Ammonium Formate in Organic Synthesis: A Versatile Agent in Catalytic Hydrogen Transfer Reductions

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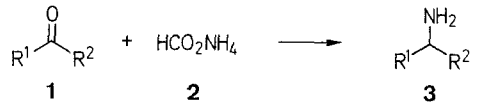
Applications of ammonium formate in organic synthesis are reviewed.

Introduction

The development of selective, mild and effective reducing agents is still an area of considerable interest, particularly when a molecule has multiple reducible or labile moieties. Recently a review on heterogeneous catalytic transfer hydrogenation has appeared in the literature.[1] The present article deals only with application of ammonium formate in organic synthesis, which has not yet been reviewed.

The preparation of ammonium formate was described in 1941.[2] It has been generally used in the precipitation of base metals from the salts of the noble metals. The use of ammonium formate in organic synthesis was first illustrated by Leucart,[3] in which various carbonyl compounds **1** were reacted with ammonium formate **(2)** to afford the corresponding amines **3**. This process was later named as the "Leucart Reation" (Scheme **A**).



1 2 3

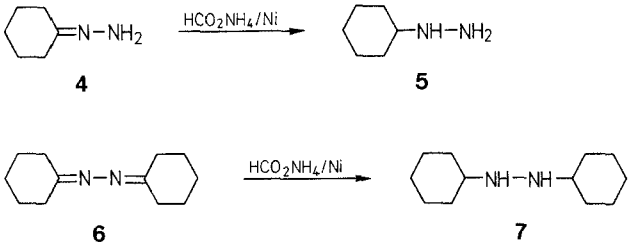
Scheme **A**

The mechanism of Leucart reaction was studied by Wallach,[4] and in 1949 a comprehensive review on the Leucart reaction was published by Moore.[5] Later, the Leucart reaction was successfully extended to the amination of 1,5-diketones[6] and unsaturated ketones.[7]

2. Reduction of Functional Groups

2.1. Initial Studies

The use of ammonium formate as a reducing agent for functional groups in moderate reaction conditions is interesting and promising. Hydrazones and azines **4** and **6**, on reduction with formic acid or its derivatives such as ammonium formate gave good yields of the corresponding hydrazines **5** and **7**[8] (Scheme **B**).



4 5

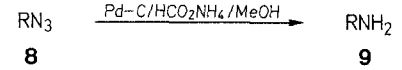
6 7

Scheme **B**

N,N-Dicyclohexyl Hydrazine Dihydrochloride (7):[8]
A mixture of cyclohexanone azine (**6**; 19.2 g, 0.1 mol), HCO_2NH_4 (30.5 g, 0.5 mol) and nickel catalyst (0.2 g) is refluxed for 6 h. The mixture is diluted with twice the amount of water and the product is extracted with benzene. The benzene layer is evaporated and the residue boiled with conc. HCl (50 mL) saturated with HCl gas; yield: 20.1 g (75%); m.p. 267°C.

2.2 Azides

Insertion of amino group in the organic molecule via azide is a well known procedure. In past years a number of reagents have been developed for the reduction of azides to amino derivatives. Recently alkyl azides **8** were successfully reduced to the corresponding primary amines **9** in the presence of palladium/carbon, using ammonium formate as the hydrogen source[9] (Scheme **C**)



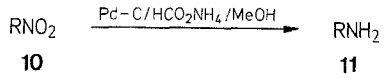
8 9

Scheme **C**.

Reduction of Azides; General Procedure:[9]
A mixture of azide (1.0 mol), HCO_2NH_4 (4.0 mol) and 5% Pd/C (6–15% of azide by weight) in CH_3OH (100 mL) is stirred for 3–4 h at ambient temperature. The catalyst is removed by filtration and the product is isolated by standard procedures; yield: 74–93%.

2.3. Nitro Groups

Aliphatic nitro compounds are traditionally reduced either by high pressure catalytic or metal-catalyzed transfer hydrogenation, both of which are time consuming processes. Recently we reported use of ammonium formate in catalytic hydrogen transfer reductions, in which nitroalkanes, nitro esters and aromatic nitro compounds such as nitrobenzene derivatives, aromatic nitro acids and esters can be selectively and rapidly reduced to the corresponding amino derivatives **11** in high yield[10,11] (Scheme **D**).



10 **11**

Scheme **D**

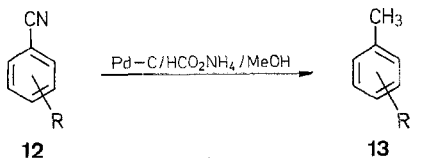
α-Nitro esters can be rapidly reduced to the corresponding α-amino esters, however, α-nitro acids on reduction decarboxylate to the corresponding alkylamines. Attempts were made to minimize the decarboxylation using sodium acetate/acetic acid buffer (pH = 5.0), but with only limited success. Reduction of nitro heterocyclic compounds such as 2-methyl-5-nitroimidazole was partial, for e.g. 5-nitrouracil was recovered as unreacted starting material. Similar result was observed with β-nitro styrene.

In most cases (excluding the above exceptions), the reaction is over in 3–40 min.[10,11] These results demonstrate a rapid versatile and selective reducing system for wide variety of nitro compounds in the presence of other functional groups such as nitrile, carbonyl etc.

Reduction of Nitro Groups; General Procedure:[10,11]
To a stirred suspension of the appropriate nitro compound (5 mmol) and 10% Pd/C (0.2–0.3 g) in dry CH_3OH (10 mL) at room temperature is added anhydrous HCO_2NH_4 (23 mmol) in a single portion under an argon atmosphere. The resulting mixture (slightly exothermic and effervescent) is stirred at room temperature for 3–40 min, the catalyst is removed by filtration through a celite pad and washed with dry CH_3OH (10 mL). The filtrate is evaporated either under reduced or at normal pressure. The residue is triturated with water (10 mL–25 mL), the product is extracted with organic solvents, i.e. ether, CH_2Cl_2 or $CHCl_3$ and dried (Na_2SO_4). The filtrate on evaporation gives the desired amino derivatives. Some products are directly converted into the hydrochloride salt with ethereal HCl without evaporation of the ether solution; yield: 31–98%.

2.4. Nitriles

Reduction of the nitrile group to an alkylamine by complex metal hydrides or catalytic hydrogenation under pressure is a general procedure.[12] Direct conversion of the nitrile group into a methyl group often requires drastic conditions.[13] Recently, a mild direct transformation of aromatic nitriles **12** into the corresponding methyl derivative **13** with ammonium formate was reported[14] (Scheme **E**). This general procedure is only applicable for reduction of aromatic nitriles to methyl derivatives.



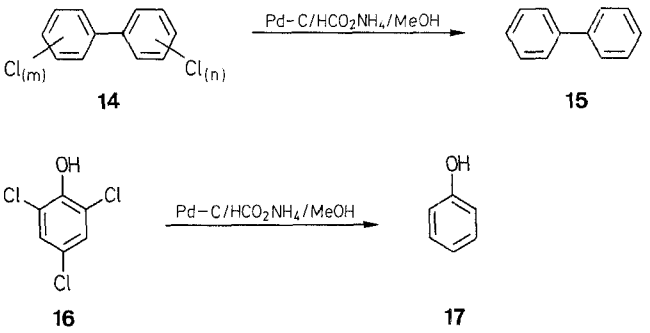
12 **13**

Scheme **E**

Reduction of Nitriles to Methyl Groups; General Procedure:
See *Synthesis* **1982**, 1036.

3. Dehalogenation of Aromatic Chlorocarbons

Dehalogenation is generally carried out by high pressure catalytic hydrogenation, hydride reductions using lithium aluminum hydride or diisobutylaluminum hydride or pyrolysis. During our search for a mild reducing agent for the reduction of nitro compounds, we had observed that 2-iodo-4-nitrobenzamide can be reduced and deiodinated to the corresponding 4-aminobenzamide using Raney nickel/ammonium formate system, however no reaction takes place when 10% palladium-/carbon-ammonium formate system was used. We did not explore this further, however, recently similar observation has been made,[15] in which various mono- or polychlorinated aromatic compounds **14** or **16**, on treatment with ammonium formate in presence of palladium on carbon at room temperature, afforded dehalogenated compounds **15** or **17** (Scheme **F**). This reaction is very mild and rapid.



14 **15**

16 **17**

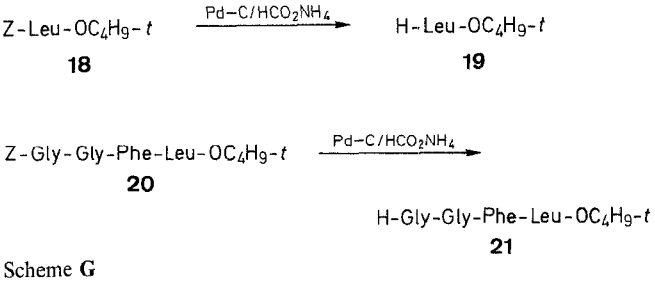
Scheme **F**

Dehalogenation of Aromatic Chlorocarbons; General Procedure:
To a solution of the aryl halide (1 mmol) and HCO_2NH_4 (4 to 5 mmol) in MeOH or AcOH (10 mL), the catalyst 10% Pd/C (1/4 of the wt. of aryl halide) is added under N_2 atmosphere. The reaction progress is monitored by reverse phase high pressure liquid chromatography. After completion of the reaction, the catalyst is removed by filtration and the filtrate concentrated under reduced pressure. The product is isolated either by precipitation with water or by extraction with an organic solvent ($CHCl_3$ or EtOAc).

4. Deprotection of Functional Groups

4.1. Deprotection of Polymer and Carbobenzyloxy Group from Protected Peptides

Rapid and selective removal of protecting groups under moderate reaction conditions is often a necessary step in the area of peptide chemistry. A number of reagents have been developed for this purpose. Recently ammonium formate has been used at several stages in the synthesis of leucine-enkephalin[16] for the reductive cleavage of the benzyloxycarbonyl group (Scheme **G**).



18 **19**

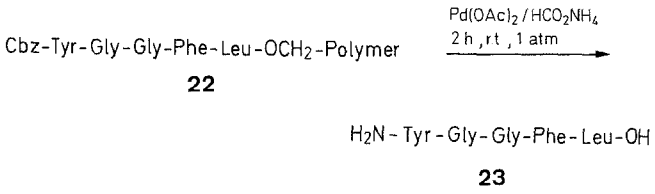
20 **21**

Scheme **G**

The yields of final products are > 90% and the reactions are complete within 1 minute at room temperature and ambient pressure. It was shown that deprotection with ammonium formate is faster than formic acid under identical reaction conditions.[16]

Deprotection of Protected Peptides; General Procedure:
See *Synthesis* **1980**, 929.

Further, ammonium formate has been applied to the simultaneous deprotection and release of pentapeptide leucine-enkephalin **(23)** from the Merrifield peptide polystyrene resin **22**[17-18] under moderate reaction conditions and pressure in a neutral medium (Scheme **H**). The yields were quantitative.

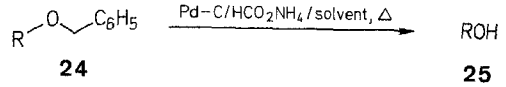


Scheme **H**

Polymer Deprotection and Removal of Peptides Using Ammonium Formate, Typical Procedure:[17]
Cbz–Tyr–Gly–Gly–Phe–Leu–OCH$_2$*-Polymer* (**22**; 1.0 g) is swelled in DMF (12 mL) containing $Pd(OAc)_2$ (1.0 g) for 2 h. Upon addition of a solution of HCO_2NH_4 (1.0 g) in water (0.5 mL), a deposition of palladium is observed with rapid evolution of gases following a 1 min induction period. After stirring for 2 h, the resin is filtered and washed with 50% aqueous AcOH (2 × 30 mL). The filtrate is evaporated under reduced pressure at low temperature and the residue is purified by column chromatography on Sephadex G-15 using 30% aqueous AcOH as an eluent. The appropriate fractions on evaporation gives *leucine-enkephalin acetate* (**23**); yield: 231 mg (94%).

4.2. Deprotection of *O*-Benzyl Group

Benzyl ethers play an important role in carbohydrate chemistry. Deprotection of the benzyl group is generally carried out either by catalytic or chemical hydrogenolysis, bromination-hydrolysis or bromination-acetolysis. Formic acid/palladium carbon[19] or palladium hydroxide on carbon/cyclohexene[20] has been used for deprotection of *O*-benzyl group. The reported results are variable in both cases. The *O*-benzyl group in **24** was selectively cleaved by catalytic hydrogenation using 10% palladium/carbon and ammonium formate[21] as the hydrogen donor (Scheme **I**). In these reactions glycosidic *O*-methyl groups are unaffected.

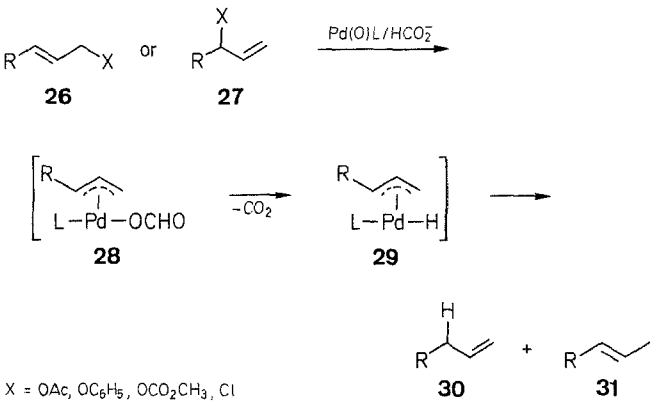


Scheme **I**

Cleavage of *O*-Benzyl Group; General Procedure:
See *Synthesis* **1985**, 76.

5. Regioselective Synthesis of 1-Olefins

A useful regioselective synthetic method for 1-olefins has been developed,[22,23] in which various terminal allylic compounds such as allylic esters, phenyl ethers, carbonates, chlorides and vinyl epoxides **26** or **27** were reacted with ammonium formate in the presence of palladium-tributylphosphine complex as a catalyst to afford 1-olefins **30** (Scheme **J**).

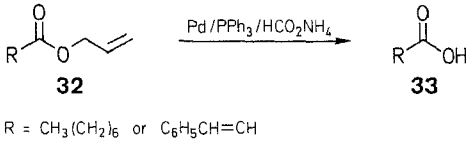


Scheme **J**

It was also demonstrated that the role of the catalyst palladium-tributylphosphine, is critical. If other catalysts such as palladium-triphenylphosphine, $Pd[P(C_6H_5)_3]_4$ or $Pd(dba)_3CHCl_3–P(OC_2H_5)_3$ are used, the yield of isomeric 2-olefins is significantly increased. The best results were obtained with palladium-tributylphosphine.

1-Octene-7-one[30, R = $CH_3CO(CH_2)_3$]; Typical Procedure:[22]
A mixture of $Pd_2(dba)_3CHCl_3$ (0.0125 mol), PBu_3 (0.1 mmol), HCO_2NH_4 (2 mmol) and the allylic acetate **26** [R = $CH_3CO(CH_2)_3$] (1 mmol) in dioxane (3 mL) is stirred at 100 °C for 1 h and then filtered (Florisil). Removal of the solvent followed by elution on silica gel with ether/hexane (1:20) gives the product; yield: 79% (100% selectivity, GC).

Allyl esters **32** were also converted into the corresponding acids in very good yield **33** using $Pd[P(C_6H_5)_3]_4$ and ammonium formate system (Scheme **K**).



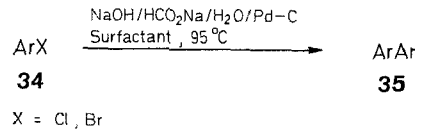
Scheme **K**

In the above reaction the allyl group was removed by hydrogenolysis, but the double bond in the acid molecule remained intact. Other salts of formic acid were also used to study the reaction.[23]

6. Miscellaneous Applications and other Formic Acid Derivatives

Ammonium formate also has been used in ester plasticizers[24] and in the synthesis of copper formate.[25] Besides ammonium formate, sodium formate and triethylammonium formate also have been studied in organic synthesis.

Sodium formate[26] in the presence of surfactant has been applied to the preparation of biaryls **35** from aromatic halides **34** (Scheme **L**).

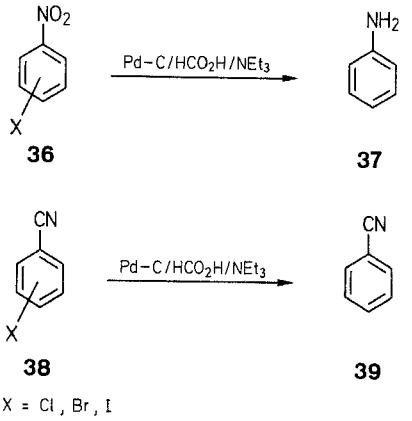


Scheme **L**

The yield of biaryl is dependent on the surfactant used, which apparently plays an important role in this reaction.[26] Cetyltrimethylammonium bromide is the most generally applicable surfactant for a wide variety of compounds. Xylene is also used as a cosolvent.

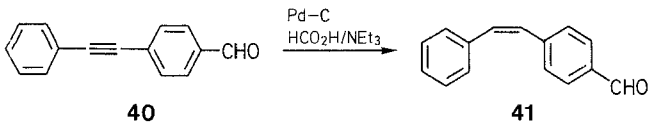
Biaryls; General Procedure:
See *Synthesis* **1978**, 537.

Various nitro and cyano aromatic halides **36, 38** were reduced to the corresponding dehalogenated amino and cyano derivatives **37, 39**, respectively, with triethylammonium formate[27] in the presence of palladium/carbon or a soluble triarylphosphine-palladium acetate catalyst (Scheme **M**)



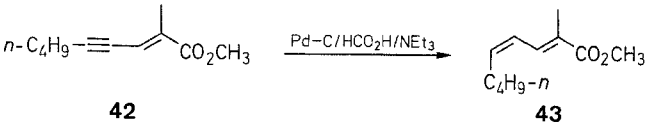
Scheme **M**

Phenyl conjugated and double bond conjugated acetylenes **40** have been reduced with triethylammonium formate using palladium on carbon as a catalyt.[28] In general *cis* olefins were obtained in very good yield (Scheme **N** and **O**).



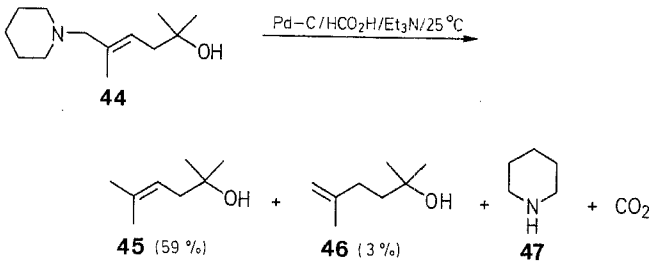
Scheme **N**

The reaction in general leads only to the reduction of the acetylenic bond and not the double bond, however, sometimes completely reduced products were obtained.



Scheme **O**

This method was further extended to the reduction of allylic amine derivatives **44**.[28] All reductions give mixture of two isomeric olefins **45** and **46** arising from both direct reduction of the amine carbon atom and addition of hydrogen to the more distant carbon of the double bond with double bond migration and loss of amino group (Scheme **P**). This may be due to a allylic palladium hydride species as an intermediate in the reduction.



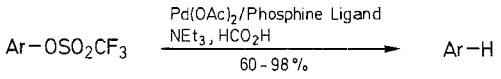
Scheme **P**

The usefulness of reaction is limited since a mixture of isomeric olefins are produced. The reduction of secondary allylic amine and diallyl amine gave mainly *N*-allyl formamide.

Reduction of Acetylenes and Allylic Amines; General Procedure:[28]
To a stirred mixture of the substrate, catalyst and NEt_3 is added dropwise 97% formic acid at room temperature. The reaction is allowed to proceed at the desired temperature until GC analysis shows that all of the substrate has been reduced or no further reduction has taken place. The catalyst is removed by filtration and the residue is washed twice with ether. The combined filtrate is washed with distilled water, dried ($MgSO_4$), and evaporated *in vacuo* to give the desired product.[28]

Isoprene has been reductively dimerised with formic acid and triethylamine at room temperature using 1% palladium-organophosphine catalyst.[29] This dimerization proceeds head to tail to give monoterpenes in up to 79% yield.

Recently phenols have been selectively deoxygenated by reducing the corresponding aryl triflates with triethylammonium formate in the presence of a homogenous palladium catalyst (Scheme **Q**).[30]



Scheme **Q**

7. Conclusion

The ammonium formate-palladium on carbon is very versatile, selective and rapid method for catalytic hydrogenolysis of wide variety of functionalities. Ammonium formate also has advantages of being readily available, inexpensive, stable and non-toxic and can be used in conjunction with either palladium on carbon (or other palladium derivates) or Raney-Nickel catalyst. Moreover it can be added to the reaction in a single portion and products can be easily separated from the reaction mixture.

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