Reductive Arylation of Maleic and Fumaric Acid Derivatives by Arenediazonium and Titanium(III) Salts

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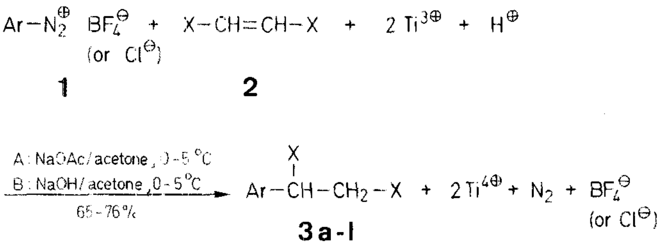
The titanium(III)-induced decomposition of substituted benzenediazonium salts in the presence of maleic and furamic acids, alkyl esters, amides, and nitriles gives the corresponding arylsuccinic acid derivatives.

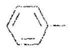
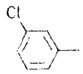
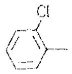
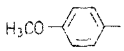
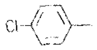
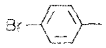
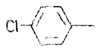
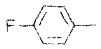
The homolytic reductive arylation of electron-deficient olefins by arenediazonium salts induced by monoelectronic reducing metal cations[1] appears to be a promising alternative to the Meerwein reaction (oxidative arylation)[2], allowing the preparation in moderate to good yields of substituted β-arylethyl derivatives. With vinyl monomers, a large excess of reducing salt is necessary in order to selectively reduce the intermediate aryl radical adduct to the olefin[3]; moreover, the efficiency of the arenediazonium salt to give the arylation products decreases with the increase of the reducing properties of the metal cation used and its concentration. Titanium(III) salts used in stoichiometric amounts gave good results only with vinyl ketones and acrolein; other olefins substituted with electron-withdrawing groups (i.e. COOH, CN, $CONH_2$, COOR, etc.) afford low yields of reductive arylation products and significant amounts of side products resulting from telomerization[4], dimerization or diazo-coupling[5] of the intermediate radical adduct.

In order to extend the reaction with titanium(III) salts to these substituents, we attempted the reductive arylation of 1,2-disubstituted olefins, which can present less problems as they are less polymerizable than vinyl monomers. We now report the results of the synthesis of 2-arylsuccinic acid derivatives (**3**) by the titanium(III)-induced decomposition of substituted benzenediazonium salts (**1**) in the presence of maleic and fumaric acids (**2**; X = COOH), their alkyl esters (**2**; X = COOR), amides (**2**; X = $CONH_2$), and nitriles (**2**; X = CN).

As shown in the Table, compounds **3** were prepared in moderate to good yields by slow addition at room temperature of the arenediazonium salt **1** (as solid tetrafluoroborate or as chloride in water solution) to a solution of **2** and commercial 15% titanium(III) chloride solution in water/acetone (or only water in the experiments with maleic acid). Partial neutralization of the strongly acidic titanium(III) chloride solution improves the yield of **3**. As base was used sodium acetate [1 mol per mol of titanium(III), Method A] or, in the case of maleic and fumaric acids, the corresponding disodium salts (Method B). Sodium maleate can be conveniently obtained by dissolving the maleic anhydride in 4 molar aqueous sodium hydroxide solution at 0 °C.



$$\underset{\mathbf{1}}{Ar-N_2^{\oplus}\ BF_4^{\ominus}\ (\text{or } Cl^{\ominus})} + \underset{\mathbf{2}}{X-CH=CH-X} + 2\,Ti^{3\oplus} + H^{\oplus} \xrightarrow[65-76\%]{\substack{A:\ NaOAc/acetone,\ 0-5\,^{\circ}C\\ B:\ NaOH/acetone,\ 0-5\,^{\circ}C}} \underset{\mathbf{3a-l}}{Ar-\overset{X}{\overset{|}{C}}H-CH_2-X} + 2\,Ti^{4\oplus} + N_2 + BF_4^{\ominus}\ (\text{or } Cl^{\ominus})$$

3	Ar	X	3	Ar	X
a		$-\overset{O}{\overset{\|}{C}}-OH$	**g**		$-\overset{O}{\overset{\|}{C}}-OC_2H_5$
b		$-C\equiv N$	**h**		$-\overset{O}{\overset{\|}{C}}-OH$
c		$-\overset{O}{\overset{\|}{C}}-NH_2$	**i**		$-\overset{O}{\overset{\|}{C}}-OH$
d		$-\overset{O}{\overset{\|}{C}}-OCH_3$	**j**		$-\overset{O}{\overset{\|}{C}}-OH$
e		$-\overset{O}{\overset{\|}{C}}-OH$	**k**		$-\overset{O}{\overset{\|}{C}}-OH$
f		$-C\equiv N$	**l**		$-\overset{O}{\overset{\|}{C}}-OH$

The yield of **3** cannot be improved by using copper(I) or copper(II) salts as catalyst (in amounts of 1–5%) and, generally, fumaric acid derivatives gave better yield than the corresponding maleic acid derivatives[6]. Several substituents on the ring of the arenediazonium salt do not interfere with the reaction; however, some problems were experimented with oxidant groups (i.e. nitro and sulphonyl).

Minor amounts (1–5%) of side products (1,2-diarylsuccinic acid derivatives, substituted benzenes and biphenyls) were generally found in the reaction mixture but were easily separated. Therefore, the procedure reported here offers a simple, inexpensive, one-pot alternative to the previous synthesis of 2-arylsuccinic acid derivatives[6,7].

2-Arylsuccinic Acid Derivatives 3a–l; General Procedures:

Method A: Sodium acetate (3.28 g, 40 mmol) is added with stirring at 10 °C to a 1.19 molar solution of titanium(III) chloride [15% solution from Carlo Erba, titrated against 0.1 normal cerium(IV) sulphate; 33.6 ml]. The solution is cooled at 0–5 °C and a solution of the maleic or fumaric acid derivative **2** (20 mmol) in acetone (50 ml) is added. The cooling bath is removed and the solid arenediazonium tetrafluoroborate **1** (4.25 g, 20 mmol) is added during 1.5 h. The nitrogen evolution stops after 15–40 min. The solution is concentrated under vacuum to 40 ml, extracted with diethyl ether (4 × 30 ml). The combined extracts are washed with saturated

Table. 2-Arylsuccinic Acid Derivatives **3a–l** prepared

Product[a]	Configuration of **2**	Yield [%] by		m.p. [°C]	
		Method A	Method B	found	reported
3a	*Z*	52[b]; 64	68; 67[c]	164–166°	165–166°[8]
3a	*E*	–	73	165–166°	
3b	*E*	70	–	67–68°	65°[9]
3b	*Z*	62	–		
3c	*Z*	65	–	208–210°	212°[10]
3d	*Z*	66	–	57–58°	57.5–58.5°[11]
3d	*E*	72	–		
3e	*Z*	–	70	206–208°	207–208°[12]
3f	*E*	69	–	88–89°	–
3g	*E*	76	–	27–28°	26–27°[12]
3h	*Z*	–	73	161–162°	–
3i	*Z*	–	68	165–166°	181°[13]
3j	*Z*	–	61	204–205°	–
3k	*Z*	–	71	211–212°	210–211°[12]
3l	*Z*	–	70	190–192°	192–193°[12]

[a] For all compounds **3a–l** satisfactory microanalyses were obtained: C ±0.15, H ±0.10, N ±0.02.

[b] Without sodium acetate.

[c] A solution of benzenediazonium chloride in water (1.1 molar) was added in 1 h (maintained at 0°C), instead of the corresponding solid tetrafluoroborate.

sodium chloride solution, dried, evaporated to dryness, and chromatographed on silica gel (eluting with hexane/ethyl acetate mixture) or crystallized from water when solid products are formed. The yields and the melting points of the compounds **3a–l** prepared are reported in the Table.

Method B: Maleic anhydride (1.72 g, 20 mmol) is added with cooling to a 4 molar aqueous solution of sodium hydroxide (10 ml). The resulting solution is added at 0–5°C to the 15% titanium(III) chloride solution (32 ml, 1.25 molar). Acetone (50 ml) is added; the cooling bath is removed and 4-chlorobenzenediazonium tetrafluoroborate (4.52 g, 20 mmol) is added in 2 h. The suspension is stirred at 20°C for 2 h, then concentrated to 60 ml, and filtered. The solid is washed twice with water and dried under vacuum. For purification, it was suspended for 1 h in boiling dichloromethane, filtered, dissolved in a minimum amount of acetone, and then added dropwise to water (60 ml). The precipitated **3e** is collected, washed with water, and dried; yield: 3.2 g (70%); m.p. 206–208°C; (Ref.[12], m.p. 207–208°C).

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