Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2023, **14**, 4346

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 13th January 2023
Accepted 12th March 2023

DOI: 10.1039/d3sc00257h

rsc.li/chemical-science

Catalytic utilization of converter gas – an industrial waste for the synthesis of pharmaceuticals†

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Converter gas is a large scale waste product that is usually burned to carbon dioxide and contributes to the world emission of greenhouse gases. Herein we demonstrate that instead of burning the converter gas can be used as a reducing agent in organic reactions to produce valuable pharmaceuticals and agrochemicals. In particular, amide-based selected drug molecules have been synthesized by a reaction of aromatic nitro compounds and carboxylic acids in the presence of converter gas. In addition, we showed that this gas can also be conveniently utilized to carryout classical reductive amination reaction.

Introduction

Converter gas is one of the largest waste products of the steel industry.[1] Each year millions of tons of converter gas is formed.[2] Typically this gas is burned to carbon dioxide which is then released to the atmosphere and makes a significant contribution to the world emission of greenhouse gases (Fig. 1).[3,4] While the emission of greenhouse gases from burning fossil fuels can be reduced by using other energy sources (such as electricity from solar, hydro, or nuclear plants), emissions from steel production are currently unavoidable. Therefore, it is highly desirable not to burn converter gas but rather to apply it in the chemical industry for the synthesis of valuable products. Herein, we address this challenge and demonstrate that converter gas can be used as a reducing agent for the production of a variety of organic chemicals including pharmaceuticals.

The composition of converter gas depends on the temperature of the steel-making process, but typically it contains 60–95% of CO, as well as N_2 and CO_2 as the main components.[5] During the traditional burning process, the converter gas acts essentially as a reducing agent for atmospheric oxygen. Therefore, it may be also possible to use it in a similar manner for reduction of organic compounds. Recently we and others have used CO as a reducing agent in various transformations.[6–9] In the course of these studies, we found that converter gas can be used for the direct amidation of nitroarenes and carboxylic acids without any additives or coupling agents (Scheme 1). This atom- and step-economic process converts the industrial starting materials into valuable amide derivatives. The amide bond is one of the most important bonding motifs in organic chemistry and provides the basis for the unique physical and biological properties of many high-performance materials, natural products and biology related molecules.[10–12] Consequently, amides are found in numerous pharmaceutical drugs[13–15] and

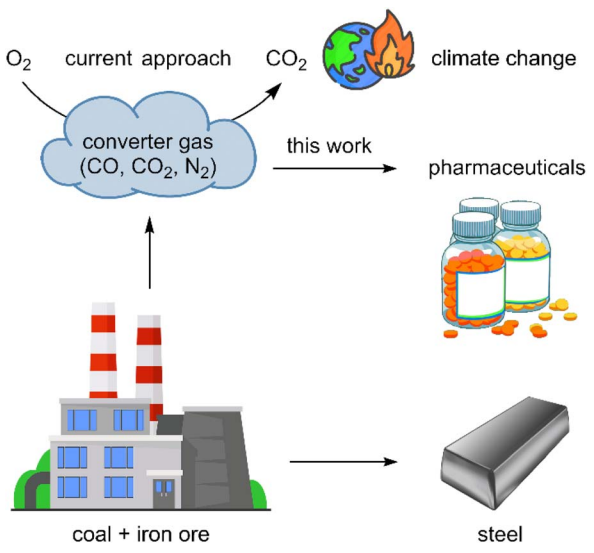

Fig. 1 The formation and possible applications of converter gas for production of pharmaceuticals, polymers, and other chemicals.

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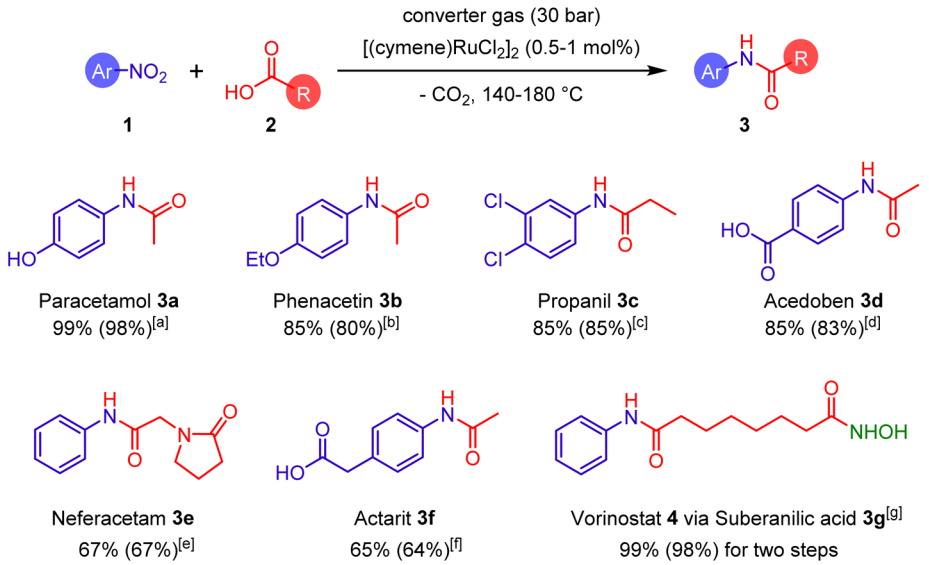
† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3sc00257h



Scheme 1 Synthesis of selected pharmaceuticals by catalytic amidation of nitroarenes and carboxylic acids with the aid of converter gas. Reaction conditions (detailed reaction conditions are provided in the ESI†): [a] 1 mol% of $[(cymene)RuCl_2]_2$, 1 equiv. of **2**, 10 equiv. of **1**, 30 bar of converter gas, 140 °C, 20 h; [b] 0.5 mol% of $[(cymene)RuCl_2]_2$, 1 equiv. of **2**, 10 equiv. of **1**, 50 bar of converter gas, 180 °C, 20 h; [c] 0.5 mol% of $[(cymene)RuCl_2]_2$, 1 equiv. of **2**, 10 equiv. of **1**, 30 bar of converter gas, 160 °C, 20 h; [d] 0.5 mol% of $[(cymene)RuCl_2]_2$, 1 equiv. of **2**, 10 equiv. of **1**, 30 bar of converter gas, 170 °C, 20 h; [e] 0.5 mol% of $[(cymene)RuCl_2]_2$, 1 equiv. of **2**, 5 equiv. of **1**, 30 bar of converter gas, 170 °C, 20 h; [f] 0.75 mol% of $[(cymene)RuCl_2]_2$, 1 equiv. of **2**, 10 equiv. of **1**, 30 bar of converter gas, 140 °C, 20 h; [g] for preparation of **3g**: 0.75 mol% of $[(cymene)RuCl_2]_2$, 1 equiv. of **2**, 5 equiv. of **1**, 30 bar of converter gas, 170 °C, 20 h. NHOH group highlighted by green color was introduced in a second step.

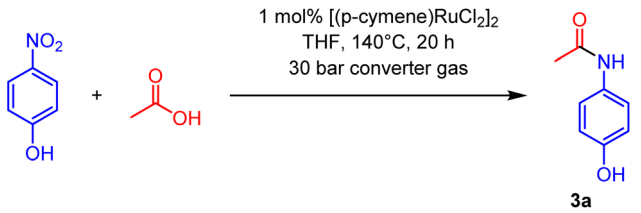
agrochemicals. To show the practical potential of the amidation reaction using converter gas, we applied it for the synthesis of various pharmaceuticals.

Results and discussion

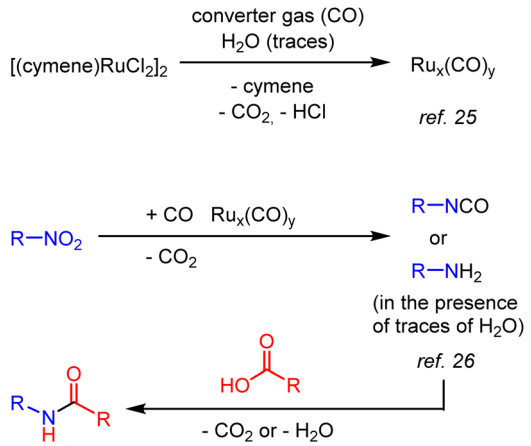
First, we studied the reaction of 4-nitrophenol with acetic acid in the presence of converter gas to produce paracetamol (**3a**). In accordance with previous reports on related processes,[7,16–19] we found that ruthenium complexes are efficient catalysts for this transformation. Under optimal conditions, the commercially available ruthenium catalyst $[(cymene)RuCl_2]_2$ (at 1 mol% loading) allowed us to obtain paracetamol (**3a**) in 99% yield (Table 1, entry 1). Noteworthy, other ruthenium complexes can be used as catalysts but reaction did not proceed at all in the absence of the ruthenium source or in the absence of the converter gas (Table 1, entry 7; full details of conditions optimization are provided in the ESI†). Both $Ru(acac)_3$ and $RuCl_3$ can be used as catalysts indicating that the nature of ligands is not crucial for the process (Table 1, entries 2 and 3). Water can be used as a solvent for the reaction, which makes the reaction attractable for the industrial chemistry (Table 1, entry 4). The optimal conditions are 140 °C and 30 bar; reactions at lower temperature or pressure gave lower yields (Table 1, entries 5 and 6).

In a similar manner, other important pharmaceuticals such as phenacetin (**3b**), propanil (**3c**), acedoben (**3d**), nefiracetam (**3e**), and actarit (**3f**) were produced in 65–85% yields (Scheme 1). It is important to note that this amidation reaction is compatible with various functional groups including hydroxyl (in paracetamol), chloride (in propanil), amide (in nefiracetam), and carboxylic acid (in actarit and acedoben). In addition, vorinostat (**4**), one of the main drugs against T cell lymphoma,[20] was synthesized in two steps from suberic acid, nitrobenzene, and hydroxylamine in almost quantitative yield. The function of converter gas in these syntheses is essential to capture and remove the excessive oxygen atoms from the nitro- and carboxylic groups of the reagents. Since the industrial converter gas may contain sulfur-based impurities,[21] we tested the catalytic amidation in the presence of thiophene. Fortunately, this did not lead to poisoning of the catalyst (see ESI, Table S7†).

Table 1 Selected optimization results



Entry	Deviation from the optimal conditions	Yield of **3a**
1	None	99%
2	$Ru(acac)_3$ instead of $[(cymene)RuCl_2]_2$	84%
3	$RuCl_3$ instead of $[(cymene)RuCl_2]_2$	31%
4	Water instead of THF	85%
5	20 bar of converter gas	47%
6	130 °C instead of 140 °C	56%
7	No catalyst or CO_2 instead of converter gas	0%
8	CO instead of converter gas	86%

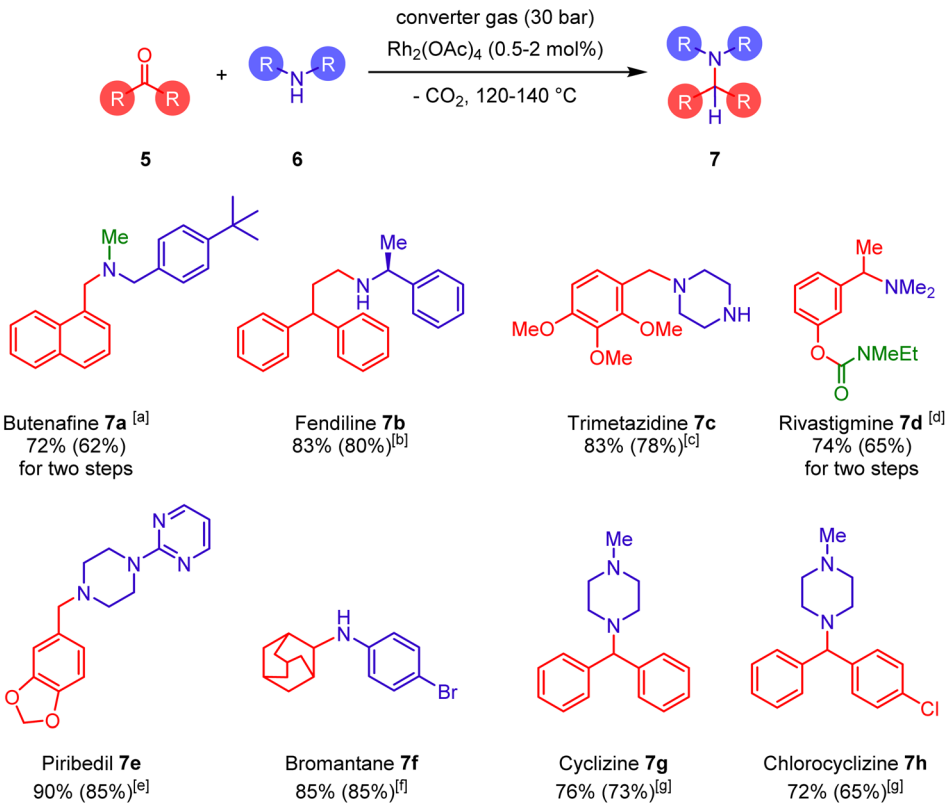


Scheme 2 Possible mechanism of the catalytic amidation reaction.

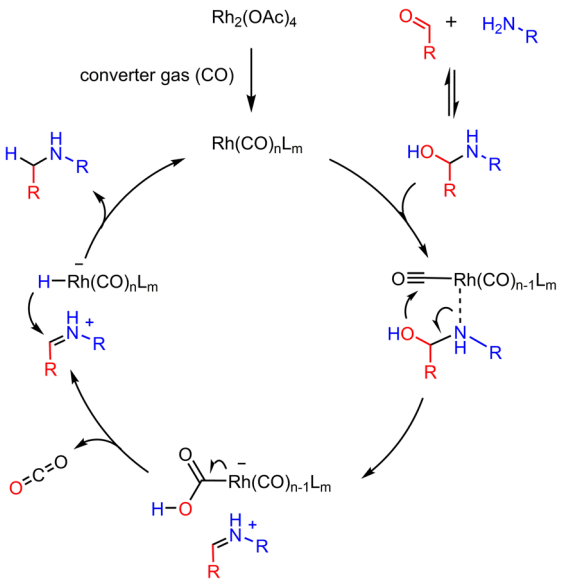
The exact mechanism of the catalytic amidation is not clear, but we can propose a possible sequence based on experimental observations and previous literature reports[7,22–24] (Scheme 2). First the nitro compounds are reduced by CO in the presence of ruthenium carbonyl species[25] $Ru_x(CO)_y$ to give isocyanates or amines.[26] Then isocyanates or amines can react with carboxylic acid to give the desired amide similar to the known organic transformation. The detailed discussion of the possible mechanism is provided in the ESI.†

In order to prove that converter gas can be used in a general manner for other reductive transformations, we explored another important reaction involving the formation of C–N bonds, namely, the reductive amination (Scheme 3).[27–32]

Indeed, it was found that this reaction between readily available carbonyl compounds and amines proceeded in the presence of converter gas and was catalysed by a simple rhodium acetate without any additional expensive ligands. This way we synthesized antifungal agent butenafine (**7a**) directly from formaline, naphthaldehyde, and 4-*tert*-butylbenzylamine. Further expansion of this method provided other drugs such as fendiline (**7b**), trimetazidine (**7c**), rivastigmine (**7d**), piribedil (**7e**), bromantane (**7f**), cyclizine (**7g**), and chlorocyclizine (**7h**) (detailed reaction conditions are provided in the ESI†). Once again, the reaction displayed excellent selectivity and was not inhibited by various functional groups.



Scheme 3 Catalytic reductive aminations using converter gas: synthesis of selected pharmaceuticals. Reaction conditions (detailed reaction conditions are provided in the ESI†): [a] 0.5 mol% of $Rh_2(OAc)_4$, 1.5 equiv. **6**, 1 equiv. of **5**, 30 bar of converter gas, 120 °C, 22 h. After 22 h 2.20 equiv. of formaline were added for an additional 22 h to achieve methylation (highlighted by green color); [b] 0.5 mol% of $Rh_2(OAc)_4$, 1.1 equiv. of % **6**, 1 equiv. of **5**, 30 bar of converter gas, 140 °C, 22 h; [c] 1 mol% of [(η^4-cyclooctadiene)Rh(η^6-2,3,6,7-tetramethoxy-9,10-dimethylanthracene)]BF_4, 10 equiv. of **6**, 1 equiv. of **5**, 30 bar of converter gas, 120 °C, 22 h; [d] reductive amination step: 0.5 mol% of $Rh_2(OAc)_4$, 5 equiv. of **6**, 1 equiv. of **5**, 30 bar of converter gas, 120 °C, 48 h. C(O)NMeEt group highlighted by green color was introduced in the next step; [e] 0.5 mol% of $Rh_2(OAc)_4$, 1 equiv. of **6**, 1 equiv. of **5**, 30 bar of converter gas, 120 °C, 22 h; [f] 0.5 mol% of $Rh_2(OAc)_4$, 1 equiv. of **6**, 2 equiv. of **5**, 42 bar of converter gas, 120 °C, 22 h; [g] 2 mol% of $Rh_2(OAc)_4$, 5 equiv. of **6**, 1 equiv. of **5**, 45 bar of converter gas, 130 °C, 48 h.



Scheme 4 Possible mechanism for reductive amination by CO in the presence of a rhodium catalyst.

As in the previous case, the main role of converter gas is to remove the oxygen atoms from the carbonyl molecules. We assume that rhodium species first coordinate with CO, which is then attacked by the OH group of the hemiaminal intermediate to give the Rh–COOH group. Its further decarboxylation gives rhodium hydride species, which immediately reduce the iminium cation similar to previous reports[33,34] (Scheme 4).

Experimental

Preparation of converter gas

The model converter gas was prepared in a 40 liter gas cylinder at room temperature. The gas cylinder was filled with 29 bar of carbon monoxide, followed by 10 bar of carbon dioxide and 11 bar of nitrogen.[35]

General procedure for the reductive amidation

The ruthenium catalyst [(*p*-cymene)$RuCl_2$]$_2$ (0.5–1 mol%), nitroarene, acetic acid, THF, and a magnetic stirring bar were placed into an autoclave. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 30 bar of converter gas. The autoclave was placed into an oil bath preheated to the required temperature (140–180 °C). After the indicated time (typically 20 h), the autoclave was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was additionally washed with dichloromethane (2 × 1 mL). The solvents were removed using a rotary evaporator, and the residue was analyzed by NMR.

General procedure for the reductive amination

Rhodium(II) acetate (0.5–2 mol%), amine, and the carbonyl compound were placed into an autoclave. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 45 bar of converter gas. The reactor was placed into an oil bath preheated to the required temperature (120–140 °C). After the indicated time (20–48 h), the autoclave was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was additionally washed with dichloromethane (2 × 1 mL). The solvents were removed using a rotary evaporator, and the residue was analyzed by NMR.

Conclusions

To conclude, we have demonstrated that, instead of burning converter gas, it can be conveniently used to synthesize valuable organic life science products. The generality of this approach is showcased in the preparation of several current pharmaceuticals *via* the reductive amidation protocol as well as *via* more classical reductive amination. We believe that converter gas can be used for many other atom- and step-economical reduction transformations in the near future. In particular, converter gas from steel plants might replace natural gas sources in well-known large-scale industrial processes involving CO such as synthesis of acetic acid,[36–38] hydroformylation,[39–41] urea synthesis,[8,42–44] *etc.* Hopefully, this discovery will attract other researchers to develop chemical processes involving converter gas.

Data availability

All data associated with this report may be found in the ESI.†

Author contributions

S. A. R., O. I. A., E. A. K. carried out all experiments, D. S. P. carried out quantum chemical modelling. D. C. generated an idea of the paper and coordinated all project. R. V. J. and M. B. involved in the development of this project. O. I. A., D. S. P., R. V. J., M. B., D. C. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Russian Science Foundation (Grant No. 22-73-10020). The NMR data were collected using the equipment of the Center for molecular composition studies of INEOS RAS with financial support from the Ministry of Science and Higher Education of the Russian Federation (Contract No. 075-03-2023-642).

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