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Dimethylformamide, dimethylacetamide and tetramethylguanidine as nucleophilic organocatalysts for the transfer of electrophilic bromine from *N*-bromosuccinimide to alkenes

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Abstract—Dimethylformamide, dimethylacetamide and tetramethylguanidine were found to act as increasingly active catalysts for the bromolactonisation of γ,δ- and δ,ε-unsaturated carboxylic acids with *N*-bromosuccinimide. The catalysts are readily removed in the work-up by washing with water to provide the pure bromolactone products without the need for column chromatography. Catalysis of the intermolecular bromoacetoxylation of alkenes with acetic acid and NBS by TMG was also demonstrated.
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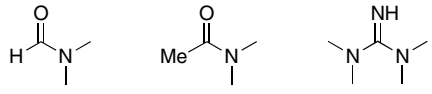
The electrophilic bromination of alkenes via a bromonium ion is a fundamental reaction in organic chemistry.[1] When the bromonium ion is not to be opened by a bromide anion, the archetypal reagent for this purpose is *N*-bromosuccinimide (NBS), where it has enjoyed widespread use as a stoichiometric reagent in the bromohydration, bromoetherification and bromolactonisation reactions of alkenes.[2] In this Letter we report that bromolactonisation reactions of γ,δ- and δ,ε-unsaturated carboxylic acids with NBS are substantially accelerated by the addition of a nucleophilic organocatalyst: dimethylformamide (DMF; **1**), dimethylacetamide (DMA; **2**) and tetramethylguanidine (TMG; **3**) show increasing activity for this purpose. TMG **3** also proves to be an effective catalyst for the intermolecular bromoacetoxylation of alkenes.



1 **2** **3**

The bromolactonisation of 4-pentenoic acid (**4**) with NBS to bromolactone **8** in $CDCl_3$ is only sluggish, proceeding to 15% conversion in 15 h at room temperature (Table 1, entry 1). In the presence of 20 mol % DMF **1**, a 43% conversion was obtained after 2 h (Table 1, entry 2). At 100 mol % loading of DMF, this bromolactonisation reaction proceeded to completion in just 30 min (Table 1, entry 3). The use of NBS and DMF has been previously noted as an effective combination for the bromination of electron-rich aromatics, but in these cases DMF was used as the solvent.[3] This is the first time that DMF has been shown to *catalyse* the transfer of electrophilic bromine from NBS. It is also only the second time that an organocatalytic bromination reaction of alkenes has been reported,[4] and DMF **1** therefore represents the first member of a new class of organocatalysts for this reaction. Intrigued by its activity, we also screened DMA **2** and TMG **3** as other potential catalysts for this reaction.

DMA was found to be a superior catalyst to DMF, catalysing the reaction of unsaturated acid **4** at just 10 mol % loading to completion in 0.5 h (Table 1, entries 4 and 5). The work-up procedure required only washing with aqueous sodium sulfite solution (2 × volumes) followed by water (3 × volumes) to leave the bromolactone product **8** pure, and without any traces of the DMA as confirmed by ^{1}H NMR (<0.6%). DMA was also an

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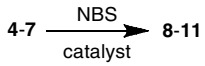
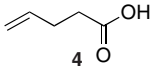
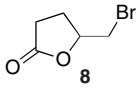
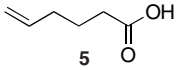
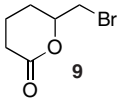
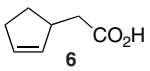
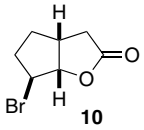
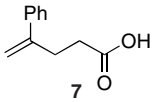
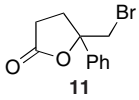
Table 1. Bromolactonisation using catalysts **1**, **2** and **3**[a]



Entry	Substrate[b]	Catalyst	Loading (mol %)	Time (h)	Product[c]	Conversion[d] (%)	Yield[e] (%)	Residual catalyst[f] (%)
1	 **4**	—	—	15	 **8**	15	nd	nd
2	**4**	**1**	20	2	**8**	43	nd	nd
3	**4**	**1**	100	0.5	**8**	100	nd	nd
4	**4**	**2**	10	0.5	**8**	100	87	1.5[g]
5	**4**	**2**	10	0.5	**8**	100	89	<0.6
6	 **5**	—	—	1	 **9**	<5%	—	—
7	**5**	**2**	10	18	**9**	100	nd	nd
8	 **6**	—	—	0.5	 **10**	0	—	—
9	**6**	**2**	10	0.5	**10**	29	17	<0.6
10	**4**	**3**	10	0.25	**8**	100	—	—
11	**4**	**3**	1	0.25	**8**	100	92	<0.2
12	**5**	**3**	1	0.25	**9**	100	89	<0.2
13	**6**	**3**	10	0.25	**10**	100	95	<0.2
14	 **7**	**3**	10	0.25	 **11**	100	85	<0.2

[a] All reactions were performed with 1.0 equiv of NBS at rt in $CDCl_3$.
[b] The acid substrates are all known compounds. For details on availability and/or preparation see Ref. 4.
[c] The bromolactone adducts are all known compounds. For full characterisation data see Ref. 4.
[d] As determined by ^1H NMR.
[e] Isolated yield after work-up.
[f] As determined by inspection of the ^1H NMR spectrum of the isolated material.
[g] The product was subjected to washing with aqueous sodium sulfite solution (2 × volumes) and water (2 × volumes) in the work-up procedure.

effective catalyst for the bromolactonisation of 5-hexenoic acid (**5**) and 2-cyclopentene-1-acetic acid (**6**) to the corresponding bromolactones **9** and **10**, respectively (Table 1, entries 6–9).

TMG **3** was found to be a superior catalyst still for these bromolactonisations (Table 1, entries 10–14) catalysing substrates **4**–**7** into their corresponding bromoadducts **8**–**11** in less than 15 min at room temperature even at just 1 mol % loading. The work-up procedure was simplified further also, requiring just 1 volume of aqueous sodium sulfite solution and 1 volume of water to completely remove any traces of TMG from the product.

Having shown TMG **3** to be an excellent catalyst for the bromolactonisation of unsaturated acids, we next explored the intermolecular bromoacetoxylation of alkenes with **12**–**15** as representative alkenes (Table 2).[7] Bromoacetoxylation of *trans*-stilbene **12** proceeded smoothly to diastereomeric bromoacetates **16** and **17** in an 85:15 ratio (Table 2, entry 1). The minor diastereoisomer arises from the expected intervention of a free benzylic carbocation.[5] The overall conversion could be improved either by increasing the reaction time, or by increasing the overall reaction concentration (Table 2, entries 2 and 3). Further, the reaction was still turning over respectably at just 1 mol % TMG loading (Table 2, entry 4). Under similar conditions, *trans*-β-methylstyrene **13** and styrene **14** gave essentially single regioisomeric products **18** and **19** consistent with the ring opening of their bromonium ions at the most-substituted position (Table 2, entries 5 and 6). Bromoacetoxylation of *cis*-stilbene gave bromoacetate **17** as a single isomer after chromatography, consistent with the ring opening of a *cis*-configured bromonium ion (Table 2, entry 7).

We consider the mechanism of catalysis by TMG **3** to proceed through *N*-bromo derivative **20** (Scheme 1).[6] The subsequent transfer of positive bromine to an alkene produces a classical bromonium ion which is trapped by a nucleophile (NuH) and regenerates TMG **3**. The superior activity of TMG over DMA and DMF is rationalised in terms of their decreasing nucleophilicity, respectively. We expect similarly nucleophilic molecules to act as organocatalysts for this reaction, and we note that the use of DMAP is also effective for the transformation of **12** into **16** and **17** (Table 2, entry

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