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A Facile One-Carbon Homologation of Aryl Aldehydes to Amides

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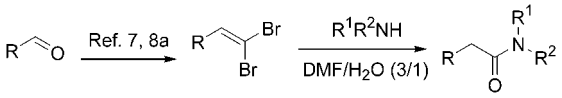
ABSTRACT

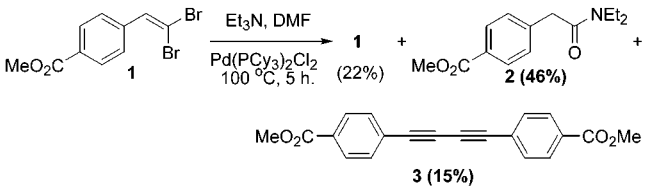


The easily accessible 2-aryl-1,1-dibromo-1-alkenes can be converted to amides under unusually mild conditions in good to excellent yields. Both electron-donating and electron-withdrawing substitutions on the aromatic rings are tolerated, and the reaction works well with hindered alkylamines. This simple homologation could find broad applications.

Homologation of carbonyl compounds by one carbon has been highly useful in organic and medicinal chemistry. The mild conditions used in Arndt−Eistert−Wolff rearrangement have led to a wide range of applications for the homologation of carboxylic acids.[1] On the contrary, even though one-carbon homologation of aldehydes[2] to carboxylic acid derivatives offers an attractive alternative, the actual process is difficult and has found only limited applications. These homologation methods have relied on the intermediacy of α-heteroatom-substituted enamines,[3] α-heteroatom-substituted nitriles,[4] ketene acetals[5] and ketene thioacetal derivatives.[6] Syntheses of these intermediates and subsequent conversions to carboxylic acid derivatives often require harsh conditions that may not be compatible with many functional groups present in the molecules.

During our investigation of the of 1,1-dibromo-1-alkenes,[7,8] amide **2** was isolated unexpectedly as the major product from the homocoupling reaction when bis(tricyclohexylphosphine)-palladium chloride was used as the catalyst (Scheme 1).[8c]

Scheme 1



Presumably, the water necessary for the transformation was introduced from the solvent or other source since the formation of diyne does not require anhydrous condiditions. It is also known that tertiary amines could be converted to

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(1) Review: Gill, G. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I, Eds.; Pergamon: Oxford, 1991; Vol. 3, p 887.
(2) Selected reviews on one-carbon homologation of aldehyde to aldehyde: (a) (via vinyl thioether) Gröbel, B.; Seebach, D. *Synthesis* **1977**, 357. (b) (via vinyl ether) Maercker, A. *Org. React.* **1965**, *14*, 270.
(3) Gross, H.; Costisella, B. *Angew. Chem., Int. Engl. Ed.* **1968**, *7*, 391.
(4) (a) Takahashi, K.; Masuda, T.; Ogura, K.; Iida, H. *Synthesis* **1983**, 1043. (b) Takahashi, K.; Shibasaki, K.; Ogura, K.; Iida, H. *J. Org. Chem.* **1983**, *48*, 3566. (c) Dinizo, S. E.; Freerksen, R. W.; Pabst, W. E.; Watt, D. S. *J. Am. Chem. Soc.* **1977**, *99*, 182.
(5) Van Schaik, T. A. M.; Henzen, A. V.; van der Gen, A. *Tetrahedron Lett.* **1983**, *24*, 1303.
(6) (a) Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1972**, 1383. (b) Jones, P. F.; Lappert, M. F. *J. Chem. Soc., Chem. Commun.* **1972**, 526. (c) Carey, F. A.; Court, S. *J. Org. Chem.* **1972**, *37*, 1926. (d) Funk, R.; Novak, P. M.; Abelman, M. M. *Tetrahedron Lett.* **1988**, *29*, 1493. (e) Seebach, D.; Grobel, B. T.; Beck, A. K.; Braun, M.; Geiss, K. H. *Angew. Chem., Int. Engl. Ed.* **1972**, *11*, 443. (f) Kruse, C. G.; Broekhof, N. L. J. M.; Wijsman, A.; van der Gen, A. *Tetrahedron Lett.* **1977**, 885.
(7) Preparation: (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769. (b) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745.
(8) (a) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873. (b) Wang, L.; Shen, W. *Tetrahedron Lett.* **1998**, *39*, 7625. (c) Shen, W.; Thomas, S. A. *Org. Lett.* **2000**, *2*, 2857. (d) Shen, W. *SynLett* **2000**, 737.

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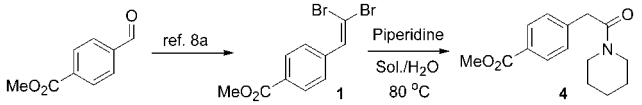
secondary amines in palladium-catalyzed reactions.[9] This observation led us to investigate the generality of this novel new transformation. As one could have expected, the use of secondary amine (piperidine)[10] instead of tertiary ones and addition of water to the reaction greatly facilitate the reaction. The optimal amount of water was found to be about 25% in the mixed solvent. Under these conditions, dibromide **1** is transformed to the desired amide **3** within 1 h at 80 °C in high yield. This transformation constitutes a novel two-step homologation of aldehydes to carboxylic acid derivatives. Furthermore, it compared very favorably with previously reported similar reactions such as the hydrolyzation of 1,1-dibromo-1-alkenes to carboxylic acids with concentrated strong base (NaOH or KOH) at high temperature[11] or the hydrolyzation of 1,1-difluoro-1-alkenes with either mercury-(II) acetate or concentrated sulfuric acid.[12]

Initially, we assumed that the transformation required catalysis by palladium, as was observed in hydrolysis of 1,1-dibromo-1-alkenes to the corresponding carboxylic acids.[11] However, the transformation occurred smoothly in the absence of a palladium catalyst. After a broad survey of reaction conditions, we report here a facile and general two-step homologation of aryl aldehydes to amides via 1,1-dibromo-1-alkenes under very mild conditions in which many functional groups could be tolerated. Further survey of the reaction conditions is summarized in Table 1. Solvents play an important role in the conversion of 1,1-dibromo-1-alkenes to amides. While the reaction proceeds readily in highly dipolar aprotic solvents such as DMF and DMSO, the transformation requires a much longer time and results in lower yields in moderately polar solvents such as 1,2-dimethoxyethane (DME) and acetonitrile. The reaction proceeds poorly in the protic solvent 2-propanol, and almost no reaction occurs in nonpolar solvent toluene. In addition, combination of slightly more than 1 equiv of piperidine with sodium carbonate works well for the reaction.

More 1,1-dibromo-1-alkenes were subjected to the reaction conditions with a variety of amines, as shown in Table 2.

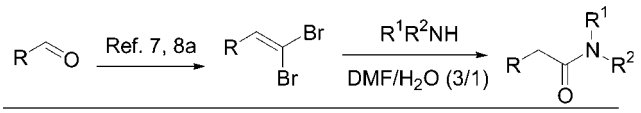
Table 1. Optimization of Dibromoalkene **1** Conversion to Amide **2**[a]

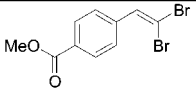
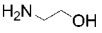
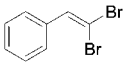
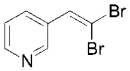
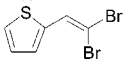
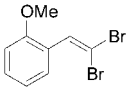
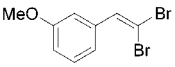
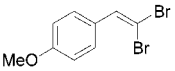
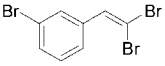
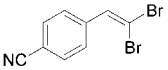
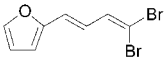


entry	solvent	base	*t* [h][b]	yield [%][c]
1	toluene	piperidine	96	10[d]
2	MeCN	piperidine	18	77
3	DME	piperidine	24	72
4	*i*-PrOH	piperidine	22	54
5	DMF	piperidine	1	92
6	DMF	Na_2CO_3[e]	1	89
7	DMSO	piperidine	1	87

[a] Reaction conditions: **1** (1.0 mmol), piperidine (5.0 mmol), solvent (3 mL), water (1 mL), 80 °C. [b] Reaction time is not optimized for those reactions completed under 1 h. [c] Yields of isolated products. [d] Recovery of **1** (50%). [e] Piperidine (1.1 mmol) and Na_2CO_3 (3.0 mmol) were used.

Table 2. Conversion of 1,1-Dibromo-1-alkenes to Amides[a]



entry	substrate	amine	*T* [°C]	t *[h]*[b]	yield [%][c]
1		$BnNH_2$	100	4	95
2		iPr_2NH	100	6	84
3			100	6	62
4		NH_3	80	2	45[d]
5		$PhNH_2$	100	24	0[e]
6			100	8	75
7			100	16	60
8			80	2	84
9			80	4	85
10			100	6	90
11			80	12	67
12			80	26	63
13			100	2	90
14			80	2	88
15			100	24	47

[a] Reaction conditions: 1,1-dibromo-1-alkene (1.0 mmol), amine (5.0 mmol), DMF (3 mL), water (1 mL). [b] Reaction time is not opimized for those reactions completed within 2 h at 80 °C. [c] Yields of isolated products. [d] Concentrated aqueous ammonium hydroxide (1 mL) was used in place of water, and *N*,*N*-dimethyl amide (6%) was also isolated. [e] Recovered starting material (23%).

(9) (a) Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* **1998**, *39*, 2559. (b) Konopelski, J. P.; Chu, K. S.; Negrete, G. R. *J. Org. Chem.* **1991**, *56*, 1355.

(10) Piperidine was used because of the availability of the chemical. Diethylamine was found to give **2** in similar yield under identical conditions.

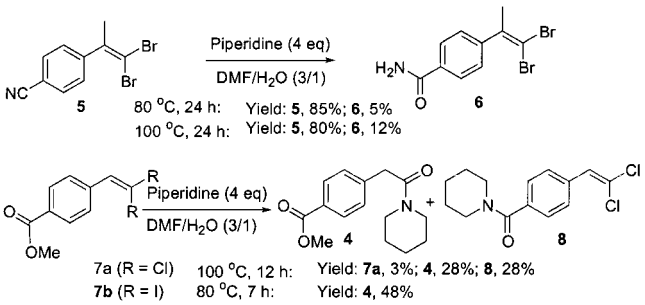
(11) Li, P.; Alper, H. *J. Org. Chem.* **1986**, *51*, 4354.

(12) (a) Hayahsi, S.; Nakai, T.; Ishikawa, N. *Chem. Lett.* **1980**, 651. (b) Hayahsi, S.; Nakai, T.; Ishikawa, N. *Chem. Lett.* **1980**, 935. (c) Hayahsi, S.; Nakai, T.; Ishikawa, N.; Burton, D. J.; Naae, D. G.; Kesling, H. S. *Chem. Lett.* **1979**, 983.

Both electron-donating (entries 9−11) and electron-withdrawing (entries 1−4, 7, 13) substitutions on the aromatic rings are tolerated, though the reactivity decreases as the electron richness of 2-aryl substitution increases. The substitution pattern has little impact on the yield. The reaction also works with 2-alkenyl-1,1-dibromo-1-alkene (entry 15), though the reaction time is longer and the yield is moderate. Generally, when sterically hindered or less nucleophilic amines are used, the reactions require longer time or higher temperature (entries 1−3, 6) to complete. It is noteworthy that the preparation of amides works for the poor nuleophile ammonia and hindered diisopropylamine. Aniline alone or in combination with sodium carbonate failed to react with 1,1-dibromo-1-alkenes.

A number of 2-alkyl-1,1-dibromo-1-alkenes were examined under the reaction conditions.[13] However, to our disappointment, no corresponding amides were observed even after prolonged heating. Only decomposition of 2-alkyl-1,1-dibromoalkenes was observed. As shown in Scheme 2,

Scheme 2



monosubstitution at the 2-position of 1,1-dibromo-1-alkene is essential for the reaction to proceed, as dibromoalkene **5** prepared from the corresponding ketone failed to convert to the expected amide. Halogens other than bromine were also examined. 1,1-Dichloro-1-alkene (**7a**)[14] is far less reactive, probably due to the stronger carbon−chlorine bond.[15] However, we were surprised that 1,1-diiodo-1-alkene (**7b**)[16] was also found to be less reactive than the corresponding dibromoalkene **1**.

In summary, a facile, mild, and general two-step homologation of aryl (alkenyl) aldehydes to the corresponding amides via 1,1-dibromo-1-alkenes was developed. To the best of our knowledge, the route reported here is the shortest and most convenient one to prepare homologated amides from aldehydes.[17] This homologation could find a wide range of applications in medicinal chemistry in particular, as amides are one of the most common functional groups encountered. A detailed mechanistic study, as well as further investigation of the reaction, will be reported soon.

Acknowledgment. We thank Drs. Saul H. Rosenberg and Michael Wendt for the support and help of this work and Dr. Thomas Pagano for NMR structural determination of the product in entry 15, Table 2.

Supporting Information Available: Detailed experimental procedures and characterizations data (^{1}H and ^{13}C spectra) for compounds **2** and **4** and products in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) 2-(2-Ethoxycarbonyl)cyclopropyl-, 2-cyclohexyl-, and 2-*tert*-butyl-1,1-dibromoethenes were studied; see ref 8 for their preparation.

(14) (a) Paquette, L. A.; Wittenbrook, L. S. *J. Am. Chem. Soc.* **1968**, *90*, 6790. (b) Hazard, R.; Tallec, A. *Bull. Soc. Chim. Fr.* **1974**, 121.

(15) Synthesis of indolidinone was achieved by treating the corresponding 2-(2-aminoaryl)-1,1-dichloroethene with sodium hydroxide and sulfuric acid sequentially (one example, 46% isolated yield): Jpn. Kokai Tokkyo Koho, JP 56115772, 1981.

(16) Gavina, F.; Luis, S. V.; Ferrer, P.; Costero, A. M.; Marco, J. A. *J. Chem. Soc., Chem. Commun.* **1985**, 296.

(17) During the preparation of this manuscript, pyrrolidine amide was isolated as an unexpected product in the Sonogashira coupling of 2-aryl-1,1-dibromoethene (only one example reported by the author): Lee, H. B.; Huh, D. H.; Oh, J. S.; Min, G. H.; Kim, B. H.; Lee, D. H.; Hwang, J. K.; Kim, Y. G. *Tetrahedron* **2001**, *57*, 8283.