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Reductive cleavage of azo compounds catalyzed by commercial zinc dust using ammonium formate or formic acid

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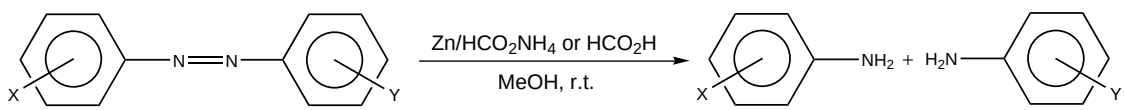
Abstract—Azo compounds, both symmetric and unsymmetric, are cleaved to amine(s) by using commercial zinc dust and ammonium formate or formic acid in methanol, tetrahydrofuran or dioxane at room temperature. The reductive cleavage occurs without hydrogenolysis or hydrogenation of reducible moieties, such as -OH, $-CH_3$, $-OCH_3$, -COOH, $-COCH_3$, halogen, etc. The cleavage is very fast, clean, cost effective and high-yielding if compared with earlier methods, such as those using cyclohexene/5% Pd on asbestos, cyclohexene/10% Pd–C or hydrazine/10% Pd–C or Raney nickel.

Metal-mediated reactions have a wide scope in organic synthesis because of their simple work-up and selectivity.[1–6] For example, the utility of zinc for the synthesis of β,γ-unsaturated ketones and homoallylic alcohols by the reaction of an acid chloride with allyl bromide[7,8] has been demonstrated. Furthermore, zinc-mediated amide bond formation,[9] Friedel–Crafts acylation[10] and carbamate formation[11] have also been demonstrated.

The application of ammonium formate[12–14] and formic acid[12,13] in the field of catalytic transfer hydrogenation for the reduction of a variety of organic compounds and the synthesis of peptides has been reviewed. The application of catalytic transfer hydrogenation for reduction and reductive cleavage of organic compounds and in peptide synthesis is mainly centered on the use of expensive catalysts, such as Pd–C, Ru–Ca, Pd–$CaCO_3$, Ru–C and Raney Ni.[12–14] Some systems, like hydrazine/Raney Ni, have been developed for the reduction of azo compounds to hydrazo compounds[15–17] and for reductive cleavage to amines.[17–20] These systems require reaction times as long as 23–48 h at reflux and expensive catalysts, such as 10% Pd–C, 5% Pd on asbestos and Raney Ni. Raney Ni catalyst is flammable in the presence of air and presents considerable hazards during handling. If the azo compounds contain reducible or hydrogenolysable groups, such as a halogen or a nitrile, then systems like 10% Pd–C/$HCOONH_4$[21] and 10% Pd–C/triethyl ammonium formate[22] reduce the nitrile group to a methyl group and remove the halogen from aromatic rings. Moreover, poor yields are reported during the reduction of azo compounds to amines due to the formation of intermediate hydrazo compounds.

We wish to report a rapid, selective and simple cleavage of substituted azo compounds to the corresponding amino derivative(s) by using low-cost commercial zinc dust and ammonium formate or formic acid at room temperature in methanol, tetrahydrofuran or dioxane (Scheme 1). This new system cleaved with ease a wide variety of azo compounds to the corresponding



X or Y = -H, halogen, $-OH$, $-OCH_3$, -COOH, $-CH_3$, $-COCH_3$, etc.

Scheme 1.

Keywords: ammonium formate; azo compounds; catalytic transfer hydrogenation; formic acid; reductive cleavage; zinc dust.

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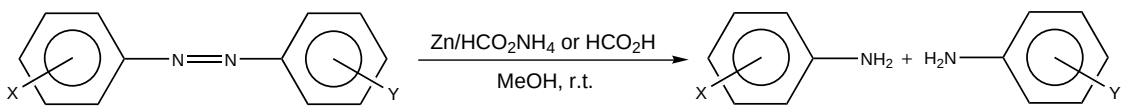
amine(s). Many primary and secondary functional groups, such as halogens, -CH_3, -OH, -COOH, -$COCH_3$, -OCH_3, etc., are tolerated.

The cleavage of an azo compound in the presence of zinc dust and ammonium formate or formic acid was complete within 3–10 min. The course of the reaction was monitored by thin layer chromatography (TLC) and IR spectra. The work-up and isolation of the products were easy. Thus, all compounds reduced (a few examples are listed in Table 1) by this system were obtained in good yields (90–95%). Products were characterized by comparison of their melting points, TLC and IR spectra with authentic samples. The disappearance of a strong absorption band between 1630 and 1575 cm^{-1} due to the -N=N- stretching and the appearance of a strong absorption band between 3500 and 3300 cm^{-1} due to the -NH_2 group clearly showed that the azo compounds had been cleaved into their constituent amine(s). Furthermore there was no absorption between 2290 and 2440 cm^{-1}, which clearly indicated the absence of the -NH–NH- group. A control experiment carried out using an azo compound with ammonium formate or formic acid but without zinc dust failed to yield the desired product. The appearance of one spot in the TLC, in the case of symmetrical azo compounds, and two spots, in the case of unsymmetrical azo compounds, clearly indicated that no hydrazo compounds were formed during the reductive cleavage of the azo compounds.

Furthermore, the ammonium formate or formic acid/zinc system is more effective than either cyclohexene/5% Pd on asbestos,[18] cyclohexene/10% Pd–C[19], hydrazine/10% Pd–C[20] or hydrazine/Raney Ni.[20] Most of the reactions are complete in less than 5 min at room temperature, as monitored by TLC by the disappearance of the starting materials and concomitant formation of the product(s). In addition, the methods mentioned earlier require long reaction times, e.g. 16–48 h, and high temperatures.

Thus, the cleavage of azo compounds can be accomplished at room temperature in a short time with commercial zinc dust instead of expensive platinum or palladium, etc., without affecting the reduction of any reducible or hydrogenolysable substituents. The yields are virtually quantitative and the products were analytically pure. This procedure will therefore be of general use, especially in cases where rapid, mild and selective reduction or cleavage is required. Further investigations of other useful applications related to the deblocking of protecting groups in peptide synthesis are in progress.

Table 1. Reductive cleavage of azo compounds catalyzed by commercial zinc dust using ammonium formate or formic acid



Substrate Product

Substrate		Product		Duration (min)	Yield (%)[a]	Melting point (°C)	
X	Y	X	Y			Found	Literature
-H	-H	-H	-H	3	95	112[c]	114[23]
2-CH_3	2′-CH_3	2-CH_3	2-CH_3	6	94	142[b]	144[23]
3-CH_3	3′-CH_3	3-CH_3	3-CH_3	5	95	126[b]	125[23]
2-Br	2′-Br	2-Br	2-Br	7	93	115[b]	116[23]
3-OCH_3	3′-OCH_3	3-OCH_3	3-OCH_3	7	94	82[c]	80[23]
-H	4′-COOH	-H	4-COOH	10	95, 80	113[c], 188	114,[23] 186[23]
4-$N(CH_3)_2$	-H	4-$N(CH_3)_2$	-H	8	95, 95	52, 113[c]	53,[24] 114[23]
4-$N(CH_3)_2$	4′-SO_3Na	4-$N(CH_3)_2$	4-SO_3Na	13	92, 55[d]	52, n.d.[e]	53,[24] –
4-$N(CH_3)_2$	2′-COOH	4-$N(CH_3)_2$	2-COOH	15	91, 88	53, 146	53,[24] 145[23]
4-NH_2, 3-CH_3	2′-CH_3	4-NH_2, 3-CH_3	2-CH_3	12	92, 93	65, 144[b]	64,[23] 144[23]
3-$COCH_3$	3′-$COCH_3$	3-$COCH_3$	3-$COCH_3$	9	90	99	101[23]
4-Cl	4′-Cl	4-Cl	4-Cl	8	91	71	70[23]
4-NH_2	-H	4-NH_2	-H	5	93, 95	140, 113	141,[23] 114[23]
2-OH	2′-OH	2-OH	2-OH	7	89	172	174[23]
1,1′-Azonaphthalene		1-Aminonaphthalene		16	85	188	190[23]

In the case of unsymmetrical azo compounds, the first-mentioned data refer to the left-hand fragment azo compound and the next-mentioned data refer to the right-hand fragment of the reductively cleaved azo compound.

[a] Isolated yields are based on a single experiment and the yields were not optimized.

[b] Melting point of benzoyl derivative.

[c] Melting point of acetyl derivative.

[d] The low yield is due to its water-soluble nature, TLC analysis indicates 95–98% cleavage.

[e] n.d. Not determined.

Experimental

General procedure: A suspension of the azo compound (2 g) and zinc dust (1 g) in methanol, or in any other suitable solvent (10 mL or the requisite amount), and ammonium formate (2 g) or formic acid (3 mL) was stirred under a nitrogen atmosphere at room temperature. After the completion of the reaction (monitored by TLC or by the disappearance of the starting material color), the reaction mixture was filtered through a Celite pad and washed with solvent. When ammonium formate was used, the combined filtrate and washings were concentrated under vacuum. The residue was taken into 15 mL chloroform or ether, washed twice with 15 mL saturated brine solution and finally washed with water. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed using a rotary evaporator. For further purification/separation of products, the residue was purified either by preparative TLC or by column chromatography. When formic acid was used, the filtrate and washings were neutralized with ammonia then evaporated under vacuum and worked up, as mentioned above. After chromatographic separation/purification, the IR spectra and melting points were compared with authentic samples.

Note: some substituted amines, such as *p*-aminobenzoic acid, are soluble in water to a considerable extent. In such cases, successive extractions and careful washing optimized the yields.

References

1. Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18–30.
2. Ranu, B. C.; Dutta, P.; Sarkar, A. *Tetrahedron Lett*. **1998**, *39*, 9557–9558.
3. Gowda, D. C.; Mahesha, B.; Gowda, S. *Indian J. Chem*. **2001**, *40B*, 75–77.
4. Banik, B. K.; Suhendra, M.; Banik, I.; Becker, F. F. *Synth. Commun*. **2000**, *30*, 3745–3754.
5. Jubert, C.; Knochel, P. *J. Org. Chem*. **1992**, *57*, 5425–5431.
6. Zhou, J.-Y.; Chen, Z.-G.; Wu, S.-H. *J. Chem. Soc., Chem. Commun*. **1994**, 2783–2784.
7. Ranu, B. C.; Majee, A.; Das, A. R. *Tetrahedron Lett*. **1996**, *37*, 1109–1112.
8. Ranu, B. C.; Majee, A.; Das, A. R. *Tetrahedron Lett*. **1995**, *36*, 4885–4888.
9. Meshram, H. M.; Reddy, G. S.; Reddy, M. M.; Yadav, J. S. *Tetrahedron Lett*. **1998**, *39*, 4103–4106.
10. Yadav, J. S.; Reddy, G. S.; Reddy, M. M.; Meshram, H. M. *Synth. Commun*. **1999**, *28*, 2203–2206.
11. Yadav, J. S.; Reddy, G. S.; Reddy, M. M.; Meshram, H. M. *Tetrahedron Lett*. **1998**, *39*, 3259–3262.
12. Johnstone, R. A. W.; Wibly, A.; Entwistle, I. D. *Chem. Rev*. **1985**, *85*, 129–170.
13. Brieger, O.; Nestrick, T. J. *Chem. Rev*. **1974**, *74*, 567–580.
14. Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91–95.
15. Furst, A.; Moore, R. E. *J. Am. Chem. Soc*. **1957**, *79*, 5492–5493.
16. Hornsby, S.; Peacock, W. L. *Chem. Ind. (London)* **1958**, *27*, 858–859.
17. Gilchrist, T. L. In *Comprehensive Organic Synthesis*; Fleming, I., Ed.; Pergmon Press: Oxford, 1991; pp. 381–402.
18. Ho, T. L.; Olah, G. A. *Synthesis* **1977**, 169–170.
19. Braude, E.; Linstead, R. P.; Mitchell, P. W. D.; Wooldridge, K. R. H. *J. Chem. Soc*. **1954**, 3595–3597.
20. Stafford, W. H.; Los, M.; Thomson, N. *Chem. Ind. (London)* **1956**, *43*, 1277.
21. Brown, G. R.; Foubister, A. J. *Synthesis* **1982**, 1036–1037.
22. Cortese, N. A.; Heck, R. F. *J. Org. Chem*. **1977**, *42*, 3491–3494.
23. Vogel, A. I. *Text Book of Practical Organic Chemistry*, 5th ed.; Revised by Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R.; Addison Wesely Longman: UK, 1997; pp. 1298–1398.
24. *The Merck Index*, 11th ed.; Budavari, S., Eds; Merck & Co.: Rahway, NJ, USA, 1989; p. 3247.