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## COMMUNICATION

## Gold/copper-catalyzed activation of the *aci*-form of nitromethane in the synthesis of methylene-bridged bis-1,3-dicarbonyl compounds<sup>†</sup>

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Activation of the *aci*-form of nitromethane using Lewis acids for the attack of carbon nucleophiles was studied. 1,3-Dicarbonyl compounds in the presence of catalytic amounts of AuCl<sub>3</sub> or Cu(OTf)<sub>2</sub> in nitromethane solvent could be converted into methylene-bridged bis-1,3-dicarbonyl compounds.

Due to the strong electron withdrawing nature of the nitro group, nitroalkanes have become versatile building blocks in the synthesis of a variety of useful molecular scaffolds and fine chemicals.<sup>1</sup> The conversion of nitroalkanes into ketones, called the Nef reaction,<sup>2</sup> is achieved by acidic hydrolysis of a nitronate salt made by the basic treatment of an aliphatic nitro compound. Hydrolysis take place at the stage of the protonated aci-nitro (nitronic acid) form. In the nitro aci-nitro equilibrium, the *aci*-form is the thermodynamically unfavorable tautomer.<sup>3</sup> However, the aci-form has been the key intermediate in certain reactions. Feuer and Nielsen have reported the first example of a Nef reaction where 2-nitrooctane is directly converted into 2-octanone in acidic medium via nitronic acid formation.<sup>4</sup> Edward and Tremaine have shown that Nef and Meyer reactions of nitroalkanes happen due to the catalytic events that occur after the nitronic acid formation.<sup>5</sup> Acid-catalyzed nitronic acid formation was achieved by Erden et al., making use of a tropylium ion rather than a proton as the electrofuge from the nitroalkane.<sup>6</sup> Other ways of stabilizing nitronic acid are by aryl substitution<sup>7</sup> at the  $\alpha$ -carbon of a nitroalkane and by H-bonding.<sup>8</sup> It is therefore evident that the stabilization of nitronic acid is not trivial and hence the limited chemistry of nitronic acids is not surprising.

During our investigations on exploring the applications of the combined use of oxo- and alkynophilicities of gold catalysts,<sup>9</sup> we found that 1,3-dicarbonyl compounds, upon refluxing with catalytic AuCl<sub>3</sub> in nitromethane, gave methylene-bridged bis-1,3-dicarbonyl compounds.<sup>10</sup> It was envisaged that the bridging methylene group should have come from the solvent nitromethane. Furthermore, the reaction could have occurred *via* the initial nucleophilic attack of the 1,3-dicarbonyl compound at the carbon of the *aci*-nitro form activated by AuCl<sub>3</sub>, just like

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the attack of water taking place in the classical Nef reaction (Fig. 1).<sup>2,11</sup> The *aci*-nitro alkane is generally involved in lower acid concentrations.<sup>12</sup> However, to the best of our knowledge, direct activation of the *aci*-form of a nitroalkane by a Lewis acid catalyst and attack by a carbon nucleophile on it is not known. Nucleophilic attack of benzene at an *aci*-nitro form generated from nitronate salt is known, however this makes use of very strong acid HF as solvent.<sup>13</sup>



Methylene-bridged 1,3-dicarbonyl compounds are useful materials and precursors of ligands employed in inorganic chemistry.<sup>10b,14</sup>

The reaction of dibenzoylmethane was screened using 5-mol% of selected Lewis and Brønsted acids and the results

 $\label{eq:table_$ 

0 0

	$Ph$ $Ph$ $Ph$ $-\frac{catalyst (}{CH_3NO_2}$	5-mol%) p, reflux	Ph ∽Ph
Entry	Catalyst	Time (h)	Yield <sup>a,b</sup>
1	AuCl <sub>3</sub>	6	98
2	AuCl <sub>3</sub> /AgSbF <sub>6</sub>	3	97
3	AgOTf	24	No reaction
4	Cu(OTf) <sub>2</sub>	5	93
5	InCl <sub>3</sub>	24	5 (94)
6	$Sn(OTf)_2$	24	33 (63)
7	CuCl <sub>2</sub>	24	37 (61)
8	FeCl <sub>3</sub>	24	54 (45)
9	$BF_3OEt_2$	24	24 (25)
10	CuI	24	No reaction
11	HCl	24	10 (80)
12	HOTf	24	6 (86)
13	none	24	No reaction

<sup>*a*</sup> Isolated yield. <sup>*b*</sup> Values in the parenthesis represent the percentage of recovered unreacted starting material.

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 Table 2
 The scope of the gold/copper-catalyzed methylene-bridged bis-1,3-dicarbonyls formation



	G4				Yield (time in h) <sup><math>a</math></sup>			
Entry	material	$R^1$	$\mathbb{R}^2$	Product	AuCl <sub>3</sub>	Cu(OTf) <sub>2</sub>		
1	1a	Ph	Ph	2a	98 (6)	93 (5)		
2	1b	4-MeO-C <sub>6</sub> H <sub>4</sub>	Ph	2b	84 (2)	75 (2)		
3	1c	$4-Br-C_6H_4$	Ph	2c	96 (2.5)	76 (5.5)		
4	1d	4-Me-C <sub>6</sub> H <sub>4</sub>	Ph	2d	93 (4)	78 (4)		
5	1e	4-Cl-C <sub>6</sub> H <sub>4</sub>	Ph	2e	92 (2.5)	73 (3)		
6	1f	$4-I-C_6H_4$	Ph	2f	98 (3.5)	95 (2.5)		
7	1g	3-Br-C <sub>6</sub> H <sub>4</sub>	Ph	2g	88 (2)	86 (2.5)		
8	1ĥ	4-Me-C <sub>6</sub> H <sub>4</sub>	$4-I-C_6H_4$	2h	95 (2)	79 (2)		
9	1i	Ph	Me	2i	85 (4)	51 (3)		
10	1j	Ph	Et	2j	80 (2)	42 (3)		
11	1k	Me	Me	2k	83 (2.5)	complex		
						reaction		
12	11	Ph	OEt	21	88 (5)	82 (4.5)		
13	1m	Ph	OMe	2m	94 (2)	87 (5)		
14	1n	$4-Cl-C_6H_4$	OMe	2n	93 (2.5)	89 (3)		
15	10	$4-Br-C_6H_4$	OMe	2o	88 (2.5)	77 (3)		
16	1p	3-Br-C <sub>6</sub> H <sub>4</sub>	OMe	2p	96 (2)	98 (2.5)		
17	1q	4-MeO-C <sub>6</sub> H <sub>4</sub>	OEt	2q	93 (3.5)	86 (5.5)		
18	1r	4-Me-C <sub>6</sub> H <sub>4</sub>	OEt	2r	94 (2)	90 (4)		
19	1s	4-Br-C <sub>6</sub> H <sub>4</sub>	OEt	2s	91 (2.5)	83 (2)		
20	1t	4-MeO-C <sub>6</sub> H <sub>4</sub>	OMe	2t	89 (2)	86 (2)		
21	1u	4-Me–C <sub>6</sub> H <sub>4</sub>	OMe	2u	98 (2.5)	76 (3)		
22	1v	1-Naphthyl	OMe	2v	90 (2.5)	80 (5)		
23	1w	Me	OEt	2w	65 (5)	10 (4)		
24	1x	Et	OMe	2x	70 (2.5)	35 (3)		
25	1y	OEt	OEt	2y	no	46 (4)		
					reaction			
<sup>a</sup> Isolated yield.								

are summarized in Table 1. Among the Lewis acids screened, AuCl<sub>3</sub> and Cu(OTf)<sub>2</sub> were found to be superior catalysts, with the former being the best for the formation of methylenebridged bis-dibenzoylmethane in high yield in a shorter reaction time. It is known that gold can catalyze condensation reactions under neutral and mild conditions.<sup>15</sup> Brønsted acids, HCl and HOTf were found to be poorer catalysts. In a different set of experiments, the reaction of dibenzoylmethane was examined in different solvents taking 5 equivalents of nitromethane using AuCl<sub>3</sub> and Cu(OTf)<sub>2</sub> catalysts.<sup>16</sup> However, these conditions were not good for the efficiency of the reaction. Perhaps a large quantity of nitromethane is required to have its aci form in a sufficient amount for the reaction to take place. The substrate scope was examined with both AuCl<sub>3</sub> and Cu(OTf)<sub>2</sub> separately with a variety of substrates. The substrates include aryl and alkyl 1,3-diketones,  $\beta$ -ketoesters and 1,3-diester. The results are summarized in Table 2.

Substrates containing substituents like, I, Br, Cl and OMe on the aryl rings could be handled without any trouble. Substrates with alkyl ketone moieties resulted in slightly lesser yields of the product in the AuCl<sub>3</sub>-catalyzed reactions (entries 9–11, 23 and 24). Cu(OTf)<sub>2</sub> was found to be less efficient in these cases, resulting in poor yields of the desired products. It is notable that preparing such compounds by a base-assisted reaction between formaldehyde and 1,3-dicarbonyl compounds is cumbersome due to aldol-related side product formation. The reactions could be scaled up. By the reaction of **1a** on a 1g scale when performed using  $Cu(OTf)_2$  and  $AuCl_3$ , the product **2a** was obtained in 93% and 95%, respectively, after 8 h. Indole, a C-nucleophile, did not result in any product when it was refluxed in nitromethane with either  $AuCl_3$  or  $Cu(OTf)_2$ .

The ability of AuCl<sub>3</sub> to hydrate alkynes<sup>17</sup> could be taken as an advantage to directly convert alkynones into methylenebridged bis-1,3-dicarbonyl compounds in one pot *via* the formation of 1,3-dicarbonyl compound, using moist nitromethane as shown in the Scheme 1. This reaction did not take place when Cu(OTf)<sub>2</sub> was used as catalyst.



**Scheme 1** The gold-catalyzed one-pot conversion of alkynones into methylene-bridged bis-1,3-dicarbonyl compounds.

A simple mechanism, as shown in Scheme 2, could be envisaged, although the exact nature of the activated intermediate is unclear.<sup>18</sup> The enolic form of the 1,3-dicarbonyl compound could attack the Lewis acid-activated aci-nitromethane to account for the first C-C bond formation. Intermediate II, on elimination of H<sub>2</sub>O and HNO, as known in the mechanism of Nef reaction,<sup>2</sup> would give intermediate III. This will undergo a fast Lewis acid-catalyzed Michael addition of the 1,3-dicarbonyl compound to furnish 2. The involvement of intermediate III was inferred by trapping it with benzyl thiol, which was intentionally added to the reaction of 1a.<sup>16</sup> In another experiment, the reaction of 1,1-dibenzoylethane was studied under the present reaction conditions as the transformation of intermediate II into III is not possible with this system. However, with both AuCl<sub>3</sub> and Cu(OTf)<sub>2</sub>, only 1-phenylpropane-1,2-dione<sup>19</sup> was obtained in 25% and 30%, respectively, after 50 h of reflux. The expected nucleophilic attack on the Lewis acid-activated aci-nitromethane did not happen, perhaps for the reason that enolization is completely suppressed by the methyl substituent at the central carbon



Scheme 2 A tentative mechanism for the formation of methylenebridged bis-1,3-dicarbonyl compounds.

of the 1,3-dione.<sup>20</sup> The possibility for the involvement of formaldehyde formed by the Nef-type reaction initiated by traces of water present in the solvent cannot be neglected. A Nash test was carried out to check the formation of formaldehyde.<sup>21</sup> The outcome indicated that some amount of formadehyde is formed under the reaction condition. If this happened at all under the reaction conditions, it is a new observation as there is no literature precedent for the direct Lewis acid-catalyzed Nef reaction on a nitroalkane.

A similar reaction with nitroethane as the solvent did not take place with either  $AuCl_3$  or  $Cu(OTf)_2$ . This may be due to the famous 'nitroalkane anomaly' that the proton transfer reactions of nitroalkanes show abnormal trends.<sup>22</sup> Perhaps a detailed theoretical study might give a better picture.

To summarize, the Lewis acid-activated *aci*-form of nitromethane might have been the key intermediate in the formation of methylene-bridged bis-1,3-dicarbonyls. Theoretical and experimental studies on the Lewis acid activation of the *aci*-form could expand the scope of nitroalkane chemistry.

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