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Bromophilic substitution/carbophilic substitution cascade reactions of α,α-dibromo-2-methoxyacetophenone with *C*-, *N*- and *O*-nucleophiles

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ABSTRACT

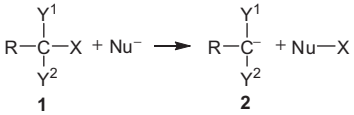
α,α-Dibromo-2-methoxyacetophenone reacts, under mild reaction conditions, with *C*-, *N*- and *O*-nucleophiles via a bromophilic substitution/protonation/carbophilic substitution cascade process to afford α-monosubstituted-2-methoxyacetophenones in moderate to good yield. The only exception from this reaction pathway is the reaction with the anion derived from malononitrile in which 2-aroyl-1,1,3,3-tetracyanopropene is obtained.

Nucleophilic substitution reactions, occurring by the attack of a nucleophile on a carbon atom, are the widely studied reactions in organic chemistry. Less familiar are nucleophilic substitutions at halogens, known as halophilic reactions[1] (S_NX, Scheme 1).

These reactions usually take place if the normal (S_NC) substitution reaction is made difficult, and/or if the resulting carbanion is stabilized by electron-withdrawing substituents. For example, perhaloalkanes are rather inert towards nucleophilic displacement reactions, but they can undergo halophilic attack by a range of nucleophiles.[2] Halophilic reactions have also been observed for α-halo sulfones,[3] α-halo ketones,[4] α-halo nitriles,[5] halogenated nitroalkanes,[6] diethyl bromo-[7] and diethyl dibromomalonate,[8] 3-methyl-5-trichloromethyl-1,2,4-oxadiazole,[9] 2-halomethyl-5-nitrofurans[10] and geminal[5] and vicinal dihalides.[5,11] In many cases halophilic attack results in protonation of the carbanion **2**, that is, reductive dehalogenation.[3,4,9,10]

Selective α-monobromination of methyl ketones can be difficult to achieve.[12] α,α-Dibromo derivatives can be formed as the side products, or even as the major products.[13] In such cases, an additional step, involving selective debromination, is needed to afford bromomethylketones,[13b] which are important synthetic intermediates. In our previous communication,[13a] we reported that *ortho*-substituted α,α-dibromoacetophenones undergo nucleophile-induced cascade reactions giving rise to α-monosubstituted acetophenone derivatives in good to high yields (Nu = CN^-, SCN^-, AcS^-, I^-, N_3^- and AcO^-). It was envisaged that this mode of reactivity could be extended to other nucleophiles, such that dibromides could be used as synthetic equivalents of monobromo derivatives, thereby circumventing the additional debromination step. For this purpose, α,α-dibromo-2-methoxyacetophenone (**3**) was chosen as a substrate, since it can easily be obtained by bromination of 2-methoxyacetophenone with bromine in $CHCl_3$; the corresponding monobromo derivative is not as easy to prepare.[13a] Herein, we report the first combined bromophilic substitution/carbophilic substitution reactions directed towards the preparation of synthetically valuable 1,4-dicarbonyl compounds,[14] α-phthalimido[15] and α-hydroxy ketones.[16]

The 1,4-dicarbonyl compounds **7a–d** were obtained, under mild reaction conditions, by the reaction of α,α-dibromo-2-methoxyacetophenone (**3**) with 3–4 mol equiv of carbanions derived from active methylene compounds **4a–d** (Scheme 2, Table 1).[17] The formation of the products **7a–d** occurs via a stepwise process beginning with a relatively rare bromophilic attack of the *C*-nucleophile on dibromide **3** yielding, after protonation of the initially formed carbanion, monobromide **6** and monobrominated active methylene compounds **5a–d**. The existence of monobromide **6** as an intermediate was confirmed by TLC[18] (eluent:toluene; R_f = 0.4), carried out



1 **2**

Scheme 1.

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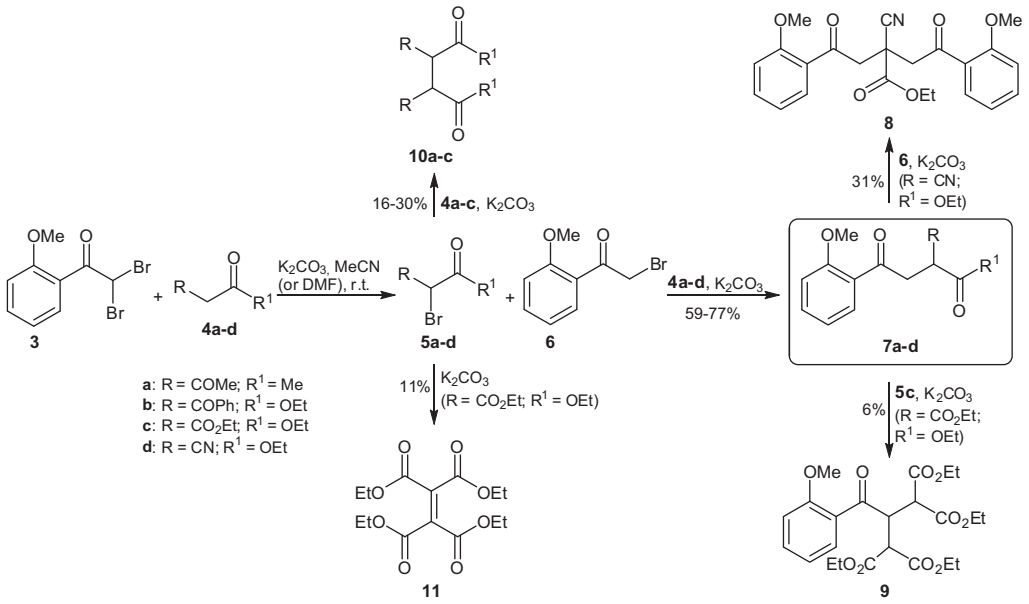


Scheme 2.

30 min after the reaction had started, and by isolation of **6** after work-up of the reaction. The next step involved nucleophilic substitution of the bromine in **6** by a second mol equiv of the *C*-nucleophile **4a–d** which resulted in the formation of products **7a–d** in moderate to good yields (59–77%). In the case of **7d** (R = CN; R^1 = OEt) a further reaction with the monobromide **6** occurred yielding 1,5-diketone **8** in 31% yield, whereas **7c** (R = CO_2Et; R^1 = OEt) was alkylated with diethyl bromomalonate (**5c**) to give the tetraester **9** in low yield (6%). On the other hand, the α-bromo compounds **5a–c** reacted with excess of *C*-nucleophiles to give dimers **10a–c** (16–30%). In the case of diethyl bromomalonate (**5c**), the base-assisted coupling followed by HBr elimination yielded the tetrasubstituted alkene **11**[19] (11%), isolated as a mixture with **10c**. A small amount of epoxide **12**[20] (8%, Table 1, entry 3) was also formed in the reaction of dibromide **3** with diethyl malonate. It accompanied the isolated main product **7c** (10% by weight) and could not be separated from it using standard techniques.

Similarly, the reactions of 2-methoxy-α,α-dibromoacetophenone (**3**) with potassium phthalimide, potassium carbonate in DMF/H_2O and the previously reported[13a] reaction with KCN proceeded via the bromophilic substitution/protonation/carbophilic substitution cascade process to give α-phthalimido ketone **13a**, α-hydroxy ketone **13b** and nitrile **13c** (Scheme 3, Table 2). In the case of CN^- as the nucleophile, the second step was slow enough to allow isolation of the monobromide **6** when 1 equiv of nucleophile was employed (Table 2, entry 4).

The reaction of 2-methoxy-α,α-dibromoacetophenone (**3**) with 3 equiv of the anion derived from malononitrile[17] took a different reaction path. Monobromide **6** was not detected as an intermediate and an intense yellow-coloured product was formed, the structure of which was assigned as 2-aroyl-1,1,3,3-tetracyanopropene **14** (Scheme 4).

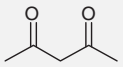
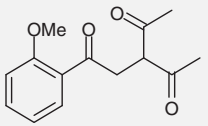
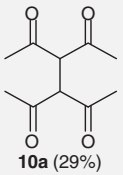
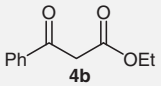
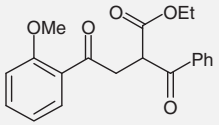
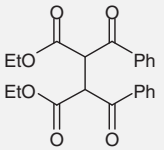
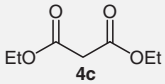
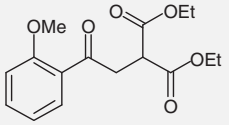
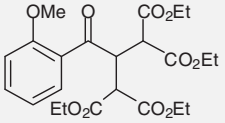
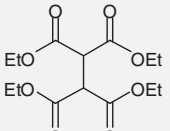
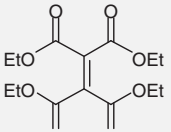
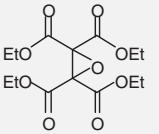
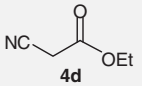
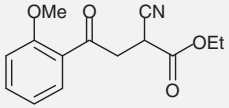
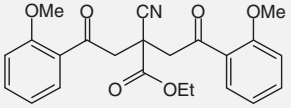
In the ^{1}H NMR spectrum of **14** only signals belonging to the aromatic portion of the molecule and OMe group could be seen, both in DMSO-d_6 and acetone-d_6 solutions. The ^{13}C NMR spectrum showed eight signals due to the 2-methoxybenzoyl group, but only four signals arising from the tetracyanopropene moiety, two for the CN groups at 115.4(DMSO-d_6)/116.4(acetone-d_6) and 117.6(DMSO-d_6)/118.5(acetone-d_6) ppm, and two signals at 169.0(DMSO-d_6)/170.2(acetone-d_6) and 49.1(DMSO-d_6)/50.1(acetone-d_6) ppm, both due to non-protonated C-atoms, as determined by a DEPT experiment. Quantitative ^{13}C NMR measurement showed that each of the signals at 115.4/116.4 ppm, 117.6/118.5 ppm and 49.1/50.1 ppm was due to two C-atoms, whereas the signal at 169.0/170.2 ppm was due to one C-atom. The latter signal was attributed to the double bonded carbon next to the carbonyl group. These data indicate the equivalence of the C(1) and C(3) atoms of the tetracyanopropene moiety, which can be explained by the existence of rapid prototropic tautomerism as shown in Figure 1. The value of 49.1/50.1 ppm corresponds to the mean value of the calculated shifts[21] for the C(1) (~87 ppm) and C(3) (~14 ppm) atoms. The non-existence of the C*H* signal in the ^{1}H NMR spectrum and inability to obtain any C–H correlation by 2D NMR techniques can be ascribed to a broadening of the C*H* signal to such an extent that it merged with the base line. Another possible explanation is that the recorded spectra are for the carbanion formed by the ionization of the highly acidic C-hydrogen in tetracyanopropenes.[22]

Although the exact mechanism for the formation of compound **14** is as yet, not known, it may be consistent with a double S_N2 displacement reaction on **3** followed by oxidation.

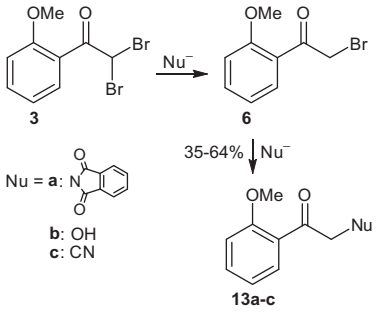
The reaction of 2-methoxy-α,α-dibromoacetophenone (**3**) with excess pyridine in wet MeCN resulted in C–C bond cleavage and the formation of 2-methoxybenzoic acid (**16**) (Scheme 5), probably via initial formation of the pyridinium salt **15** which was then cleaved to the acid **16**.[23]

In conclusion, we have shown that 2-methoxy-α,α-dibromoacetophenone reacts with 3–4 mol equiv of carbanions derived from the active methylene compounds via a three-step cascade process involving bromophilic substitution/protonation/carbophilic substitution, to give α-monosubstituted 2-methoxyacetophenones, as the main products. This reaction could be useful for the synthesis of α-monosubstituted methyl ketones when their monobromo derivatives are not readily available. If 1 mol equiv of KCN was used, only the bromophilic reaction occurred, allowing the isolation of an α-bromo-2-methoxyacetophenone. The α-brominated active methylene compounds, formed in the first step of the cascade process, react further to form dimers, or a tetrasubstituted alkene. The only exception from this reaction pathway was the

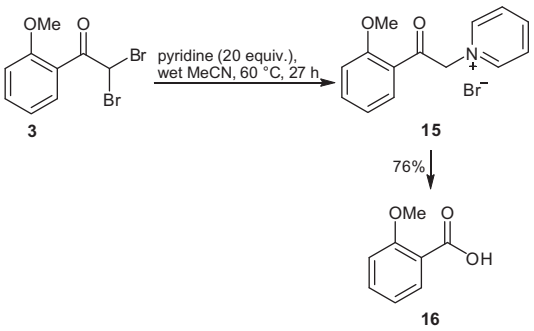
Table 1
The reactions of 2-methoxy-α,α-dibromoacetophenone (**3**) with active methylene compounds **4a–d**

Entry	Nucleophile	Conditions	Products (yields)[a]				
1	 **4a**	**4a** (3 equiv), K_2CO_3 (3 equiv), DMF, rt, 30 min	 **7a** (63%)	 **10a** (29%)			
2	 **4b**	**4b** (3 equiv), K_2CO_3 (3 equiv), MeCN, rt, 24 h	 **7b** (77%)	 **10b** (30%)			
3	 **4c**	**4c** (4 equiv), K_2CO_3 (4 equiv), MeCN, rt, 24 h	 **7c** (77%)[b]	 **9** (6%)	 **10c** (16%)[c]	 **11** (11%)[c]	 **12** (8%)[b]
4	 **4d**	**4d** (3 equiv), K_2CO_3 (3 equiv), DMF, rt, 2.5 h	 **7d** (59%)	 **8** (31%)			

[a] Yield of isolated product.
[b] Yield was determined from the ^{1}H NMR spectrum of the mixture of **7c** and **12**.
[c] Yield was determined from the ^{1}H NMR spectrum of the mixture of **10c** and **11**.



Scheme 3.

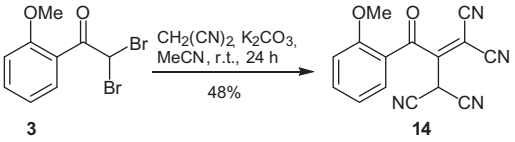


Scheme 5.

Table 2
The reactions of 2-methoxy-α,α-dibromo-acetophenone (**3**) with potassium phthalimide, K_2CO_3 in DMF/H_2O and KCN

Entry	Nucleophile	Conditions	Product (yield)[a]
1	(2 equiv)	Me_2CO/H_2O, rt, 24 h	**13a** (64%)
2	H_2O (or OH^-)	K_2CO_3 (3 equiv), DMF/H_2O, rt, 94 h	**13b** (35%)
3	CN^- (3 equiv)	Me_2CO/H_2O, rt, 24 h	**13c** (64%)
4	CN^- (1 equiv)	Me_2CO/H_2O, rt, 22 h	**6** (49%)

[a] Yield of isolated product.



Scheme 4.

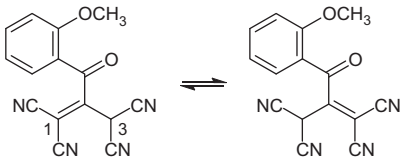


Figure 1.

reaction with the anion formed from malononitrile, yielding 2-aroyl-1,1,3,3-tetracyanopropene, which exists in a very fast prototropic equilibrium when dissolved in DMSO-d_6 or acetone-d_6.

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17. *General procedure for the synthesis of 1,4-dicarbonyl compounds* **7a–d** *and 2-aroyl-1,1,3,3-tetracyanopropene* **14**: A mixture of active methylene compound **4a–d** (0.6 mmol), or malononitrile (0.6 mmol) and K_2CO_3 (0.6 mmol) in DMF or MeCN (2.1 mL) was stirred at rt for 15 min and 2-methoxy-α,α-dibromoacetophenone (**3**) (0.2 mmol in the case of **4a**, **4b**, **4d** and malononitrile; 0.15 mmol in the case of **4c**) was added. The mixture was stirred at room temperature for the time specified in Table 1, then evaporated and the residue was partitioned between $CHCl_3$ and H_2O, or EtOAc and H_2O in the case of the reaction with malononitrile. The organic layer was dried with anhyd Na_2SO_4, evaporated and chromatographed (eluent:gradient PE/EtOAc). *Compound* **7a**: yield: 63%; colourless oil; IR (neat): ν_{max} 1725, 1699, 1666, 1595, 1242, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, keto/enol ratio:74:26): (keto form) δ 2.32 (s, 6H, 2 CH_3), 3.61 (d, 2H, J = 6.6 Hz, CH_2), 3.94 (s, 3H, CH_3O), 4.34 (t, 1H,

J = 6.6 Hz, CH), 6.96–7.04 (m, 2H, H3-Ph and H5-Ph), 7.45–7.54 (m, 1H, H4-Ph), 7.73–7.78 (m, 1H, H6-Ph), (enol form) δ 2.05 (s, 6H, 2 CH_3), 3.96 (s, 3H, CH_3O), 3.97 (s, 2H, CH_2), 6.96–7.07 (m, 2H, H3-Ph and H5-Ph), 7.45–7.54 (m, 1H, H4-Ph), 7.66–7.70 (m, 1H, H6-Ph), 16.85 (s, 1H, OH); ^{13}C NMR (50.3 MHz, $CDCl_3$): (keto form) δ 29.81, 42.92, 55.55, 63.02, 111.63, 120.73, 126.49, 130.68, 134.35, 159.13, 198.21, 203.72, (enol form) δ 23.20, 42.53, 55.55, 104.71, 111.52, 120.95, 127.96, 130.24, 133.75, 158.40, 191.76, 199.64; HRMS: calcd for $C_{14}H_{17}O_4$ $(M+H)^+$: 249.1121; found: 249.1117; *Compound* **7b**:[24] yield: 77%; colourless oil; IR (neat): ν 1736, 1683, 1597, 1245, 759 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 (t, 3H, J = 7.1 Hz, CH_3), 3.78 (dd, 2H, J = 6.8 Hz, J = 1.2 Hz, CH_2), 3.90 (s, 3H, CH_3O), 4.16 (q, 2H, J = 7.1 Hz, CH_2O), 5.10 (t, 1H, J = 6.8 Hz, CH), 6.95–7.02 (m, 2H, H3-Ph and H5-Ph), 7.43–7.64 (m, 4H, H4-Ph, *m*- and *p*-Ph), 7.76–7.80 (m, 1H, H6-Ph), 8.06–8.10 (m, 2H, *o*-Ph); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 13.84, 43.21, 49.16, 55.44, 61.47, 111.54, 120.55, 126.54, 128.60, 128.82, 130.68, 133.39, 134.17, 136.12, 159.15, 169.62, 195.20, 198.06; HRMS: calcd for $C_{20}H_{20}O_5Na$ $(M+Na)^+$: 363.1203; found: 363.1227; *Compound* **7c**: yield: 77%; colourless oil; IR (neat): ν 1753, 1597, 1248, 761 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, 6H, J = 7.2 Hz, 2 CH_3), 3.65 (d, 2H, J = 7.4 Hz, CH_2), 3.93 (s, 3H, CH_3O), 4.02 (t, 1H, J = 7.4 Hz, CH), 4.23 (q, 4H, J = 7.2 Hz, 2 CH_2O), 6.96–7.03 (m, 2H, H3-Ph and H5-Ph), 7.44–7.53 (m, 1H, H4-Ph), 7.76–7.81 (m, 1H, H6-Ph); ^{13}C NMR (50.3 MHz, $CDCl_3$): 13.86, 42.84, 47.47, 55.39, 61.40, 111.48, 120.53, 126.51, 130.57, 134.12, 159.04, 169.26, 197.77; HRMS: calcd for $C_{16}H_{21}O_6$ $(M+H)^+$: 309.1333; found: 309.1332; *Compound* **7d**: yield: 59%; yellowish oil; IR (neat): ν 2252, 1745, 1670, 1597, 1246, 762 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (t, 3H, J = 7.2 Hz, CH_3), 3.56–3.85 (m, 2H, CH_2), 3.95 (s, 3H, CH_3O), 4.11 (dd, 1H, J_{AX} = 5.6 Hz, J_{BX} = 6.6 Hz, CH), 4.29 (q, 2H, J = 7.2 Hz, CH_2O), 6.99–7.06 (m, 2H, H3-Ph and H5-Ph), 7.49–7.58 (m, 1H, H4-Ph), 7.84–7.89 (m, 1H, H6-Ph); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 13.86, 32.21, 43.17, 55.53, 62.94, 111.67, 116.73, 120.86, 125.40, 131.00, 134.99, 159.46, 165.74, 195.07; HRMS: calcd for $C_{14}H_{15}NO_4Na$ $(M+Na)^+$: 284.0893; found: 284.0894; *Compound* **14**: yield: 48%; yellow solid, mp >300 °C; IR (KBr): ν 2237, 2209, 2194, 1669, 1486, 1226, 754 cm^{-1}; ^{1}H NMR (500.26 MHz, DMSO-d_6): δ 3.89 (s, 3H, CH_3O), 7.12 (t, 1H, J = 7.5 Hz, H5-Ph), 7.24 (d, 1H, J = 8.5 Hz, H3-Ph), 7.68–7.72 (m, 1H, H4-Ph), 7.74–7.76 (m, 1H, H6-Ph); the CH signal was not observed in the ^{1}H NMR; ^{13}C NMR (125.79 MHz, DMSO-d_6): δ 49.11, 56.55, 113.63, 115.36, 117.62, 121.25, 122.87, 131.69, 137.26, 160.42, 169.01, 190.41; HRMS: calcd for $C_{15}H_9N_4O_2$ $(M+H)^+$: 277.0720; found: 277.0723.

18. The authentic monobromide, used for comparison by TLC and NMR, was obtained by reaction of α,α-dibromoacetophenone with 1 mol equiv of KCN (Table 2).
19. (a) The compound **11** was characterized on the basis of ^{1}H NMR, ^{13}C NMR and HPLC/HRMS. The ^{1}H NMR and ^{13}C NMR were also compared with the literature data (Ref. 19b,c); ^{1}H NMR (500.26 MHz, $CDCl_3$): δ 1.32 (t, 3H, J = 7.2 Hz, CH_3), 4.32 (q, 2H, J = 7.2 Hz, CH_2O); ^{13}C NMR (125.79 MHz, $CDCl_3$): δ 13.78, 62.52, 135.36, 162.33; HRMS: calcd for $C_{14}H_{21}O_8$ $(M+H)^+$: 317.1231; found: 317.1228.; (b) Peng, R.-F.; Wang, G.-W.; Shen, Y. B.; Li, Y.-J.; Zhang, T.-H.; Liu, Y.-C.; Murata, Y.; Komatsu, K. *Synth. Commun.* **2004**, *34*, 2117–2126; (c) Saalfrank, R. W.; Rost, W. *Angew. Chem.* **1985**, *97*, 870–871.
20. Since the compound **12** accompanied the main product **7c** it was characterized on the basis of additional signals which appeared in the ^{1}H NMR and ^{13}C NMR spectra of **7c** and on the basis of HPLC/HRMS. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (t, 3H, J = 7.2 Hz, CH_3), 4.31 (q, 2H, J = 7.2 Hz, CH_2O); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 13.68, 63.04, 162.19; due to a low concentration of **12**, the signal belonging to quaternary C was not visible in the spectrum; HRMS: calcd for $C_{14}H_{21}O_9$ $(M+H)^+$: 333.1180; Found: 333.1182.
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