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Original Article

N, N-dimethylformamide.diiodine complex (DMF.I_2) as an innovative efficient green catalyst in the synthesis of thiosemicarbazones by condensation of ketones with thiosemicarbazides

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ABSTRACT

In a drug discovery program aimed at finding new anti-trypanosomal drugs, we developed the *N, N*-dimethylformamide.diiodine complex (DMF.I_2) as an innovative and efficient green catalyst for the condensation reaction of aldehydes/ketones with arylthiosemicarbazides. The design of this catalyst was rationalized on the basis of a mechanistic proposal which establishes the existence of a catalytic loop regenerating I_2 at the end of the catalytic process. In general, yields were fair to good at extremely low end catalyst concentration. DMF.I_2 is the first catalyst that allows for high yield in the condensation of aldehydes/ketones with arylthiosemicarbazide at sub-micromolar concentration.

Keywords: Green chemistry; Dimethylformamide-diiodine complex (DMF.I_2); Trypanosomal infections; arylthiosemicarbazides; Thiosemicarbazones

INTRODUCTION

In order to discover news drugs for treating trypanosomiasis which causes serious damages in sub-saharian Africa and latin America populations, we explored thiosemicarbazones which are compounds which have received a lot of attention in the field of medicinal chemistry, due to their multiple pharmacological properties, such as *i.a.* antiviral [1–3], antibacterial [4–6], antifungal [7–8], antitumor [9-12] and antiparasitic activities [13]. The use of molecular iodine in organic synthesis has been known for a long time. In recent years, molecular iodine has received considerable attention as an inexpensive, nontoxic, ecofriendy and readily available catalyst for various organic transformations under mild and convenient conditions to afford the corresponding products in excellent yields with high selectivity [14]. In recent decades, the use of molecular iodine, a Lewis acid, has attracted considerable attention. It requires generally only a short reaction time, simple work-up, use of simple precursors to synthesize complex molecules and it is a moisture-stable mild Lewis acid in synthetic organic chemistry [15]. The mild Lewis acid nature of iodine has been exploited in a variety of reactions and in our research; we envisaged from the very beginning that molecular iodine could play a dual role both as a catalyst that initially promotes the formation of the first tetrahedral adduct and subsequently its decomposition [16;17].

Previous works from this group aimed at synthesizing compound libraries established the efficacy of two major catalysts in the synthesis of thiosemicarbazones in the general context of the nucleophilic generalized acid-base catalysis, *i.e.* anilinium chloride on the one hand and anthranilic acid, on the other hand [18;19]. Both catalysts, while very efficient in most instances, suffer from the fact that they are based on Brønsted acids and/or bases and may therefore interfere with acid or base sensitive functions in polyfunctional

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molecules. We therefore searched for a form of milder catalyst species that would also be endowed with Green Chemistry characteristics. In another context, our group developed the DMF.I_2 Lewis salt complex as unique efficient catalyst for Friedel-Crafts acylation of highly activated aromatic substrates [20]. We therefore attempted to use this catalyst for the synthesis of semicarbazones and thiosemicarbazones since DMF.I_2 contains both a Lewis acid (I_2) and a Lewis base (DMF) in the same way as anilinium chloride and anthranilic acid contain both a Brønsted base and acid entities and work in symbiosis as a buffer in a generalized acid-base catalysis process. To our pleasure, initial exploratory experiments using our benchmark reaction (*i.e.* condensation of 4'-nitroacetophenone with 4-phenylthiosemi carbazide) proved quite satifactory. Moreover, the DMF.I_2 complex can be considered indeed as a green catalyst since DMF is readily biodegradable and diiodine is naturally present in the biosphere (for example, in sea water).

MATERIALS AND METHODS

Experimental Section: Melting points were determined using an Electrothermal 9100 melting point apparatus and are uncorrected. ^{1} H- and ^{13}C-NMR spectrum was recorded at ambient temperature on an Avance II Bruker 400 MHz Ultrashield^{TM} spectrometer. Compounds were dissolved in $CDCl_3$ and chemical shifts are expressed in the δ scale with TMS as internal standard. Thin layer chromatography analyses were performed on Merk TLC plates (silica gel, 60 F 254, E. Merk, Darmstadt, ref. 5735). All reported compounds were routinely checked in two standard solvents, *i.e.* acetone/toluene/cyclohexane (solvent A, 5:2:3, *v/v/v*) and chloroform/methanol (solvent B, 90/10, *v/v*). Reverse-phase thin layer chromatography conditions were: HPTLC plates RP-18 F-254 S (Merk), methanol: water (75/25, v/v). All compound reported were found homogenous under such TLC and HPLC conditions. All reagents were purchased from ACROS. All solvents were of the ACS reagent grade. Compounds were also subjected to RP-HPLC analysis using standard conditions.

(1-(4-nitrophenyl)ethylidene)-4-phenyl-thiosemicarbazide: This synthesis is representative of the standard conditions used in all of the preparations listed in the Table 1, 2, and 3. To a room temperature solution of 4'-nitroacetophenone (50 mmol) and 4-phenylthiosemicarbazide (50 mmol) in 20 mL of methanol were added in sequence 250 mg of diiodine dissolved in 0, 50 mL of DMF. The solution turning gradually to slurry was magnetically stirred at 65° for 1 h, rapidly cooled in an ice bath, and filtered on a Büchner funnel to give 91% yield of TLC-pure vacuum-dried yellow crystals. **Mp:** 196-198°C (unaffected after multiple recrystallizations from methanol), **^{1}H-NMR** ($CDCl_3$) δ(ppm): 9.35 (s, 1H, NH), 8.92(s, 1H, NH), 8.27-7.27(m, 9H, ArH), 2.41(s, 3H, CH_3), **^{13}C-NMR** ($CDCl_3$) δ(ppm) : 177.13, 148.99, 145.05, 143.82, 138.23, 129.60, 128.21, 127.81, 127.20, 125.00, 124.61, 14.44

4-phenylthiosemicarbazide: Rf (n-hexane/ethyl acetate, *v/v*: 8/2): 0.20. **^{1}H- NMR** (DMSO-d6 δ en ppm): 9.68 (s, 1H, -CSNH-Ph), 9.15 (s, 1H, -CSNH-), 7.67 to 7.08 (m, 5H, H-aromatic), 4.80 (s, 2H, -NH_2). **^{13}C- NMR** (DMSO-d6 δ (ppm): 179.31 (C=S), 139.25 (C aromatic-NH-), 128.02, 124.05, 123.51 (C-aromatic).

1-tetralone-4-phenylthiosemicarbazone: Rf (*n*-hexane/ethyl acetate, *v/v*: 8/2): 0.31. **^{1}H-NMR** (DMSO-d6 δ (ppm): 10.52 (s, 1H, -CSNH-Ph), 10.11 (s, 1H, =NNH-), 8.44, 8.42 and 7.62 to 7.19 (m, 9H, H-aromatic), 2.82 to 2.76 (m, 4H, H-cyclohexane), 1.85 (s, 2H, H-cyclohexane). **^{13}C-NMR** (DMSO-d6 δ (ppm) : 176.83 (C=S), 148.87 (C=N), 140.27, 139.18, 131.73, 129.34, 128.43, 128.05, 126.15, 125.81, 125.63, 125.50 (C-aromatic), 28.92, 26.12, 21.39 (CH_2-cyclohexane).

4'-bromo-acetophenone)-4-phenyl thiosemicarbazone: Rf (n-hexane/ethyl acetate, *v/v*: 8/2): 0.25. **^{1}H-NMR** (DMSO-d6 δ (ppm) : 10.65 (s, 1H, -CSNH-Ph), 10.10 (s, 1H, =NNH-), 8.02 to 7.21 (m, 9H, H-aromatic), 2.38 (m, 3H, -CH_3). **^{13}C-RMN** (DMSO-d6 δ (ppm) : 177.12 (C=S), 147.69 (C=N), 139.14, 136.69, 131.10, 128.92, 128.07, 126.01, 125.43, 122.43, 122.92 (C-aromatic), 14.23 (CH_3).

Fluorenone-4-phenylthiosemicarbazone: Rf (n-hexane/ethyl acetate, *v/v*: 8/2): 0.35. **^{1}H-NMR** (DMSO-d6 δ (ppm): 11.31 (s, 1H, -CSNH-Ph), 10.56 (s, 1H, =NNH-), 8.19 to7.25 (m, 13H, H-aromatic). **^{13}C-RMN** (DMSO-d6 δ en ppm): 177.99 (C=S), 146.67 (C=N), 141.51 à 120.22 (C-aromatic).

1-4'-nitro-benzaldehyde-4-phenylthiosemicarbazone: Rf (n-hexane/ethyl acetate, *v/v*: 8/2): 0.12. **^{1}H-NMR** (DMSO-d6 δ ppm): 12.11 (s, 1H, -CSNH-Ph), 10.34 (s, 1H, =NNH-), 8.19 (s, 1H, -CH=N-), 8.10 to 7.84 to7.57 à 7.31 (m, 9H, H-aromatic). **^{13}C-RMN** (DMSO-d6 δ (ppm) : 176.51 (C=S), 147.65 (C=N), 140.52 à 138.91 et 128.97 à 123.71 (C- aromatic).

Benzophenone-4-phenylthiosemicarbazone: Rf (n-hexane/ ethyl acetate, v/v: 8/2): 0.51. **^{1}H-NMR** ($CDCl_3$-d6 δ (ppm): 8.75 (s, 1H, -CSNH-Ph), 9.45

(s, 1H, =NNH-), 7.60 to7.25 (m, 15H, H-aromatic). **^{13}C-RMN** (DMSO-d6 δ (ppm) : 176.47 (C=S), 149.22 (C=N), 137.11, 135.73, 130.49, 129.65, 129.15, 128.02, 127.75, 125.38 (C-aromatic).

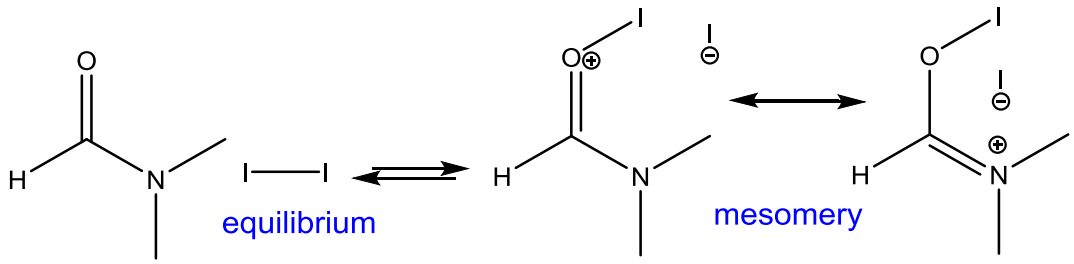
RESULTS & DISCUSSION

In Table 1, we present the performance of DMF. I_2 in comparison with other catalyst based on Brønsted systems. As can be seen, DMF.I_2 works quite satisfactorily and performs more or less at the level of other excellent catalysts. Encouraged by these results, we studied the influence of the ratio substrate: catalyst. Contrarily to the behavior of other catalysts, we found that DMF.I_2 was able to boost the condensation of 9-fluorenone with 4- transformation is nearly quantitative with a local concentration of 500 mg of diiodine in the reaction medium, when for example equimolecular amounts 50 mmol of 4-nitroacetophenone and 4-phenylthiosemicarbarbazide were refluxed in 20 ml of methanol for 1h in the presence of 250 mg of diiodine dissolved in 0.5 mL of DMF, a consistent yield of 91 % of crystalline thiosemicarbazone was obtained. In the same conditions, dividing the amount of catalyst by 8 barely affected the yield (86%). Even better results were obtained using 9-fluorenone as ketone partner (see Table 2), especially considering the striking 76% yield with 2mg of catalyst.

Table 1: Comparison of catalytic systems with regard to the actual yield in the condensation of 4'-nitroacetophenone with 4-phenylthiosemicarbazide in the same reaction conditions

Entry(#)	Catalyst	Yield (%)
1	Aniline/acetic acid	70
2	Aniline/formic acid	82
3	Aniline/hydrochloric acid	88
4	L-Proline	75
5	Guanidine hydrochloride	59
6	Acetic acid	86
7	Montmorillonite K-10	32
8	Anthranilic acid	90
9	DMF.I_2	91

All reactions were performed in the same conditions: methanol, 65°C, 1 h

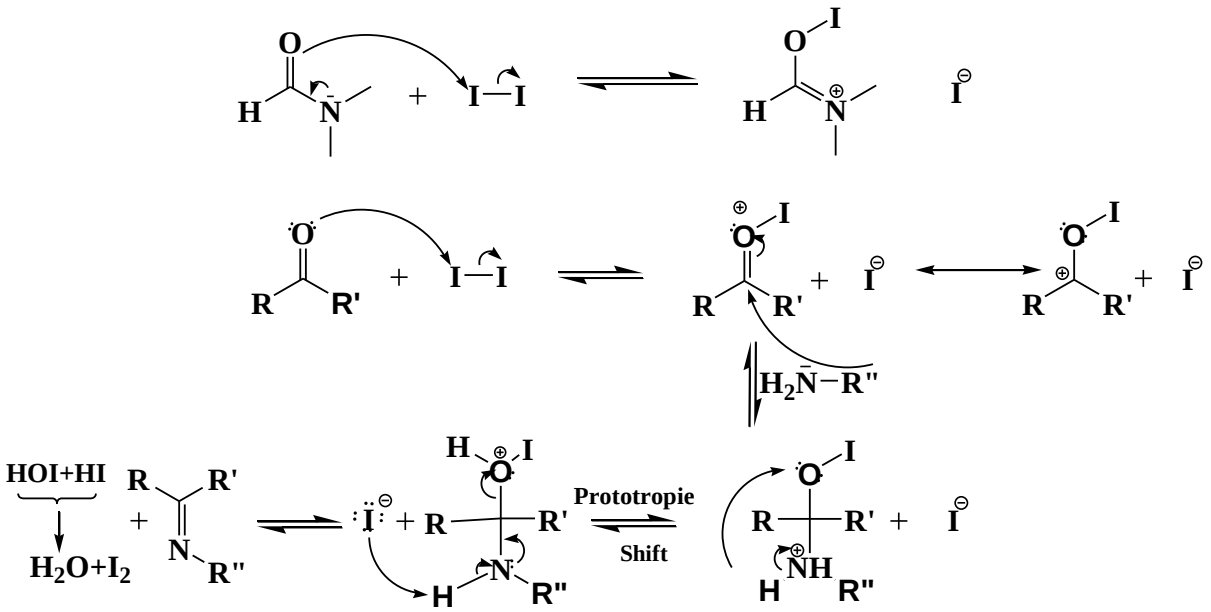


Scheme 2: Mechanism of DMF.I_2 complex formation showing equilibration between the free species and the Lewis salt stabilized by mesomery

Table 2: Synthesis of some thiosemicarbazones using DMF.I_2 as catalyst under standard conditions

Entry(#)	Compounds	Yield (%)
1	1- tetralone-4-phenylthiosemicarbazone	59
2	1-bromoacetophénone-4-phenylthiosemicarbazone	68
3	1-fluorenone-4-phenylthiosemicarbazone	99
4	9-fluorenone-4-chlorophenylthiosemicarbazone	79
5	4-acetylbiphenyl-4-phenylthiosemicarbazone	92
6	4'-nitroacetophenone-4-chlorophenylthiosemicarbazone	65
7	1-4'-nitroacetophénone-4-phenylthiosemicarbazone	91
8	1-3'-nitro-benzaldehyde-4-phenylthiosemicarbazone	62
9	Benzophenone-4-phenylthiosemicarbazone	45

In Table 3, we have exemplified the versality of our catalyst on a variety of situations. Good to excellent yields were always observed, with a bemol for benzophenone derivatives. In most cases, isolation of the resulting product is most straightforward as the pure product (TLC) spontaneously crystallizes out from the reaction medium. We are now fostering this technique for the further elaboration of a compound library of antitrypanosomal arylthiosemicarbazones. As illustrated in Scheme 1, we propose a mechanism to rationalize the catalysis offered by DMF.I_2. When dissolved in DMF, diiodine interacts with the solvent to generate a reservoir of both diiodine and iodide anions. The former will then act in the condensation as a Lewis acid while the latter anion will act simultaneously as a Lewis base (*Cfr* Scheme 2). Formally speaking, the mechanism proposed over here is essentially the same as that published elsewhere [13; 18; 19]. using Brønsted based catalyst. At the end of the process, HI serves as leaving group. Interestingly enough, reaction of leaving group HIO with HI concomitantly produced a regenerated diiodine to end up in a functional catalytic loop, and this explains the paucity of catalyst required to efficiently effect this reaction in high yield.



Scheme 1: Mechanism of the catalysis offered by Lewis's complex DMF.I_2

Table 3: Catalytic effect of DMF.I_2 upon catalyst dilution

Name of products	Weight of I_2 (mg)	Yields (%)
1-fluorenone-4-phenylthiosemicarbazone	500 mg	99
1-4'-nitroacetophénone-4-phenylthiosemicarbazone	250 mg	96
1-4'-nitroacetophénone-4-phenylthiosemicarbazone	125 mg	88
1-fluorenone-4-phenylthiosemicarbazone	32 mg	86
1-fluorenone-4-phenylthiosemicarbazone	2 mg	76
1-fluorenone-4-phenylthiosemicarbazone	0 mg	0

CONCLUSION

In an effort to find a greener alternative to anilinium chloride as catalyst in the condensation of aldehydes/ketones with thiosemicarbazide derivatives, we developed the complex DMF.I_2 as an innovative and efficient catalyst. In this paper, we have shown that DMF.I_2 (Scheme 2) is an efficient green catalyst in the condensation reaction of (thio)semicarbazides with a variety of ketones. This technique is now applied for the elaboration of a compound library of antitrypanosomal pharmacomolecules. A mechanistic proposal based on the existence of a catalytic loop is also suggested to explain why DMF.I_2 is catalytic even at low concentrations.

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