Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4585–4588

Microwave-assisted deformylation of *N*-aryl formamide by KF on basic Al_2O_3

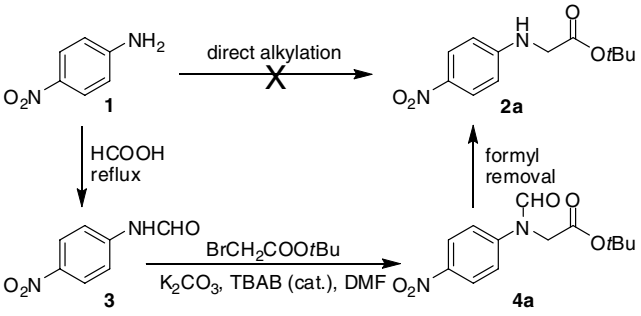
Yiyu Ge[a] and Longqin Hu[a,b,*]

[a]*Department of Pharmaceutical Chemistry, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA*
[b]*The Cancer Institute of New Jersey, New Brunswick, NJ 08901, USA*

Received 17 January 2007; revised 20 April 2007; accepted 25 April 2007
Available online 1 May 2007

Abstract—The formyl group was successfully removed from *N*-aryl formamide by KF on a solid support of basic Al_2O_3 in 4–20 min with microwave irradiation. The conditions mimic base-catalyzed hydrolysis of formamide and are compatible with carbamates and *t*-butyl esters, but not methyl, ethyl, and benzyl esters.
© 2007 Elsevier Ltd. All rights reserved.

To avoid over-alkylation in direct alkylation of primary amines or to facilitate alkylation of weak nucleophilic aromatic amines, formyl group has been used as an activating/protecting group during the synthesis of secondary amines.[1–5] However, it has been limited from wide use due to the harsh conditions needed to remove the formyl group. In our work, we needed to alkylate 4-nitroaniline (**1**) to obtain *N*-(4-nitrophenyl)glycine *t*-butyl ester (**2a**). Due to the reduced nucleophilicity of the aromatic amine by the electron withdrawing nitro group at the *para* position, direct alkylation with an alkyl halide such as *t*-butyl bromoacetate was not possible. To facilitate alkylation, we introduced a formyl group on the aromatic amine in the form of formamide as in **3**. The amide hydrogen was subsequently removed by a strong base and the resulting amide nitrogen anion readily underwent an S_N2 displacement of the bromide in *t*-butyl bromoacetate to give *N*-formyl-*N*-(4-nitrophenyl)glycine *t*-butyl ester (**4a**), which, upon removal of the formyl group, would afford the desired product **2a** (Scheme 1). Thus, the formyl group here acts as an activating group of aryl amine for alkylation. Known methods for removal of the formyl group include reflux in a strong basic solution of sodium hydroxide[1] and treatment with a strong acidic solution of HCl[6–10] or TFA.[11] However, these conditions are too harsh for functional groups such as the *t*-butyl esters and carbamates. This prompted us to develop a more efficient method for the removal of the formyl group under mild conditions.



Scheme 1. Formyl group used as an activating group for alkylation.

Due to the convenience and high efficiency of microwave irradiation, microwave-assisted organic synthesis has seen wide application since the mid-1980s.[12,13] Microwave irradiation is cleaner and provides more efficient heating than the conventional oil bath or heating mantle and the desired temperature can be reached within seconds. In addition, microwave-assisted reactions can be carried out under solvent-free conditions and often performed on a solid support, providing opportunities to explore new chemistry under neat 'Green' conditions.

Basic aluminum oxide has been used as a solid support for reactions such as *N*-acylation,[14] organometallic coupling,[15,16] and Suzuki coupling.[17] However, when used

* Corresponding author. Tel.: +1 732 445 5291; fax: +1 732 445 6312; e-mail: LongHu@rutgers.edu

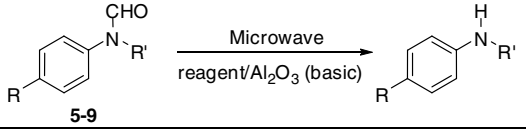
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.127

alone, basic aluminum oxide failed to efficiently remove the formyl group from *N*-methyl-*N*-(4-nitrophenyl)-formamide (**5**), a model compound we selected to test the deformylation conditions. As shown in Table 1, deformylation with microwave heating for 4 min in the presence of basic Al_2O_3 alone gave only 46% of the desired amine (entry 1). Based on an earlier report that the addition of KF to Al_2O_3 helped cleave sulfonates and sulfonamides,[18] we added 1 equiv of KF relative to the formamide and the deformylation yield was improved to 54% with the same 4 min of microwave irradiation (Table 1, entry 2). Increasing the amount of KF from 1 equiv to 2 and 3 equiv increased the yield of deformylation to 79% and 97%, respectively, with 4 min of microwave irradiation (Table 1, entries 3 and 4). Thus, the combination of KF with basic Al_2O_3 and microwave irradiation worked well to remove the formyl group from *N*-aryl formamides.

We also evaluated and found that other salts, such as CsF, NaF, KCl, KBr, and KI, could catalyze the removal of the formyl group from **5** in good to excellent yields (Table 1, entries 5–9). Apparently, KI, NaF, and CsF have similar catalytic activity as KF in the case of deformylation of **5** (Table 1, entries 7, 8, and 9 vs 4). The nitro group at the *para* position in **5** increased the electrophilicity of amide carbonyl through the conjugative system and, thus, the reactivity of the formyl group is relatively high, making it difficult to differentiate the effectiveness of the most active inorganic salts. When *N*-methyl-*N*-phenyl formamides were substituted with an electron donating group or a group that is less electron withdrawing at the *para* position of the phenyl ring (e.g., **6** and **8**), the effect of KI and NaF was significantly differentiated from that of KF and CsF. Deformylation of *N*-methyl-*N*-(4-chlorophenyl)formamide (**6**) in the presence of 12 equiv of KI or NaF with 20 min of microwave irradiation gave the desired amine in only 24% and 80% yield, respectively (Table 1, entries 12 and 13) as compared to 94% and 93% yield when KF and CsF were used (Table 1, entries 11 and 14). These results indicate that the rate of deformylation increases with increasing strength of Lewis basicity of the inorganic salts used. Both KF and CsF were equally effective as a catalyst in deformylation. As KF is cheaper and more commonly used than CsF, we selected KF as the catalyst in our further study of the microwave-assisted deformylation.

Various substitutions on the phenyl ring were also used to explore the electronic effects of the substituents on the rate of microwave-assisted deformylation. For *N*-methyl-*N*-phenyl formamides with electron donating groups on the phenyl ring, the deformylation was much slower even in the presence of 3 equiv of KF. The yield improved with increased amount of KF and increased time of microwave irradiation (Table 1, entries 10 vs 11, 15 vs 16, 17 vs 18). As the *para* substituent was changed from Cl to the more electron-donating group CH_3O, the reaction was slow even in the presence of 12 equiv of KF and the yield of the deformylation was only 44%

Table 1. Effects of phenyl substitutions and the inorganic salts on the reaction time and yield of deformylation[a]



5-9

Entry	Starting material	R	R′	Reagent[b] on Al_2O_3	Time (min)	Yield[c] (%)
1	**5**	NO_2	CH_3	None	4	46
2	**5**	NO_2	CH_3	1 equiv KF	4	54
3	**5**	NO_2	CH_3	2 equiv KF	4	79
4	**5**	NO_2	CH_3	3 equiv KF	4	97
5	**5**	NO_2	CH_3	3 equiv KCl	4	83
6	**5**	NO_2	CH_3	3 equiv KBr	4	71
7	**5**	NO_2	CH_3	3 equiv KI	4	99
8	**5**	NO_2	CH_3	3 equiv NaF	4	90
9	**5**	NO_2	CH_3	3 equiv CsF	4	97
10	**6**	Cl	CH_3	3 equiv KF	20	35
11[d]	**6**	Cl	CH_3	12 equiv KF	20	94
12	**6**	Cl	CH_3	12 equiv KI	20	24
13	**6**	Cl	CH_3	12 equiv NaF	20	80
14	**6**	Cl	CH_3	12 equiv CsF	20	93
15	**7**	H	CH_3	3 equiv KF	20	0
16[d]	**7**	H	CH_3	12 equiv KF	20	76
17	**8**	CH_3O	CH_3	12 equiv KF	20	44
18	**8**	CH_3O	CH_3	30 equiv KF	20	75
19	**9**	Cl	H	12 equiv KF	20	66

[a] General conditions: Formamide (0.03 mmol) on Al_2O_3 (0.21 g) in the absence or presence of an inorganic reagent as a catalyst was heated with microwave irradiation for the given time period.

[b] Equivalents of inorganic reagent relative to the formamide starting material.

[c] Conversion yield as monitored by LC–MS.

[d] In addition to the 0.03 mmol scale, formamides **6** and **7** were also deformylated on a larger scale of 2 mmol with 14 g of Al_2O_3 in the presence of 12 equiv KF to give 96% and 80% isolated yields, respectively, of the desired deformylation products.

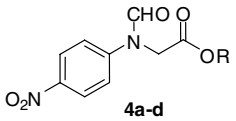
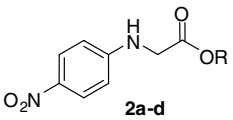
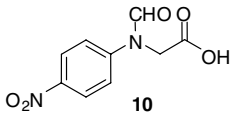
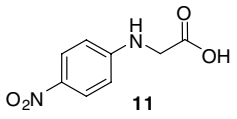
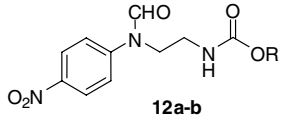
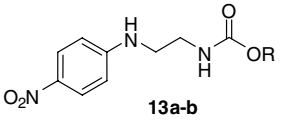
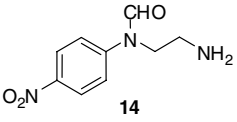
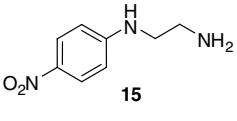
after being heated in the microwave for 20 min (Table 1, entry 17). Increasing the amount of KF to 30 equiv improved the yield of deformylation to 75% (Table 1, entry 18). These electronic effects of aromatic substituents and the correlation of catalyst activity with Lewis basicity suggest that the deformylation with KF on the surface of Al_2O_3 goes through a mechanism of base-catalyzed hydrolysis.

It should be noted that alkylation on the formamide nitrogen also facilitated the removal of formyl group under our conditions. For example, microwave irradiation of 4-chlorophenylformamide (**9**) for 20 min in the presence of 12 equiv of KF on Al_2O_3 gave a deformylation yield of 66% whereas irradiation of the corresponding methylated analog **6** gave a 94% yield of the desired product under the same conditions (Table 1, entries 19 vs 11). This enhanced rate of deformylation upon alkylation could be explained by the removal of the acidic hydrogen that would otherwise exist in secondary amides and hinder any nucleophilic attack on the amide carbonyl.

Upon optimization of the reaction conditions, we developed the following general deformylation procedure. Al_2O_3 (0.21 g for every 0.03 mmol of starting formamide) was first mixed with an aqueous solution of KF (3 equiv to formamide) in a volume sufficient to fully cover the solid support surfaces (in our case, 180 μL of 0.5 M KF in H_2O).[19] The mixture was mixed well by vortexing and most of the water was removed in a loosely-capped vial by heating in a microwave oven (GE, 700W, 2×4 min). The starting formamide was loaded onto the solid support as a solution in methylene dichloride or acetone. After thorough mixing by vortexing, the solvent was removed by blowing with N_2 or by a rotavap depending on the scale. The resulting solid mixture was then heated in a loosely-capped vial with a domestic GE microwave oven (700W).[20] The heating was stopped every 4 min to allow monitoring of the reaction using LC–MS. Aliquots of the mixture (2 mg) were taken and extracted with a mixed solvent of acetonitrile/water (1:1, 100 μL) for analysis. Upon completion of the reaction, the products were washed off the solid support with EtOAc/CH_3CN (1:1). After removal of the solvent via rotavap, the products were often sufficiently pure without the need for further purification. For reactions that were terminated before completion, flash column chromatography was used to purify the product. The reactions can be scaled up to at least 2 mmol scale without affecting the yield of deformylation (Table 1, note d).

The above general procedure was applied to several formamide substrates designed to explore the functional group compatibility of the deformylation conditions. As shown in Table 2, the conditions worked well on our formamide **4a** and efficiently removed the formyl group to give the desired product **2a** in 98% yield with the bulky *t*-butyl ester unaffected (entry 2). However, when formamides containing simple esters like methyl, ethyl, or benzyl esters were used, two other products were found resulting from an additional ester hydrolysis reaction. With formamide containing a methyl ester, the major product was the *N*-(4-nitrophenyl)glycine (**11**), resulting from both deformylation and ester hydrolysis, with 5% still retaining the formyl group (Table 2, entry 3). When formamides containing ethyl and benzyl esters were used, ester hydrolysis remained as a major concurrent reaction (Table 2, entries 4–6). These results suggest

Table 2. Microwave-assisted deformylation of substrates containing esters and carbamates[a]

Entry	Starting material	Scale (mmol)	Time (min)	Yield[b] (%)		
	 **4a-d**			 **2a-d**	 **10**	 **11**
1	**4a**: R = $C(CH_3)_3$	0.10	4	73 (**2a**)	0	0
2	**4a**: R = $C(CH_3)_3$	0.10	8	98 (**2a**)	0	0
3	**4b**: R = CH_3	0.03	4	0.7 (**2b**)	5	94
4	**4c**: R = C_2H_5	0.03	4	14 (**2c**)	19	63
5	**4d**: R = CH_2Ph	0.03	4	21 (**2d**)	29	23
6	**4d**: R = CH_2Ph	0.03	8	18 (**2d**)	32	32
	 **12a-b**			 **13a-b**	 **14**	 **15**
7	**12a**: R = $C(CH_3)_3$	0.14	8	97 (**13a**)	0	0
8	**12b**: R = C_2H_5	0.11	12	92 (**13b**)	0	0

[a] General conditions: Formamide on Al_2O_3 (0.21 g per 0.03 mmol of formamide) in the presence of 3 equiv of KF was heated with microwave irradiation for the given time period.

[b] Conversion yield as monitored by LC–MS.

that simple esters are more readily hydrolyzed than the formamide group under these conditions. We also selected two carbamates (**12a**–**b**) to test the compatibility of these conditions with carbamates. Microwave heating of compounds **12a** and **12b** for 8 and 12 min exclusively gave the desired deformylated product **13a** and **13b** in a conversion yield of 97% and 92%, respectively (Table 2, entries 7 and 8). No hydrolysis of the carbamates was observed.

In conclusion, a set of microwave-assisted deformylation conditions were developed to efficiently remove the formyl group from *N*-aryl formamides using basic Al_2O_3 as the solid support and KF as the catalyst. Carbamates and bulky *t*-butyl esters were not affected while simple esters were hydrolyzed under these conditions. This method should be useful in organic synthesis, especially for the synthesis of electron-deficient secondary aromatic amines.

Acknowledgments

We gratefully acknowledge the financial support of a research grant from the State of New Jersey Commission on Cancer Research and a research scholar grant from the American Cancer Society.

References and notes

1. Manikowski, A.; Verri, A.; Lossani, A.; Gebhardt, B. M.; Gambino, J.; Focher, F.; Spadari, S.; Wright, G. E. *J. Med. Chem.* **2005**, *48*, 3919–3929.
2. Imamura, S.; Nishikawa, Y.; Ichikawa, T.; Hattori, T.; Matsushita, Y.; Hashiguchi, S.; Kanzaki, N.; Iizawa, Y.; Baba, M.; Sugihara, Y. *Bioorg. Med. Chem.* **2005**, *13*, 397–416.
3. Nagata, T.; Masuda, K.; Maeno, S.; Miura, I. *Pest Manag. Sci.* **2004**, *60*, 399–407.
4. Murali Dhar, T. G.; Liu, C. J.; Pitts, W. J.; Guo, J. G.; Watterson, S. H.; Gu, H.; Fleener, C. A.; Rouleau, K.; Sherbina, N. Z.; Barrish, J. C.; Hollenbaugh, D.; Iwanowicz, E. *J. Bioorg. Med. Chem. Lett.* **2002**, *12*, 3125–3128.
5. Wright, J. E.; Rosowsky, A. *Bioorg. Med. Chem.* **2002**, *10*, 493–500.
6. Couture, A.; Deniau, E.; Woisel, P.; Grandclaudon, P. *Tetrahedron Lett.* **1995**, *36*, 2483–2486.
7. Imamura, S.; Kurasawa, O.; Nara, Y.; Ichikawa, T.; Nishikawa, Y.; Iida, T.; Hashiguchi, S.; Kanzaki, N.; Iizawa, Y.; Baba, M.; Sugihara, Y. *Bioorg. Med. Chem.* **2004**, *12*, 2295–2306.
8. von Geldern, T. W.; Tu, N.; Kym, P. R.; Link, J. T.; Jae, H.-S.; Lai, C.; Apelqvist, T.; Rhonnstad, P.; Hagberg, L.; Koehler, K.; Grynfarb, M.; Goos-Nilsson, A.; Sandberg, J.; Osterlund, M.; Barkhem, T.; Hoglund, M.; Wang, J.; Fung, S.; Wilcox, D.; Nguyen, P.; Jakob, C.; Hutchins, C.; Farnegardh, M.; Kauppi, B.; Ohman, L.; Jacobson, P. B. *J. Med. Chem.* **2004**, *47*, 4213–4230.
9. Matulenko, M. A.; Lee, C. H.; Jiang, M. Q.; Frey, R. R.; Cowart, M. D.; Bayburt, E. K.; DiDomenico, S.; Gfesser, G. A.; Gomtsyan, A.; Zheng, G. Z.; McKie, J. A.; Stewart, A. O.; Yu, H. X.; Kohlhaas, K. L.; Alexander, K. M.; McGaraughty, S.; Wismer, C. T.; Mikusa, J.; Marsh, K. C.; Snyder, R. D.; Diehl, M. S.; Kowaluk, E. A.; Jarvisa, M. F.; Bhagwata, S. S. *Bioorg. Med. Chem.* **2005**, *13*, 3705–3720.
10. Lee, S. K.; Heo, S.; Lee, J. G.; Kang, K.-T.; Kumazawa, K.; Nishida, K.; Shimbo, Y.; Takanishi, Y.; Watanabe, J.; Doi, T.; Takahashi, T.; Takezoe, H. *J. Am. Chem. Soc.* **2005**, *127*, 11085–11091.
11. Kikuchi, H.; Saito, Y.; Sekiya, J.; Okano, Y.; Saito, M.; Nakahata, N.; Kubohara, Y.; Oshima, Y. *J. Org. Chem.* **2005**, *70*, 8854–8858.
12. Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945–4948.
13. Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279–282.
14. Kidwai, M.; Misra, P.; Bhushan, K. R.; Saxena, R. K.; Singh, M. *Monatsh. Chem.* **2000**, *131*, 937–943.
15. Kidwai, M.; Misra, P.; Bhushan, K. R. *Polyhedron* **1999**, *18*, 2641–2643.
16. Kidwai, M. *Pure Appl. Chem.* **2001**, *73*, 147–151.
17. Kabalka, G. W.; Pagni, R. M.; Wang, L.; Namboodiri, V. *Green Chem.* **2000**, *2*, 120–122.
18. Sabitha, G.; Abraham, S.; Subba Reddy, B. V.; Yadav, J. S. *Synlett* **1999**, 1745–1746.
19. The commercially available 40% KF/Al_2O_3 can also be used, although the amount of KF would be more than is needed for efficient deformylation.
20. Although the deformylation reactions on a solid support were performed safely with a domestic microwave in loosely-capped vials under atmospheric pressure, we found, in a comparison study, that the same reaction using compound **6** (Table 1, entry 11) was more efficiently done (<5 min) with a commercial microwave synthesizer (CEM Discover® with ChemDrive 3.6.0 software) in a sealed tube under pressure at 100 °C.