pd(OH)_2/C$ induces decarboxylation of the model substrate **4** (Scheme 2).

SCHEME 2. Observed Catalytic Decarboxylation[5]



Bearing in mind the information expressed in the Introduction, we were intrigued by the indicated transformation. To systematically evaluate the catalytic activity of $Pd(OH)_2/C$, we prepared an array of 2-alkynoic acids **8a**−**i**, putting emphasis on functional groups potentially interfering with the catalyst (Scheme 3).

SCHEME 3. Synthesis of 2-Alkynoic Acids



(1) *Acetylene Chemistry: Chemistry, Biology and Material Science*; Diederich, F., Stang, P., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005.

(2) (a) Trost, B. M.; Weiss, A. H. *Org. Lett.* **2006**, *8*, 4461–4464. For other examples, see: (b) Zimmerman, H. E.; Dodd, J. R. *J. Am. Chem. Soc.* **1970**, *112*, 6507–6515. (c) Caporusso, A. M.; Lardicci, L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 949–953.

(3) (a) Poulsen, T. B.; Bernardi, L.; Alemán, J.; Overgaard, J.; Jörgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 441–449. Original example: (b) Okamoto, S.; Ono, N.; Tani, K.; Yoshida, Y.; Sato, F. *Chem. Commun.* **1994**, 279–280.

(4) 2-Acylacrylic acids serve as substrate in crystallization-induced asymmetric transformations: (a) Jakubec, P.; Berkeš, D.; Kolarovič, A.; Považanec, F. *Synthesis* **2006**, 4032–4040. (b) Berkeš, D.; Kolarovič, A.; Manduch, R.; Baran, P.; Považanec, F. *Tetrahedron: Asymmetry* **2005**, *16*, 1927–1934. (c) Kolarovič, A.; Berkeš, D.; Baran, P.; Považanec, F. *Tetrahedron Lett.* **2005**, *46*, 975–978.

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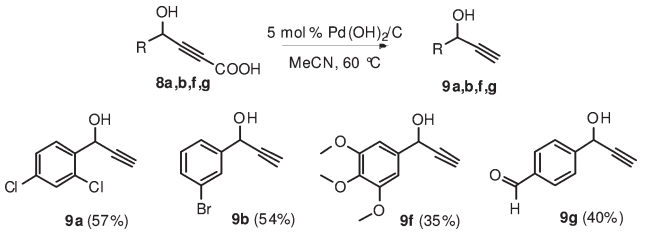
For the substrate synthesis we employed a combination procedure published by Midland (≡-COOR/*n*-BuLi)[6] and Tishler (≡-COOH/EtMgBr).[7] The synthetic approach chosen turned out to be reliable and enabled access to derivatives **8a**−**i** in good to excellent yields. Acids **8e**−**f,i** proved to be prone to decomposition, evincing as gradual darkening on manipulation. This was particularly true for acid **8i**, which we did not isolate as a pure compound, and the samples used contained 15−20% of products of decomposition (purity determined by ^{1}H NMR with internal standard). Under similar conditions, Koide reports a yield of <2%, in our opinion as a result of low stability of the compound.[8] Decarboxylative experiments on acids **8a,b,f,g** were disappointing and led to just average or low yields (Scheme 4).[5]

SCHEME 4. Decarboxylation Catalyzed by $Pd(OH)_2/C$



We set out to perform a short screening of reaction conditions. As model substrates we chose acids **8a,b** (Table 1).

When using 5 mol % $Pd(OH)_2/C$, we observed a gradual increase in rate of conversion (entries 2 and 4), as was confirmed by screening of the reaction in 15-min intervals. Addition of an amine base (entry 3) caused a slight retarding of the reaction. $Pd(OAc)_2$ as an alternative catalyst led to low yields (entry 5). Much better results were provided by 5 mol % CuCl, which induced a complete decarboxylation of the substrate and yielded 94% of **9a** (entry 7). Catalytic activity of $CuCl_2$ compared to CuCl is lower (entry 6). In this context it was interesting to observe that quality of the CuCl used had a profound impact on the rate of decarboxylation. Older samples of CuCl (green color) exhibited a significantly higher activity in comparison with the newer ones (white color). When using stock solutions of CuCl/MeCN, catalytic activity of a freshly prepared solution was lower in comparison with older solutions as well. For instance, when we employed a 3-day-old solution of CuCl/MeCN in entry 20, in 120 min the conversion was complete. For the purpose of reproducibility, in all experiments in Table 1 new packages of CuCl (from white to light-green color) were used or freshly prepared solutions of CuCl/MeCN (maximum age of 24 h). However, one can expect faster conversions when using older samples of CuCl. The samples of CuCl, if exposed to air moisture, undergo disproportionation to Cu^0 and Cu^{II}, which we assume might be the cause of their increasing activity. The catalytic activity of $CuCl_2$ was lower in comparison to that of CuCl (entries 6 and 7). Equimolar mixtures of Cu bronze/$CuCl_2$ or CuCl/$CuCl_2$ (entries 10 and 11)

TABLE 1. Effect of Reaction Conditions on the Decarboxylation of Acids 8a,b[a]

entry	acid	catalyst (5 mol %)	additive (3 equiv)	time (min)	conv (%)	yield (%)[b]
1	**8a**			120	0	
2	**8a**	$Pd(OH)_2/C$		45	12	
3	**8a**	$Pd(OH)_2/C$	Et_3N	45	8	
4	**8a**	$Pd(OH)_2/C$		120	100	57
5	**8a**	$Pd(OAc)_2$		120	100	25
6	**8a**	$CuCl_2$		120	31	28
7	**8a**	CuCl		120	100	94
8	**8a**	CuCl		60	100	92
9	**8a**	Cu bronze		60	9	8
10	**8a**	Cu/$CuCl_2$[e]		60	45	41
11	**8a**	CuCl/$CuCl_2$[f]		60	35	32
12	**8a**	$CuSO_4$		60	0	
13	**8a**	$CuSO_4.5H_2O$		60	0	
14	**8a**	CuO		60	0	
15	**8a**	Cu_2O		60	100	90
16	**8a**	CuCl		20	35	
17	**8a**	CuCl	Et_3N	20	100	90[c]
18	**8a**	CuCl	Et_3N	10	89	86
19	**8a**		Et_3N	120	44	39
20[d]	**8a**	CuCl	Et_3N	120	54	49
21	**8b**	CuCl	Et_3N	30	100	96
22	**8b**	CuCl		60	100	95[c]
23	**8b**	CuCl	AcOH	60	21	
24	**8b**	CuCl	NH_4Cl	60	42	
25	**8b**	CuCl	HC≡CTMS	60	49	

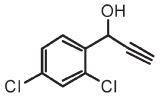
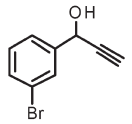
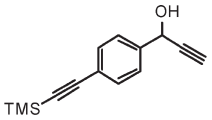
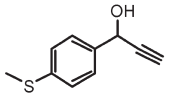
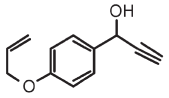
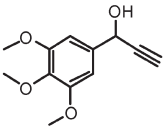
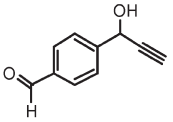
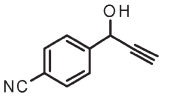
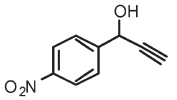
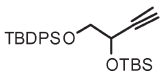
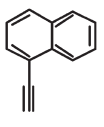
[a]Reactions were performed on 50.0 mg scale in MeCN (1 mL) under argon. Experiments 9 and 14 were executed on 200.0 mg scale. [b]Yields based on ^{1}H NMR with internal standard are reported unless otherwise noted. [c]After isolation. [d]Reaction at rt. [e]2.5 mol % of Cu bronze/2.5 mol % $CuCl_2$. [f]2.5 mol % of CuCl/2.5 mol % $CuCl_2$.

were less active than CuCl itself (entry 8). On the other hand, Cu_2O (entry 15) led to a complete conversion as well. Additional experiments with CuCl revealed that addition of a base (3 equiv of Et_3N) was reflected in accelerated reaction (entries 16−18) and similar yields of terminal alkyne **9a** (entries 7 and 17). As expected, addition of an acid (entries 23 and 24) or a competitive triple bond (entry 25) retarded the reaction. Striking was the fact that under these mild conditions Et_3N itself can perform decarboxylation, though much more slowly (entry 19). Our idea was to take advantage of the synergic effect of the CuCl−Et_3N combination, potentially leading to the best performance, whereas in inevitable cases one can optionally choose not to use the base at the cost of prolonged reaction times (Table 2, acids **8g,h**).

In the case of substrate **8c** the method enabled a selective deprotection (decarboxylation) of one triple bond. As published, presence of Cu^I[9] or a base (DBU)[10] triggers cleavage of TMS from triple bonds. Under the present conditions we observed desilylation as a side reaction only in a limited range (<5%). With acid **8e** we did not succeed in finding chemoselective conditions leading to one major product and with both methods we observed formation of a mixture of several compounds. In the presence of base (method B), substrates **8g,h** containing strong electron-withdrawing groups underwent a redox isomerization, in accordance with published data.[11] In both cases we isolated a mixture

(5) The yields were determined by ^{1}H NMR with internal standard.
(6) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28–29.
(7) Jakubowski, A. A.; Guziec, F. S. Jr.; Sugiura, M.; Chan Tam, C.; Tishler, M.; Omura, S. *J. Org. Chem.* **1982**, *47*, 1221–1228.
(8) Shahi, S. P.; Koide, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 2525–2527; methyl propiolate was used instead of propiolic acid.
(9) Ito, H.; Arimoto, K.; Sensui, H.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 3977–3980.
(10) Yeom, Ch. E.; Kim, M. J.; Choi, W.; Kim, B. M. *Synlett* **2008**, 565–568.
(11) (a) Koide, K.; Sonye, J. P. *J. Org. Chem.* **2006**, *71*, 6254–6257. (b) Koide, K.; Sonye, J. P. *Org. Lett.* **2006**, *8*, 199–202. (c) Arcadi, A.; Cacchi, S.; Marinelli, F.; Misiti, D. *Tetrahedron Lett.* **1988**, *29*, 1457–1460.

TABLE 2. Substrate Scope of the Decarboxylation of 2-Alkynoic Acids

entry	acid	product	method[a]	time (h)	yield[b] (%)
1	**8a**	 **9a**	A B	2 0.5	(94) 90
2	**8b**	 **9b**	A B	1 0.5	95 (96)
3	**8c**	 **9c**	A	2	94 (96)
4	**8d**	 **9d**	A B	15 0.5	(83) (90)
5	**8e**	 **9e**	A B	15 2	[c] [c]
6	**8f**	 **9f**	A	2	64
7	**8g**	 **9g**	A B	15 0.5	(88) [d]
8	**8h**	 **9h**	A B	15 0.5	88 (92) [d]
9	**8i**	 **9i**	A	15	63 (86)
10	**8j**	 **9j**	B	1	82 (86)
11	**8k**	 **9k**	B	2	67

[a] Method A: 5 mol % CuCl, MeCN, 60 °C. Method B: 5 mol % CuCl, 3 eq. Et_3N, MeCN, 60 °C. [b] Yields determined by ^{1}H-NMR with the internal standard are in parenthesis. [c] Mixture of several compounds. [d] Product of isomerization

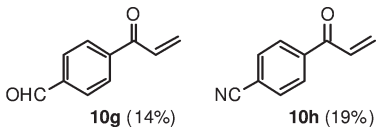


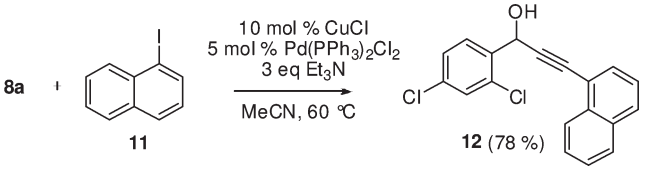
FIGURE 2. Products of redox isomerization.

containing **10g** or **10h** (Figure 2), whereas decarboxylation was complete.

To exclude a direct dependence of the described decarboxylative method on the assistance of hydroxyl group at C-4, the reaction conditions were analogically used on substrates **8j,k** (Table 2, entries 10 and 11).

Transition-metal-catalyzed decarboxylative cross-coupling represents a particularly topical area of organic synthesis.[12] Carboxylic acids are in general easily available and thus constitute an appealing source of carbon nucleophiles. Furthermore, thanks to the carboxylic function, they can be easily isolated and purified or eventually resolved. Decarboxylation releases CO_2, which is considered to be a harmless human metabolite in low concentrations. To the best of our knowledge, there is only one precedent describing decarboxylative cross-coupling of 2-alkynoic acids, which appeared very recently and is based on Pd-chemistry.[13a] We consider the presented method of decarboxylation of 2-alkynoic acids as inviting to be utilized for the purpose. The illustrative verification of the concept was executed under standard Sonogashira coupling conditions (Scheme 5).

SCHEME 5. Illustrative Decarboxylative Coupling



In 1 h, the one-pot decarboxylation/coupling reaction product **12** was isolated in 78% yield. We believe this approach has a potential to become a straightforward and efficient method allowing synthesis of unsymmetrical alkynes, a highly desired class of compounds.

In summary, we have established an efficient and straightforward method for catalytic decarboxylation of 2-alkynoic acids, tolerating a wide range of functional groups. The method was further utilized in illustrative decarboxylative coupling.

Experimental Section

Representative Procedure: Preparation of 8a. A 100-mL three-necked flask was charged with dry THF (60 mL) and propynoic

(12) Free carboxylic acids, selected examples: (a) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373–1375. (b) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103–7106. (c) Wang, Z.; Ding, Q.; He, X.; Wu, J. *Org. Biomol. Chem.* **2009**, *7*, 863–865. Allyl or dienyl esters, selected examples: (d) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510–13511. (e) Yeagley, A. A.; Chruma, J. J. *Org. Lett.* **2007**, *9*, 2879–2882. (f) Sim, S. H.; Park, H. J.; Lee, S. I.; Chung, Y. K. *Org. Lett.* **2008**, *10*, 433–436. (g) Shintani, R.; Park, S; Shirozu, F.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 16174–16175. (h) Pi, S. F.; Tang, B. X.; Li, J. H.; Liu, Y. L.; Liang, Y. *Org. Lett.* **2009**, *11*, 2309–2312.

(13) (a) Moon, J.; Jang, M.; Lee, S. *J. Org. Chem.* **2009**, *74*, 1403–1406. Analogy in synthesis of diarylalkynes: (b) Moon, J.; Jeong, M.; Nam, H.; Jinhun, J.; Moon, J. H.; Jung, H. M.; Lee, S. *Org. Lett.* **2008**, *10*, 945–948.

acid (780 μL, 1.1 equiv, 12.6 mmol) under an argon atmosphere. The solution was stirred and cooled to −70 °C, and MeLi (3.0 M in diethoxymethane, 8.4 mL, 25.2 mmol, 2.2 equiv) was added over 5 min. The resulting milky suspension was stirred for ca. 25 min at −70 to −40 °C, and successively a solution of 2,4-dichlorobenzaldehyde (**7a**, 2.00 g, 11.4 mmol) in dry THF (10 mL) was added over 1 min. The mixture was stirred for 50 min at −40 to 0 °C and poured into 0.5 M H_2SO_4 (35 mL), the aqueous layer was extracted with ethyl acetate (3 × 40 mL), and the combined organics were washed with a half-diluted brine (30 mL), dried over Na_2SO_4, filtered, and concentrated to yield a yellow oil. The crude product was dissolved in toluene (ca. 3 Pasteur pipettes) and placed in a freezer. After the acid started to crystallize, the slurry was gently diluted with hexanes under vigorous stirring. The mixture was allowed to stand for several hours in a refrigerator. Successive filtration yielded 2.49 g (89%) of acid **8a** as a sandy light-brown precipitate. Mp 114−117 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 5.91 (s, 1H), 7.49 (dd, J = 2.1, 8.4 Hz, 1H), 7.54 (d, J = 2.1 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 60.7, 77.6, 86.1, 128.6, 130.0, 130.2, 133.6, 135.2, 137.6, 153.9; HR-MS-MS (m/z) calcd for $C_{10}H_5Cl_2O_3$ $[M - H]^-$ 242.9616, found 242.9705.

Representative Procedure: Preparation of 9b. (Table 1, entry 14; method A). A 10-mL flask equipped with a magnetic stir bar was charged with acid **8b** (200 mg, 0.784 mmol) and CuCl (3.9 mg, 0.039 mmol, 5 mol %), sealed with septum, and gently flushed with a stream of argon. MeCN (4.0 mL) was added via syringe, and the resulting solution was placed in an oil bath (60 °C) and stirred for 1 h. The mixture was cooled in a water bath and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/hexanes = 7/3) to give 156 mg (95%) of alkyne **9b** as a pale yellow amorphous glass. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67 (d, J = 2.1 Hz, 1H), 3.20 (bs, 1H), 5.37 (bs, 1H), 7.21 (dd, J = 8.1, 8.1 Hz, 1H), 7.40−7.45 (m, 2H), 7.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.4, 75.4, 82.7, 122.5, 125.2, 129.6, 130.1, 131.4, 141.9; GC-MS (EI, 70 eV) m/z 212, 210.

Acknowledgment. This work was supported by the Slovak Research and Development Agency under contract no. LPP-0238-06

Supporting Information Available: Experimental details, characterization data, and copies of NMR spectra of **8a**−**j**, **9a**−**d**,**f**−**j**, **12**, HR-MS-MS of **8a**, and GC-MS of **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.