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Microwave-induced selective synthesis of α-bromo and α,α-dibromoalkanones using dioxane–dibromide and silica gel under solvent-free conditions

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Abstract—Selective synthesis of α-bromo and α,α-dibromoalkanones using dioxane–dibromide and silica gel in solvent-free conditions under microwave irradiation has been reported. The amount of dioxane–dibromide, silica gel and time of irradiation are keys for the selective synthesis of α-bromo and α,α-dibromoalkanones.

α-Bromoalkanones and α,α-dibromoalkanones are significant synthons used for the synthesis of a variety of biologically active heterocyclic compounds.[1–4] In general, α-bromoalkanones have been synthesized by the reaction of alkanones with bromine in an appropriate solvent such as water, chloroform, carbon tetrachloride, acetic acid or *N*,*N*-dimethylformamide.[5] Copper(II) bromide,[6] 1,4-dioxane bromooxonium bromide,[7] tribromoacetophenone[8] and *N*-bromosaccharin[9] have been used as brominating agents instead of bromine. Furthermore, the solid organic ammonium tribromides, such as pyridinium,[10] phenyl-trimethylammonium,[11] tetramethylammonium[12] and tetrabutylammonium tribromides[13] have also been used as selective brominating agents. Recently, benzyltrimethylammonium tribromide[14] has been used for the selective synthesis of α,α-dibromoalkanones. All these methods involve use of expensive reagents and solvents, long reaction times and high temperature. So a safer, economic and environmentally friendly method is needed to be developed within the frame of *Green Chemistry* principles.[15]

Supported reagents on mineral oxide surfaces have been widely employed in organic synthesis.[16] Reagents immobilized on porous solid materials present a lot of advantages over the conventional solution phase reactions because of the good dispersion of active sites leading to improved reactivity and milder reaction conditions. The solvent-free use of supported reagents in combination with microwave (MW) irradiation, under so-called 'dry media' conditions, provides ideal reaction medium with special attributes such as reduced reaction times, easier work-up procedures as well as increased purity in products.[17] The recyclability of the inorganic solid support is often possible rendering thus the procedure environmentally acceptable.[18] MW induced selective bromination was described once in the case of 1,4-quinones and coumarins using bromine adsorbed on neutral alumina or iodine monobromination in acetic acid.[19]

Keeping in view our general interest in the development of environmentally friendlier synthetic alternatives using microwaves,[20] we became interested in an expeditious synthesis of these compounds. We report here the selective synthesis of α-bromoalkanones and α,α-dibromoalkanones (Table 1) from the corresponding alkanones using dioxane–dibromide and silica gel under microwave irradiation by regulating the amount of brominating agent and the time of irradiation (Scheme 1). In all the reactions reported in this paper, we worked under solvent-free conditions utilizing neat starting materials and silica gel, wherein the reactions are completed within a few minutes and in high yields (72–95%) using an unmodified household microwave oven.

Different solid supports including silica gel, different aluminas, strongly acidic montmorillonite (K10 clay) were checked to ascertain the most effective. Amongst

Keywords: acetophenones; cycloalkanones; dioxane–dibromide; silica gel; selectivity; solvent-free conditions; microwave activation.

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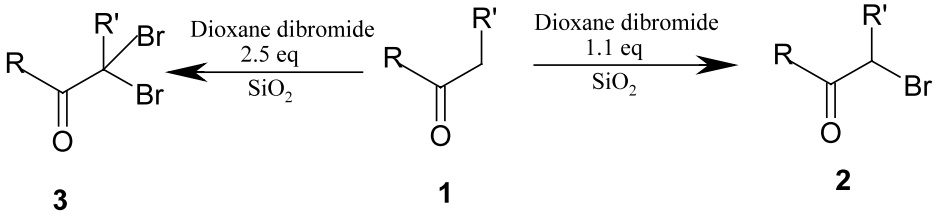
Table 1. Microwave-assisted synthesis of α-bromoalkanones/cycloalkanones and α,α-dibromoalkanones using dioxane–dibromide and silica gel (power = 300 W)

Compound[a]	R	R′	Time (min)	Yield[b] (%)	Mp or bp/lit. mp or bp (°C)
2a	C_6H_5	H	1	75	46–47/48–51[24]
2b	4-ClC_6H_4	H	1.5	79	95–96/96–97[24]
2c	4-$(NO_2)C_6H_4$	H	1.75	80	99–100/100–01[24]
2d	4-MeC_6H_4	H	1	77	44–45/45–48[24]
2e	4-BrC_6H_4	H	1	76	107–08/108–10[24]
2f	3-$(NO_2)C_6H_4$	H	1	78	91–92/90–96[24]
2g	4-$(OMe)C_6H_4$	H	1.5	73	69–70/69–71[24]
2h	4-FC_6H_4	H	1.75	78	48–49/48–50[24]
2i	4-$(OEt)C_6H_4$	H	1.5	80	59–61
2j	3-BrC_6H_4	H	1	83	47–48
2k	4-$(C_6H_{11})C_6H_4$	H	2	75	69–70
2l	-$(CH_2)_4$-		7	73	68–70/74[25] (bp)
2m	-$(CH_2)_5$-		6	75	78–80/83[26] (bp)
2n	-$(CH_2)_6$-		4	75	78/79–81[27] (bp)
3a	C_6H_5	H	7	89	35–36/36–37[24]
3b	4-ClC_6H_4	H	8	90	91–92/92.5[14]
3c	4-$(NO_2)C_6H_4$	H	8.5	95	64–65/67.4[28]
3d	4-MeC_6H_4	H	6	94	95–96/93–94[29]
3e	4-BrC_6H_4	H	6	85	93–94/92–93[30]
3f	3-$(NO_2)C_6H_4$	H	5	92	58–59/59[31]
3g	4-$(OMe)C_6H_4$	H	5	77	90–91/93–94[32]
3h	4-FC_6H_4	H	9	80	37–38
3i	4-$(OEt)C_6H_4$	H	4	73	111–12
3j	3-BrC_6H_4	H	7	87	43–44
3k	4-$(C_6H_{11})C_6H_4$	H	13	72	73–74

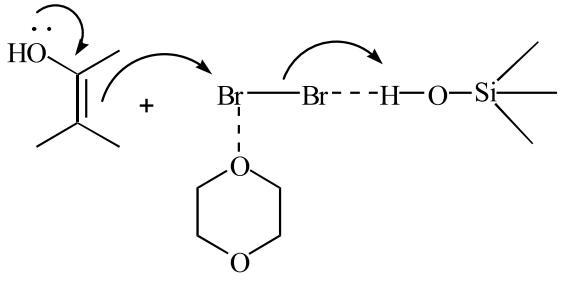
[a] Products **2a**–**n** and **3a**–**k** were crystallized using petroleum ether and ethyl acetate:petroleum ether, respectively.
[b] Yield of isolated products.



Scheme 1.

these, silica gel was found to be the most efficient support for the selective α-bromination and α,α-dibromination of alkanones. The role of silica gel as an acid catalyst can be twofold: (i) to promote enol formation from ketone and (ii) to induce electrophilic assistance to Br–Br bond breaking (Scheme 2).

The molar ratios of the reagents, irradiation times, and microwave power levels were optimized to achieve higher yields. In the case of α-bromination, optimum conditions employed 1 mmol of alkanone, 1.1 mmol of dioxane–dibromide and 3 g of silica gel were the most adapted ratios. For α,α-dibromination 1 mmol of alkanone, 2.5 mmol of dioxane–dibromide and 5 g of silica gel. The power level of 300 W was found to be the most appropriate for bromination (higher power level leads to fumes in the oven and reduced yields). During the synthesis of α-bromoalkanones, traces of dibromo products were formed which can be easily removed during crystallization. Monobromination or dibromination depends upon the nature of the substrate. In the case of acetophenones, both mono- and dibromoalkanones were obtained, whereas, for cycloalkanones, only monobromo products were formed (traces of dibromo products were detected on TLC even after extension of irradiation time period up to 30–45 min). Tribromo products have not been obtained even with acetophenones.



Scheme 2.

Table 2. Comparative results under both microwave or thermal conditions (power = 300 W)

Product	Method	Time (min)	Final temp.[a] (°C)	Yield (%)
2b	MW	1.5	77–82	79
	Δ	1.5	77–82	40
	Δ	25[b]	77–82	60
3b	MW	8	75–78	90
	Δ	8	75–78	20
	Δ	120[c]	75–78	48

[a] Final temperature was measured by immersing a glass thermometer in the reaction mixture at the end of exposure during microwave experiment and was approximate temperature range.
[b] After 25 min no further increase in yield was observed.
[c] After 120 min no further increase in yield was observed. At this time, 48% of dibromo and 52% of monobromo product was formed.

Finally, the syntheses of 2-bromo-4′-chloroacetophenone and 2,2-dibromo-4′-chloroacetophenone using dioxane–dibromide and silica gel were attempted using a thermostated oil-bath under identical conditions as those employed for the microwave-assisted method (Table 2). By far lower yields were obtained under thermal conditions, demonstrating clearly that the effect of microwave irradiation is not purely thermal. This observation is consistent with the mechanism of the reaction (Scheme 2) which involves a polar transition state starting from a neutral ground state. This enhancement in polarity during the reaction progress can thus induce an improved stabilization of the transition state by microwaves (due to dipole–dipole interaction), and then to a lowering in the activation energy.[21]

General procedure employed for the synthesis of α-bromoalkanones and α,α-dibromoalkanones. Alkanone (1 mmol), dioxane–dibromide[22] (1.1 mmol for **2** and 2.5 mmol for **3**) and silica gel (60–120 mesh, 3 g for **2** and 5 g for **3**) were taken in a borosil beaker (100 mL) and mixed properly until free flowing powder was obtained. The beaker was then introduced in the domestic microwave oven BPL BMO 800 T for an appropriate time (Tables 1 and 2, reaction was monitored by TLC). After irradiation, the contents were cooled to room temperature and extracted with methylene chloride (3× 15 mL). The solid inorganic support material was filtered and the solvent was removed under reduced pressure to afford the product, which was purified by crystallization from suitable solvent.

The structures of the products were confirmed by ^{1}H NMR, IR and mass spectral data[23] and comparison with authentic samples prepared according to the literature methods.

In conclusion, a rapid, economic and environment-friendly method has been developed for selective mono- and dibromination of alkanones. The reagent system described here may be a good alternative to well known methods since the bromination proceeds expeditiously with high yields under solvent-free conditions. Selectivity can be achieved only by regulating the amount of reagent and time of MW irradiation.

Spectral data of compounds. **2i**: ^{1}H NMR: δ 1.5 (t, 3H, -OCH$_2$CH_3), 4.05 (q, 2H, -OCH_2CH$_3$), 4.5 (s, 2H, -CH$_2$), 6.60–7.10 (m, 2H$_{arom}$), 8.05–8.50 (m, 2H$_{arom}$). IR (KBr): 1675 cm^{-1} (C=O). m/z: 243 (M$^+$). **2j**: ^{1}H NMR: δ 4.38 (s, 2H, -CH$_2$), 7.20–8.20 (m, 4H$_{arom}$). IR (KBr): 1672 cm^{-1} (C=O). m/z: 278 (M$^+$). **2k**: ^{1}H NMR: δ 1.0–2.1 (m, 10H, 5×-CH$_2$), 3.2 (m, 1H, CH$_{hexyl}$), 4.5 (s, 2H, -CH$_2$), 7.20–8.23 (m, 4H$_{arom}$). IR (KBr): 1680 cm^{-1} (C=O). m/z: 280 (M$^+$). **3h**: ^{1}H NMR: δ 6.70 (s, 1H, -CH), 7.05–7.50 (m, 2H$_{arom}$), 8.10–8.40 (m, 2H$_{arom}$). IR (KBr): 1690 cm^{-1} (C=O). **3i**: ^{1}H NMR: δ 1.52 (t, 3H, -OCH$_2$CH_3), 4.03 (q, 2H, -OCH$_2$CH$_3$), 6.65 (s, 1H, -CH), 6.72–7.05 (m, 2H$_{arom}$), 8.0–8.61 (m, 2H$_{arom}$). IR (KBr): 1695 cm^{-1} (C=O). **3j**: ^{1}H NMR: δ 6.75 (s, 1H, -CH), 7.20–8.28 (m, 4H$_{arom}$). IR (KBr): 1700 cm^{-1} (C=O). m/z: 357 (M$^+$). **3k**: ^{1}H NMR: δ 1.2–2.1 (m, 10H, 5×CH$_2$), 6.78 (s, 1H, -CH), 7.30–8.35 (m, 4H$_{arom}$). IR (KBr): 1687 cm^{-1} (C=O).

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22. Dioxane–dibromide was prepared by adding drop wise bromine (8 mL) to dioxane (5 mL), until a yellow solid product was obtained. It was filtered, dried in a vacuum desicator and stored in a refrigerator (yield 10 g, mp 61–62°C).
23. ^{1}H NMR spectra was recorded in $CDCl_3$ on JNM-PMX 60 NMR (60 MHz) and Jeol FX90Q (90 MHz) using TMS as an internal standard; IR spectra (ν_{max} in cm^{-1}) was recorded on Hitachi 270-30 spectrophotometer using KBr disc; mass spectral data was recorded on Jeol D-300 spectrophotometer.
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