Tetrahedron Letters 50 (2009) 700–703

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Reactions of *ortho*-substituted α,α-dibromoacetophenones with nucleophiles: first examples of combined carbophilic and bromophilic attack on C–Br bonds

Jovana Tatar [a], Marija Baranac-Stojanović [a,b], Milovan Stojanović [a], Rade Marković [a,b,*]

[a] Center for Chemistry ICTM, PO Box 473, 11000 Belgrade, Serbia
[b] Faculty of Chemistry, University of Belgrade, Studentski trg 16, PO Box 158, 11001 Belgrade, Serbia

ARTICLE INFO

Article history:
Received 29 October 2008
Revised 19 November 2008
Accepted 26 November 2008
Available online 30 November 2008

ABSTRACT

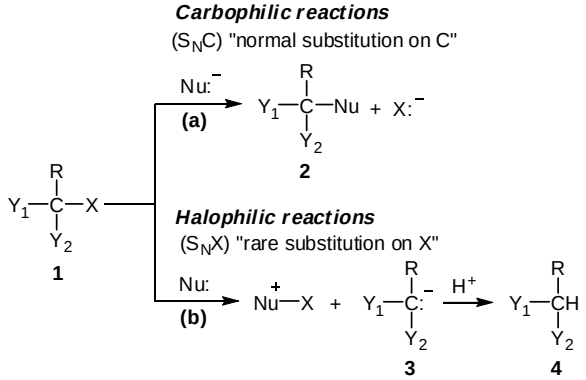
An efficient method for the formation of α-carbonyl-monosubstituted acetophenones from *ortho*-methoxy- and *ortho*-hydroxy-α,α-dibromoacetophenones and a range of selected nucleophiles, occurring via a *carbophilic substitution/bromophilic substitution/protonation* cascade process, is described. In turn, the preparation of α,α-dibromoacetophenones, isolated in high yields, relies on the neighboring group participation of the *ortho*-substituents in the starting *ortho*-substituted acetophenones.

Nucleophilic substitutions occurring by attack at the carbon atom of a large number of alkyl halides **1**, that is, *carbophilic reactions* (S_NC), have far-reaching theoretical and synthetic significance in organic chemistry (Scheme 1, route a).

By contrast, relatively little information on nucleophilic substitutions taking place at the halogen atom X (route b), with the expulsion of a carbanion **3** as a leaving group, has thus far been presented.[1] Referred to in the literature as *halophilic reactions* (S_NX),[2] they have been observed for a range of preferably, soft nucleophiles with specific reactants **1**. The reported examples involve substrates which, after forming reactive carbanions **3**, may undergo diverse transformations. The products of reductive dehalogenation, being frequently neglected (step **3**→**4**, Scheme 1), are significant as evidence for halophilic reactions. Research focusing on the structural and electronic features of the reactants **1** has shown that they preferably contain one or more fluorine atoms, and/or another electron-withdrawing group at the α-C atom, thus providing the necessary stabilization of the incipient carbanion **3**. Based on the increased suppression of these reactants toward nucleophiles in common carbophilic reactions, especially if they are highly fluorinated, the utilization of diverse geminal and vicinal perhalo[3] and haloalkanes,[4] halogenated nitroalkanes,[5] α-halo-β-ketosulfones,[6] diethyl dibromo- and bromomalonate,[7] *N*-chloroacetanilides,[8] and *N*-bromosuccinimide[9] in halophilic reactions comes as no surprise.

Recently, we have shown that pyridine and a variety of pyridine derivatives[10] possess the chemical potential to rearrange efficiently 5-unsubstituted 4-oxothiazolidine vinyl bromides **5** into a class of new pyridinium salts **6** (Scheme 2) via a reaction sequence initiated by a bromophilic step of the general type depicted in Scheme 1 (route b).

As part of our ongoing project involving the synthesis of diverse 4-oxothiazolidines **5** (EWG = COAr; R^1 = H, Me, CH_2CO_2Et),[11] we observed that the key step in the preparation of one of the precursors, that is, *ortho*-methoxy-α-cyanoacetophenone **10a** (Scheme 3, R = Me; Nu: CN^-) from *ortho*-methoxy α,α-dibromoacetophenone **7a**, is an unexpected cyanide-induced bromophilic reaction (step ii). It seemed highly desirable to further probe if this new mode of reactivity of **7a** can be extended to other nucleophiles. We now report, to the best of our knowledge, the first examples of synthetically useful nucleophile-induced cascade reactions of *ortho*-substituted α,α-dibromoacetophenones **7a**,**b**, giving rise to α-substituted acetophenone derivatives **10** (Scheme 3) through



Scheme 1. General equations for carbophilic and halophilic reactions.

* Corresponding author. Tel.: +381 11 3666 741; fax: +381 11 2636 061.
E-mail address: markovic@chem.bg.ac.yu (R. Marković).

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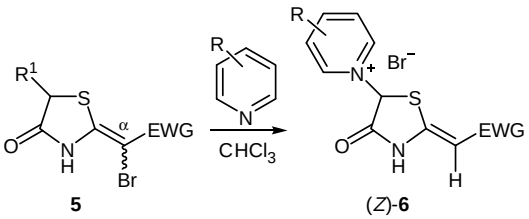
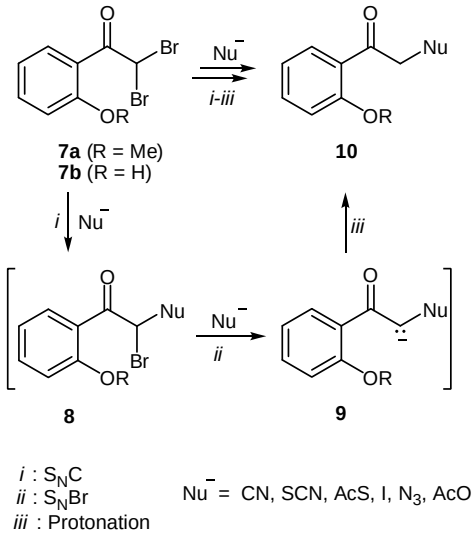
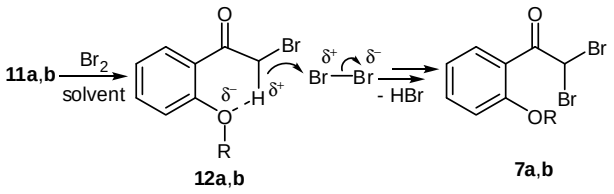
doi:10.1016/j.tetlet.2008.11.104



Scheme 2. Synthesis of pyridinium salts (*Z*)-**6** bearing the 4-oxothiazolidine moiety.



Scheme 3. Suggested cascade process leading to α-carbonyl-substituted products **10**.



Scheme 4. Effect of neighboring group participation of the *ortho*-groups in intermediates **12a**,**b** on the formation of α,α-dibromoacetophenones **7a**,**b**.

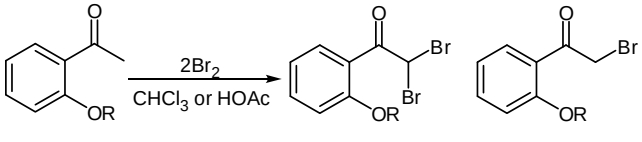
combined carbophilic attack and bromophilic attack on C–Br bonds (steps i and ii), followed by protonation (step iii).

After some experimentation with various bromination reagents, the α,α-dibromo derivative **7a** (R = Me) required for the nucleophile-induced carbophilic–bromophilic sequence was obtained, as a single compound in high yield (Table 1, entry 1), by treatment of **11a** with 2 M equiv of bromine in $CHCl_3$ at −10 °C. The corresponding derivative **7b** was obtained in 92% yield from **11b**, employing bromine in HOAc (Table 1, entry 3). In spite of the existence of numerous brominating reagents for α-mono- and α,α-dibromination of acetophenone derivatives,[12,13] there is no specific reaction regarding the synthesis of *o*-methoxy dibromo derivative **7a**.[14] In addition, a single preparation of *o*-hydroxy derivative **7b** (Table 1, entry 5), based on in situ generated zinc bromide, has been described.[12a]

It is worth mentioning that the previously reported experiments[12b–d] established that *o*-substituted acetophenones **11a**,**b** react with selected brominating reagents to yield, under the specified conditions presented in Table 1 (entries 5–8), monobrominated products **12a**,**b**.

Our experimental results have indicated that the presence of *ortho*-substituents with lone electron pairs is responsible for efficient formation of the dibromo derivatives **7a**,**b**. A rationale in terms of neighboring group effects, operating through space via intramolecular hydrogen bonding and through the C(α)–H bond, implies that the reaction of an in situ formed monobrominated intermediate **12** (Scheme 4) with another molar equivalent of bromine is apparently assisted due to an increase of the electron density at the C(α) atom. Furthermore, in the case of equimolar ratios of aromatic ketones **11a**,**b** and bromine, this reaction pathway was

Table 1
α-Bromination and α,α-dibromination of *ortho*-methoxy- and *ortho*-hydroxyacetophenones **11a**,**b**



Entry	Substrate	Reagent (mmol)	Solvent	Temp (°C)	Time	Product **7** (%)	Product **12** (%)
1	**11a**	Br_2 (2)	$CHCl_3$	−10	1–2 h	**7a** (95)[a]	**12a** (0)
2	**11a**	Br_2 (1)	$CHCl_3$	−10	1–2 h	**7a** (<50)	**12a** (0)
3	**11b**	Br_2 (2)	HOAc	Reflux	45 min	**7b** (92)[a]	**12b** (0)
4	**11b**	Br_2 (1)	HOAc	Reflux	45 min	**7b** (<50)	**12b** (0)
5[12a]	**11b**	Zn dust, Br_2 (2.5)	H_2O	70	Not specified	**7b** (80)	**12b** (0)
6[12b]	**11b**	$CuBr_2$ (~1.7)	$CHCl_3$	Reflux	3–5 h	**7b** (0)	**12b** (100)
7[12c]	**11b**	NBS (1), *hν*	Ether	30	10 min	**7b** (0)	**12b** (15)
8[12d]	**11a**	NBS (1), PTSA (0.1)	Solvent-free	20	2 h	**7a** (0)	**12a** (91)

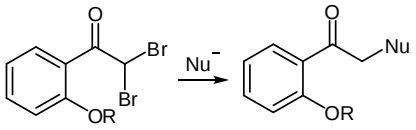
[a] Isolated yields.

again the exclusive one (Table 1, entries 2 and 4), the formation of monobrominated products **12a**,**b** not being detected.

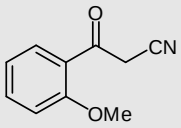
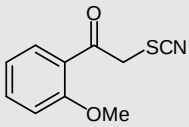
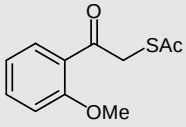
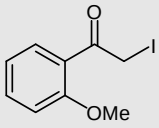
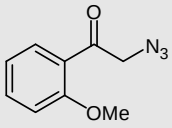
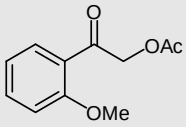
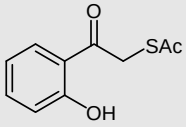
The subsequent reactions of α,α-dibromoacetophenones **7a**,**b** with soft nucleophiles (CN^-, SCN^-, AcS^-, and I^-), in a 1/3 molar ratio (Table 2, entries 1–4 and 7), were typically carried out at ambient temperature in acetone/H_2O or DMF/H_2O solvent mixture, for 40–120 min, providing the mono-α-carbonyl-substituted acetophenones **10a**–**d** and **10g** in moderate to high yields of 58–88%.[17] The generality of this transformation, under similarly mild experimental reaction conditions, has also been demonstrated for the moderately soft N_3^- nucleophile (Table 2, entry 5).

Even in the case of a hard nucleophile, that is, the acetate ion, the desired product **10f** was isolated in 74% yield after a longer reaction time (Table 2, entry 6) using the more polar DMF/H_2O solvent mixture. In contrast, no substitution product **10f** was formed in acetone/H_2O mixture after 3 h at ambient temperature.

Table 2
Carbophilic/bromophilic/protonation cascade reactions of **7a**,**b** with selected nucleophiles



7a,**b** **10a**-**g**

Entry	Substrate (1 mmol)	Nu^- (3 mmol)	Solvent[a]	Time (min)	Product		Yield[b] (%)
1	**7a**	CN	Acetone/H_2O	40		**10a**	58
2	**7a**	SCN	Acetone/H_2O	120		**10b**[15]	88
3	**7a**	AcS	Acetone/H_2O	60		**10c**	78
4	**7a**	I	DMF/H_2O	40		**10d**	78
5	**7a**	N_3	Acetone/H_2O	45		**10e**	84
6	**7a**	AcO	DMF/H_2O	150		**10f**[16]	74
7	**7b**	AcS	Acetone/H_2O	60		**10g**	75 (29)[c]

[a] In all experiments, 0.32 mmol of substrate **7a**,**b**, 0.96 mmol of nucleophile, and 5.5 cm^3 of acetone/H_2O or DMF/H_2O solvent mixture in 10/1 (v/v) ratio were used.
[b] Isolated yield after column chromatography purification.
[c] Combined yields of 2-hydroxy- and 2-OAc compounds. Isolated yield of the 2-OAc product is indicated in parentheses.

As shown in Scheme 3, the formation of the α-carbonyl- substituted acetophenones **10a**–**g** is consistent with the stepwise nature of the reaction of **7a**,**b** with anionic nucleophiles. As a result of the carbophilic reaction (Scheme 3, step i), the initially formed intermediate in the reactions of **7a**,**b** with a range of nucleophiles is the α-bromo-α-substituted species **8**, which was not isolated. Changing the one α-carbon substituent in **7a**,**b** from Br to an electron-withdrawing substituent presumably makes the intermediate **8** susceptible to bromophilic attack (step ii), allowing the formation of the fairly stable carbanion **9**, which is subsequently protonated to the corresponding product **10**.[18]

In summary, we have found that *o*-methoxy- and *o*-hydroxy-α,α-dibromoacetophenones react in an unexpected and facile manner with various soft, moderate, and hard anionic nucleophiles, giving rise to α-carbonyl-substituted acetophenones. The new type of reactivity of these compounds is attributed to the ambident nature of the C–Br bonds which undergo stepwise, nucleophile-induced carbophilic and bromophilic reactions.

Acknowledgment

This research was partially supported by the Ministry of Science of the Republic of Serbia, Grant No. 142007 (to R.M.).

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12. For selective mono- and dibromination of *o*-hydroxy- and *o*-methoxyacetophenones, see: (a) Juneja, S. K.; Choudhary, D.; Paul, S.; Gupta, R. *Synth. Commun.* **2006**, 2877–2881; (b) King, L. C.; Ostrum, G. K. *J. Org. Chem.* **1964**, *29*, 3459–3461; (c) Arbuj, S. S.; Waghmode, S. B.; Ramaswamy, A. V. *Tetrahedron Lett.* **2007**, *48*, 1411–1415; (d) Pravst, I.; Zupan, M.; Stavber, S. *Tetrahedron* **2008**, *64*, 5191–5199.
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14. Selected spectroscopic data for 2,2-dibromo-1-(2-methoxyphenyl)ethanone (**7a**): Mp 50–51 °C. Yield: 95%; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.97 (s, 3H, OCH_3), 6.98–7.11 (m, 2H, *m*-Ph), 7.12 (s, 1H, $CHBr_2$), 7.51–7.60 (m, 1H, *p*-Ph), 7.82–7.87 (m, 1H, *o*-Ph); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 44.8 ($CHBr_2$), 55.9 (OCH_3), 111.7 (*m*-Ph), 121.4 (*m*-Ph), 132.6 (*p*-Ph), 135.2 (*o*-Ph), 158.2 (OCH_3C2-Ph), 187.8 (CO); MS (EI, 70 eV): *m*/*z* (rel. intensity): 312 (M^++4, 4), 310 (M^++2, 8) 308 (M^+, 4), 215 (12), 169 (4), 135 (100), 91 (10), 78 (19), 43 (21). Anal. Calcd for $C_9H_8Br_2O_2$: C, 35.10; H, 2.62. Found: C, 35.32; H, 2.78.
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17. *General experimental procedure*: To a stirred solution of 0.32 mmol of α,α-dibromoacetophenone **7a**,**b** in 5.5 cm^3 of acetone/H_2O or DMF/H_2O in 10/1 (v/v) ratio, 0.96 mmol of the corresponding nucleophile was added. The reaction mixture was stirred at rt for the time specified in Table 2 when TLC indicated complete consumption of the substrate **7a**,**b**. After extraction of the mixture with $CHCl_3$, washing with H_2O, drying, and evaporation, the crude products **10a**–**g** were purified by column chromatography on silica gel, using petroleum ether/ethyl acetate gradient 100:0 to 80:20 (v/v).
18. At the present time it is not possible to rule out that the bromophilic step precedes the carbophilic step.