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Probing the Effect of Gegenions in Heck Reactions of Arenediazonium Salts : Arenediazonium Perchlorates and Fluorides as New Heck-Substrates

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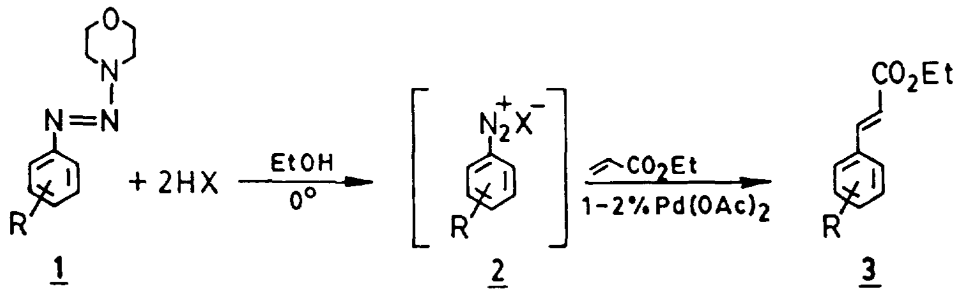
Abstract : A study on the gegenion effect in Heck reaction of arenediazonium salts has given rise to arenediazonium perchlorates and fluorides as alternate Heck-substrates to the tetrafluoroborate salts. © 1997, Elsevier Science Ltd. All rights reserved.

In recent years, palladium catalyzed arylation of olefins, the Heck reaction,[1] has evolved as a powerful synthetic tool for organic chemists. Since its discovery in the early seventies,[2] the reaction has undergone several modifications especially with regard to solvents, catalysts and additives,[1a] which has not only improved its overall efficacy and general synthetic appeal but has also provided strategic handles to control regio- and stereoselectivities, where applicable. As a result, today Heck reaction is the most widely used transition metal catalyzed C-C bond forming reaction in organic synthesis.[3] However, despite all these modifications and improvements, little attention has so far been given to the choice of the aromatic component in Heck reactions which, to date, remains largely confined to the conventional bromides and iodides. In addressing this limitation, we[4] and others[5] have reported that arenediazonium tetrafluoroborates are useful alternatives to aryl halides for Heck reactions. The use of arenediazonium salts, especially under our *aqueous-alcoholic* protocol,[4] offered several advantages over the aryl halides : short reaction times, mild and aqueous reaction conditions, operational simplicity and most significantly, superior reactivity of the diazonium nucleofuge over the bromides and iodides. While the former features i.e. short reaction times and mild reaction conditions, has allowed us to carry out Heck reactions on arenediazonium salts derived from sensitive substrates like L-phenylalanine and L-tyrosine[4c] and thus provide a semisynthetic modification of these aromatic amino acids, the latter characteristic has enabled selective coupling at the diazonium end in p-bromo- and p-iodoarenediazonium salts, thus opening-up a new vista in differential Heck reactions. Moreover, we have shown that for diazonium tetrafluoroborates which are unstable and / or difficult to isolate, the corresponding 1-aryltriazenes can be used as 'bench-stable' diazonium surrogates from which the tetrafluoroborate (or the trifluoroacetate) salts can be easily and quantitatively generated *in-situ* with 42% HBF_4 (or trifluoroacetic acid) and subsequent Heck reaction, in the same pot, can be carried out in high overall yields.[4b] Otherwise, the aniline itself can be induced into a 'one-pot diazotization-Heck reaction' sequence in aqueous alcohol to provide comparable yields of the Heck- products[4d]. Recently, cross coupling of arenediazonium salts with arylboronic acids has been achieved in methanolic medium[6].

In course of these studies, it came to our notice that Heck reaction of arenediazonium salts are highly dependent on the nature of the diazonium counteranion which led us to investigate the gegenion effect in these reactions. Results of this investigation which, in turn, has given rise to arenediazonium-perchlorates and fluorides as alternate Heck-substrates to the terafluoroborates are described in this paper.

Several reports have already testified the usefulness of diazonium tetrafluoroborates in Heck reaction.[4,5] In the present study, we found that salts having Cl^-, Br^-, I^- and HSO_4^- as counteranions are totally ineffective for the purpose, pointing out the fact that perhaps non-reducing counteranions like BF_4^- are essential for the success of these reactions. However, further probe in this regard proved difficult due to lack of general preparative methods for diazonium salts having non-reducing counteranions other than BF_4^-. For example, diazotization of p-chloroaniline with $NaNO_2$ and aq. 40% HF produced a salt which was highly soluble in water and could not be isolated. The 'one-pot diazotization - Heck reaction' sequence[4d] gave only low yields of the Heck product when it was carried out in 40% HF. Lack of sufficient knowledge regarding the stabilities of such salts was a further deterrent.[7] In view of these, we decided to generate, *in-situ*, a series of arenediazonium salts $ArN_2^+BF_4^-$ (**2**) having different gegenions X^- via treatment of the 1-aryltriazenes (**1**) with the corresponding conjugate acid HX and study the gegenion-effect of their Heck reaction with ethyl acrylate according to Scheme 1.



a: R = p–Cl ; b: R = p-OMe ; c: R = p–Me ; d: R = p-Br ; e: R = o–Me ; f: R = o–Me

HX = HOAc, $HClO_4$, HF, CH_3SO_3H, HBF_4, TFA

SCHEME 1

The triazene **1a** was chosen as the model substrate from which a number of diazonium salts $p\text{-}Cl\text{-}C_6H_4N_2^+X^-$ (**2a**) were generated *in-situ* with two equivalents of HX in 95% ethanol and each subjected to Heck reaction, in the same pot, with ethyl acrylate in presence of 1-2% of $Pd(OAc)_2$. Results of this study are collected in Table 1. Acetic acid (entry 1) gave a complex product mixture from which no appreciable amount of the Heck-product **3a** could be isolated. Similar lack of Heck reactivity was previously observed by us during attempted 'one-pot diazotization- Heck reaction,[4d] of anilines using HOAc. On the other hand, $HClO_4$, HF and CH_3SO_3H each produced clean Heck reactions giving rise to **3a** in high yields (entries 2-4). The high yields of **3a** obtained in the latter cases are similar to those previously reported by us using HBF_4 and TFA (cf. entries 6, 7).[4b] However, Dowex 50W-X8 (H^+ - form) resin, a polymer bound sulfonic acid, was not as effective as CH_3SO_3H and produced very low yields of **3a** together with unconverted triazene **1a** and other unidentified side products (entry 5).

Table 1. Heck Reaction of **1a** with Various Acids HX (Scheme 1).

	HX	X^- in **2a**	Yield (%) of **3a**[a]
1	HOAc	AcO^-	--[b]
2	$HClO_4$	ClO_4^-	73
3	HF	F^-	75
4	CH_3SO_3H	$CH_3SO_3^-$	80
5	Dowex 50W-X8 (H^+-form)	P-SO_3	--[b]
6	HBF_4	BF_4^-	78
7	CF_3CO_2H	$CF_3CO_2^-$	83

[a]isolated yields; [b]complex product mixture.

The above study thus revealed that, in addition to diazonium tetrafluoroborates, salts having ClO_4^- , F^-, $CF_3CO_2^-$ and $CH_3SO_3^-$ as counteranions are also effective for Heck reaction.The high yields obtained from the perchlorate and fluoride salts were particularly attractive since 70% $HClO_4$ and 40% HF used for their generation are considerably

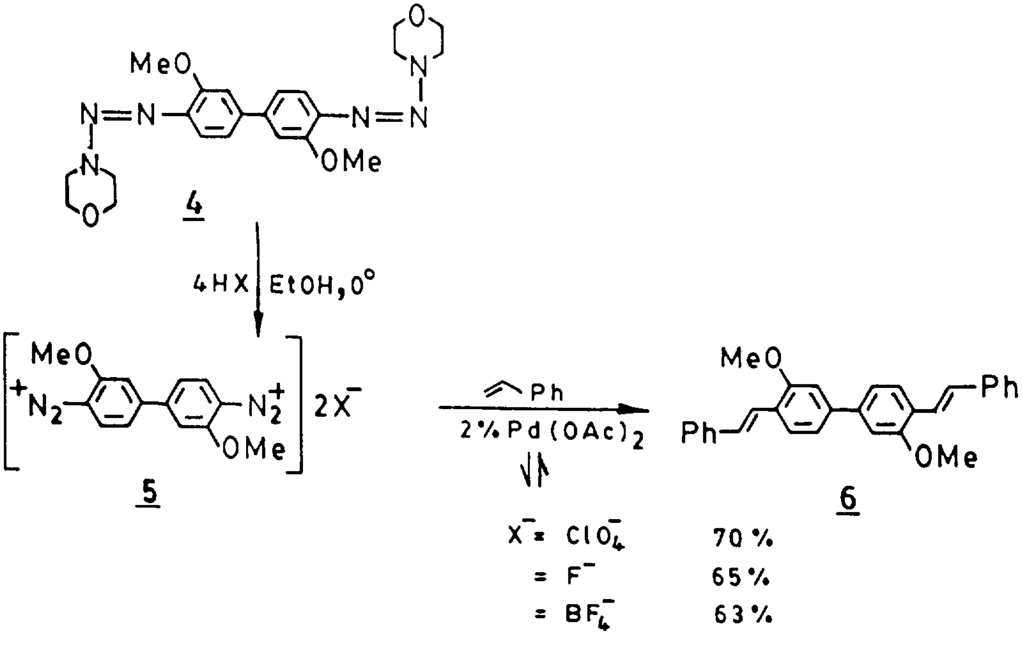
Table 2. Heck Reaction of Arenediazonium Perchlorates and Fluorides. (Scheme 1).

	Triazene	HX	Arenediazonium Salt 2(X^-)	Product 3	Yield (%)[a]
1	**1b**	$HClO_4$	**2b** (ClO_4^-)	**3b**	81
		HF	**2b** (F^-)	"	86
2	**1c**	$HClO_4$	**2c** (ClO_4^-)	**3c**	88
		HF	**2c** (F^-)	"	78
3	**1d**	$HClO_4$	**2d** (ClO_4^-)	**3d**	84
		HF	**2d** (F^-)	"	78
4	**1e**	$HClO_4$	**2e** (ClO_4^-)	**3e**	90
		HF	**2e** (F^-)	"	97
5	**1f**	$HClO_4$	**2f** (ClO_4^-)	**3f**	85
		HF	**2f** (F^-)	"	75

[a]isolated yields.

cheaper than the rest. This gave rise to the prospect of using these salts as cost-effective alternatives to the diazonium tetrafluoroborates and hence, we looked into their Heck reaction in some more details. A number of 1-aryltriazenes **1b-f** having diverse substitution patterns were selected and their Heck reactions were studied with ethyl acrylate either in presence of 70% $HClO_4$ or 40% HF (Scheme 1, Table 2). As evident from Table 2, for all the cases studied, diazonium perchlorates and fluorides, within experimental error, are equally effective as Heck-substrates. Quite noteworthy are the high yields achieved throughout the series of diazonium salts examined, including *ortho*-substituted ones (**2c,f**). Moreover, compared to yields of Heck reaction using isolated diazonium tetrafluoroborates,[4d] the perchlorates and fluorides consistently gave better results.

Bis-Diazonium perchlorates and fluorides (**5**, $X^- = ClO_4^-, F^-$) could be similarly derived from the *bis* -triazene **4** and also proved to be useful substrates for Heck reaction, for example, with styrene (Scheme 2). Here, again, the perchlorates, fluorides and tetrafluoroborates gave very similar yields of the Heck-product **6**.



SCHEME 2

In summary, a study on the gegenion-effect in Heck reactions of arenediazonium salts showed that, apart from the commonly used tetrafluoroborates, those salts having ClO_4^-, F^-, $CH_3SO_3^-$ and $CF_3CO_2^-$ as counteranions are also effective for Heck reaction. The latter salts could be conveniently generated, *in-situ*, via treatment of 1-aryltriazenes with the corresponding conjugate acids. Of these, the perchlorates and fluorides emerged as better alternatives to the tetrafluoroborates in terms of cost-effectiveness and improved reactivity profile.[8]

EXPERIMENTAL

The 1-aryltriazenes **1a-f** were prepared according to literature procedures.[4b] *Preparation of the bis-triazene* **4**: 3,3′-Dimethoxybenzidine (1.0 g, 4.0 mmol) was heated in a mixture of conc. HCl (1.0 ml) and water (10 ml) for 5 min. It was then cooled to 0°, conc. HCl (0,7 ml) added and then treated dropwise with a solution of $NaNO_2$ (0.55 g, 8.0 mmol) in water (1.5 ml). The contents were strirred for 10 min, filtered rapidly and the filtrate cooled in an ice-salt bath. Morpholine (0.83 g, 2.4 mmol) was added dropwise to the filtrate and the whole stirred for 15 min. The reaction mixture was then basified with $NaHCO_3$ solution and the separated solid filtered, washed with water and dried in air. Recrystallization (benzene) gave **4** as brown crystals (1.27 g, 70 %); m. p. 205-6°; IR : 1450, 1370, 1100 cm^{-1}; ^{1}HNMR ($CDCl_3$) : 3.92 (8H, br s), 4.04 (3H, s), 7.16-7.40 (2H, m), 7.41-7.64 (1H, m) ; found C : 59.52, H:6.27, N:18.88, $C_{22}H_{28}N_6O_4$ requires C : 60.0, H:6.36, N: 19.09%.

Representative procedure for Heck reaction of 1-aryltriazenes (1a-f) in presence of acids : To an ice-cold solution of the triazene **1** (1.85 mmol) in 95% ethanol (5 ml) was added dropwise the desired acid (3.7 mmol). Ethyl acrylate (3.7 mmol) and Pd $(OAc)_2$ (5.0 mg) were then added and the mixture was heated under reflux for 45 min. Standard work-up with ether followed by silica-gel chromatography (5-10% EtOAc in Pet. ether) gave the respective products **3a-f** which were identified by comparision of their IR/NMR data with those reported in the literature. Yields are given in Tables 1 and 2.

Acid mediated bis-Heck reaction of the bis-triazene 4 with styrene : To a stirred solution of **4** (0.30 g, 0.68 mmol) in MeOH (10 ml) was added dropwise the desired acid (70% $HClO_4$ or 40% HF or 42% HBF_4) at 0°. After 5 min, it was brought to RT and styrene (2.0 mmol) and Pd $(OAc)_2$ (5.0 mg) were added and the whole heated under reflux for 45 min. Standard work-up with CH_2Cl_2 followed by recrystallization (CH_2Cl_2 / Pet.ether) gave the product **6** as an yellow solid, m.p. 195-6°; ^{1}HNMR ($CDCl_3$) ; 4.0 (3H, s), 6.15 - 6. 70 (10H, m) ; found C : 86.28 ; H : 6.38, $C_{30}H_{26}O_2$ requires C : 86.12; H: 6.22%.

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7. Arenediazonium perchlorates prepared via diazotization of anilines with aq. $HClO_4/NaNO_2$ can be isolated but turned out to be (mildly) shock-sensitive when dry. However, in solutions they are absolutely safe to handle.

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