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Efficient Heck Arylations of Cyclic and Acyclic Acrylate Derivatives Using Arenediazonium Tetrafluoroborates. A New Synthesis of the Antidepressant Drug (±)-Paroxetine

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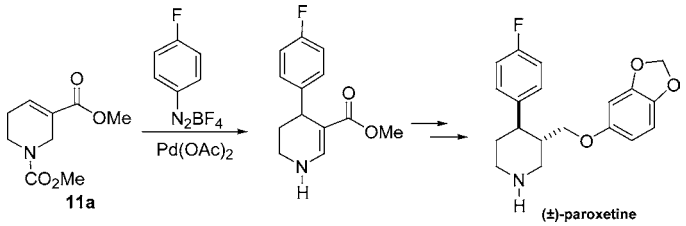
ABSTRACT



The Heck arylation of acyclic- and cyclic-substituted acrylates using several arenediazonium tetrafluoroborates was investigated. Arylations were carried out under aerobic, ligand-free conditions to provide the corresponding substituted acrylates in moderate to high isolated yields. Heck arylations were usually completed in less than 2 h in refluxing methanol. The aza-endocyclic acrylate derivative 11a was converted into the antidepressant drug (±)-paroxetine in a concise new route in good overall yield.

Palladium-catalyzed C−C coupling reactions constitute an important method in contemporary organic synthesis.[1] Among the palladium-catalyzed C−C couplings, the Heck reaction holds a prominent position due to its exceptional versatility, thus allowing ingenious applications in the total synthesis of complex organic structures.[2] Among the several arylating agents available to perform the Heck reaction, the arenediazonium salts are probably the least explored ones, although they offer considerable advantages over traditional electrophiles.[3] First, Heck arylations employing arenediazonium salts do not require the use of phosphines ("ligand-free conditions"). Second, they are also usually faster, less costly, and greener. Third, they can be carried out under aerobic conditions and are much easier to handle than traditional protocols.[4]

The Heck arylation of unsubstituted acrylates employing aryl halides, aryl triflates, or even arenediazonium salts is a well-established process.[2a] It has been used extensively as a benchmark protocol for the discovery of new palladium catalysts and/or to demonstrate new advances in Heck arylation. However, the use of complex substituted acrylates is scarce in the literature.[5] Usually, these substrates are more

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resistant to Heck arylations resulting in low conversion or yields of the desired adduct. From a synthetic standpoint, this is a considerable limitation to the Heck arylation process and poses a challenge to be addressed.[6]

Because of the higher reactivity of the arenediazonium salts in the Heck reaction, we decided to investigate the feasibility of applying the Heck arylation to the more challenging substituted acrylate derivatives. Our planning also included the application of these results in the total synthesis of pharmacologically active compounds to highlight the versatility of the procedure. One of the objectives of this initial investigation was the synthesis of 4-arylpiperidines, of which the antidepressant drug paroxetine **1**, femoxetine **2**, and the new renin inhibitor **3** are illustrative examples (Figure 1).[7] Paroxetine helps to maintain the neuronal levels

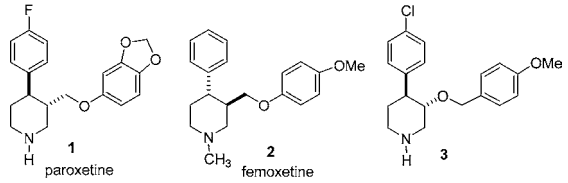


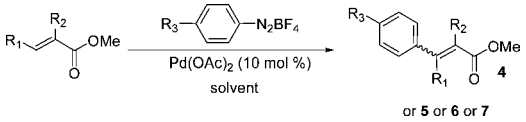
Figure 1. Representative 4-arylpiperidines.

of the endogenous neurotransmitter serotonin. This drug acts by selectively inhibiting the serotonin reuptake system on the presynaptic neurons, making the so-called SSRI drugs.[8]

Arenediazonium tetrafluoroborates bearing substituents with differing electronic affinity were evaluated. 4-Methoxy and 4-fluorobenzenediazonium tetrafluoroborates were chosen as the main arylating agents because of their exceptional thermostability and to allow introduction of an electron-rich aryl group, which is considerably more difficult to introduce when employing traditional Heck protocols. Some selected examples are presented in Table 1.

Arylations of methyl cinnamate were screened using CH_3CN, CH_3CN-H_2O (1:1), EtOH, and MeOH as solvent (Table 1, entries 1−5) without addition of bases. Arylations were observed in all solvents tested. However, these were more efficient and faster in refluxing MeOH. Heck arylations in ethanol resulted in more complex mixtures due to transesterification. Arylations were completed in 2 h to provide the

Table 1. Heck Arylation of Acyclic-Substituted Acrylates



or **5** or **6** or **7**

entry	R_1	R_2	R_3[a]	solvent[b]	T (°C)	t (h)	yield (%)[c]
1	C_6H_5	H	MeO	AC	reflux	8	40[d]
2	C_6H_5	H	F	$AC-H_2O$	60	24	43[e]
3	C_6H_5	H	MeO	MeOH	reflux	2	71[f]
4	C_6H_5	H	F	MeOH	reflux	2	67[g]
5	C_6H_5	H	MeO	MeOH	rt	8	50[h]
6	CH_3	CH_3	F	$AC-H_2O$	60	8	64[i]
7	CH_3	CH_3	F	$AC-H_2O$	60	7	59[j]
8	CH_3	CH_3	MeO	MeOH	reflux	2	66[j]
9	CH_3	CO_2Me	MeO	MeOH	reflux	5.5	31[k]
10	H	CH_2CO_2Me	F	MeOH	reflux	0.25	91[l]
11	H	CH_2CO_2Me	MeO	MeOH	reflux	0.25	86[l]

[a] 1.0−1.2 equiv of arenediazonium salts. [b] AC = acetonitrile; $AC-H_2O$ refers to a 1:1 mixture of acetonitrile/water. [c] Isolated yields. [d] Diastereoselectivity (ds, capillary GC) = 36:64. [e] ds = 95:5. [f] ds = 26:74. [g] ds = 93:7. [h] ds = 85:15. [i] Double-arylated product **5**; ds = 47:53. [j] Yields for the corresponding isomerized Heck adduct **6**. [k] Double-arylation product **7** also isolated in ~5% yield. [l] (*E*)-Stereoisomer only.

corresponding β,β-diaryl propionic esters in good yields with the diastereoselectivity depending on the arenediazonium used. Interestingly, diastereoselectivity was much higher with *p*-fluorobenzenediazonium salts than with the *p*-methoxylbenzenediazonium salts. Evidence for thermodynamic control in this latter case is observed when comparing entries 3 and 5 or when following the reaction by GC. Changes in the diastereomeric ratio are observed as the reaction proceeds, probably due to equilibration. Also somewhat surprising was the fact that no reaction was observed when using $Pd_2(dba)_3$ as catalyst. Some of the β,β-diaryl propionic esters prepared here are key intermediates in the synthesis of many important drugs.[9]

Heck arylation of methyl tiglate (entries 6−8) resulted in the double-arylated adduct **5** as the only observed adduct in 64% yield (Figure 2, R = F). This was not surprising in

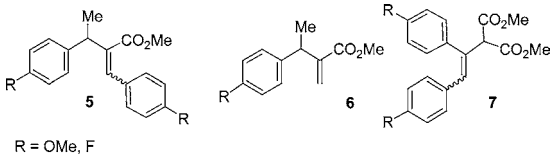


Figure 2. Heck adducts from the double and monoarylation of acyclic acrylates.

view of the formation of a reactive α-substituted acrylate as the primary Heck adduct. Nevertheless, formation of the

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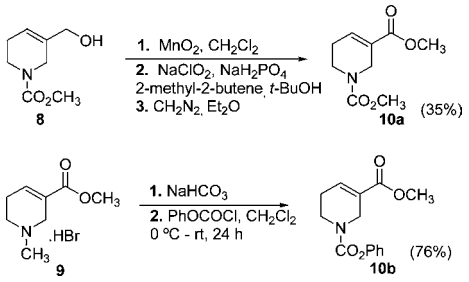
trisubstituted olefin in preference to the alternative disubstituted adduct **6** is noteworthy. The exclusive formation of the monoarylated adduct **6a** (R = F) in 59% yield and **6b** (R = OMe) in 66% yield was obtained when using an excess of the starting acrylate (>10 equiv).

Arylation of the 1,1-disubstituted olefin occurred in less than 15 min to provide the nonisomerized, monoarylated Heck adducts in high yields as single stereoisomers (entries 10 and 11). Hindered acrylates are less reactive (entry 9) providing the monoarylated Heck adduct in 31% yield, together with the double-arylated side product **7** (R = OMe, ~5% yield) (single isomer).

Azacyclic acrylate derivatives **10a** (X = NCO_2CH_3) and **10b** (X = NCO_2Ph) were chosen as cyclic substrates in part because these olefins were envisioned as potential starting materials for the synthesis of paroxetine. These acrylates were prepared from the known allylic alcohol **8** or from the commercially available alkaloid arecoline **9**[10] as indicated in Scheme 1.

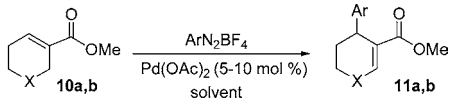
Scheme 1. Synthesis of the Aza-Endocyclic Acrylates



Heck arylation of the aza-endocyclic acrylate derivatives **10a** and **10b** occurred smoothly to provide the desired Heck adduct in good to high yields irrespective of the electronic nature of the substituents on the arenediazonium tetrafluoroborates employed (Table 2). Protection of the nitrogen as a carbamate was necessary because arecoline as the free base proved to be inert under the Heck arylation conditions used.

As observed previously, arylations were faster in methanol when compared to CH_3CN/H_2O (1:1). However, contrary to the results observed with methyl tiglate, no double-arylated products were detected with these substrates even when an excess of the arenediazonium salts was used (1.2−1.5 equiv). Presumably, the lower reactivity of the β-amido acrylate subunit and the intrinsic steric hindrance of the Heck adducts prevent further arylation. A significant difference in reactivity between **10a** and **10b** was noticeable when using CH_3CN/H_2O as the reaction solvent (compare entries 2 and 11). Varying amounts of the hemiaminal resulting from the addition of H_2O to the acyl enamino ester functionality were observed on a few occasions when using CH_3CN/H_2O. This product can be converted to the enamino ester by refluxing it with trifluoroacetic anhydride in toluene.[11] The use of less than 5 mol % of $Pd(OAc)_2$ resulted in very low conversions (<10% after 24 h). Addition of bases (NaOAc and 2,6-di-*tert*-butyl-4-methylpyridine) do not affect yields significantly but cause a decline in reaction rates.

Table 2. Heck Arylation of the Aza-Endocyclic Acrylates



10a (X = NCO_2Me), **10b** (X=NCO_2Ph)

entry	sm[a]	Ar	solvent	T (°C)	t (h)	yield (%)[b]
1	**10a**	*p*-$MeOC_6H_4$	AC−H_2O	60	6	90
2	**10a**	*p*-FC_6H_4	AC−H_2O	60	4	87
3	**10a**	*p*-FC_6H_4	AC−H_2O	rt	4	74
4	**10a**	*p*-ClC_6H_4	AC−H_2O	60	8	91
5	**10a**	*p*-BrC_6H_4	AC−H_2O	60	8	92
6	**10a**	*p*-IC_6H_4	AC−H_2O	60	24	68
7	**10a**	*p*-$NO_2C_6H_4$	AC−H_2O	60	27	82
8	**10a**	*p*-$CO_2MeC_6H_4$	AC−H_2O	60	46	43[c]
9	**10a**	*o*-$MeOC_6H_4$	AC−H_2O	60	48	75
10	**10a**	C_6H_5	AC−H_2O	60	24	38[d]
11	**10b**	*p*-FC_6H_4	AC−H_2O	60	10	74
12	**10b**	*p*-BrC_6H_4	AC−H_2O	60	10	80
13	**10b**	*p*-$MeOC_6H_4$	MeOH	reflux	2	89
14	**10b**	*p*-FC_6H_4	MeOH	reflux	2	91

[a] Starting olefin. [b] Isolated yields. [c] 49% conversion of sm. [d] 46% conversion of sm.

The exclusive formation of the monoaryl Heck adducts **11a** and **11b** in good to high yields was gratifying and instrumental for the total synthesis of (±)-paroxetine. Despite several available methods for preparing the arylpiperidine motif, there are no reports of the Heck arylation to prepare the 4-arylpiperidine system displayed by paroxetine and related compounds.[12]

The enamino−ester functionality was efficiently reduced with Mg in methanol[13] to give a diastereomeric mixture of *cis*- and *trans*-4-(4-fluorophenyl)-piperidine-1,3-dicarboxylic acid dimethyl esters in quantitative yield in a ratio of 75:25. The amount of magnesium used significantly affects the cis−trans ratio, and the best results were obtained employing 20 equiv of magnesium. Equilibration to the thermodynamically more stable trans isomer was accomplished by refluxing the stereoisomeric mixture with sodium methoxide in methanol (68% yield). Reduction of both methoxycarbonyl groups present in **12** with lithium aluminum hydride gave the known paroxetine intermediate **13** in 80% yield (Scheme 2).[14]

The known procedure to the total synthesis of paroxetine calls for the removal of the *N*-methyl group via its conversion to a carbamate group.[15] To avoid redundancy, an alternative

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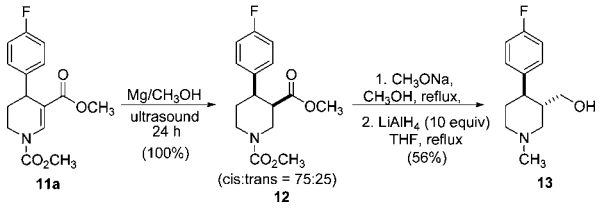
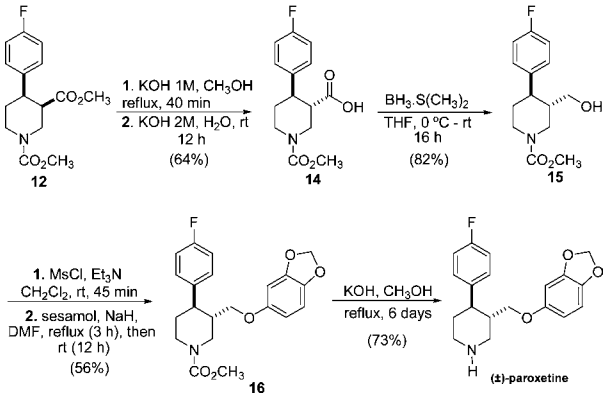
Scheme 2. Formal Total Synthesis of (±)-Paroxetine



Scheme 3. New Total Synthesis of (±)-Paroxetine



route was taken (Scheme 3). The cis−trans mixture of 4-(4-fluorophenyl)-piperidine-1,3-dicarboxylic acid dimethyl esters was equilibrated to the trans isomer using 1 M KOH in methanol under reflux for 40 min. In the sequence, the solvent was evaporated and the mixture was hydrolyzed using aqueous 2 M KOH at room temperature for 12 h, furnishing the expected carboxylic acid **14** in 64% yield. Reduction of **14** with diborane gave the primary alcohol **15** in 82% yield. The resulting alcohol was then converted into the respective mesylate followed by reaction with the sodium salt of sesamol generated in situ to provide the *N*-carbomethoxy paroxetine **16** in 56% yield. Finally, basic hydrolysis of **16** with methanolic KOH under reflux gave paroxetine **1** in 73% yield, whose spectroscopic data were identical to those described in the literature.[16]

In summary, Heck arylations of substituted cyclic and acyclic acrylate derivatives were accomplished in moderate to high yields using arenediazonium tetrafluoroborates bearing electron-neutral, electron-withdrawing, or electron-donating substituents. Acrylates bearing an α-alkyl substituent have a tendency to undergo a second arylation which can be suppressed by employing an excess of the starting olefin. The lower stereoselectivities observed for the arylation of (*E*)-methyl cinnamate with *p*-methoxybenzenediazonium salt are probably due to equilibration,[5b] and efforts are underway to achieve kinetic control of these reactions. In the present study, the Heck adduct 4-(4-fluorophenyl)-tetrahydropyridine **11a** was used as a key intermediate in a new total synthesis of the antidepressant drug paroxetine in seven steps in an overall yield of 20%. Some of the Heck adducts synthesized herein hold great potential as synthetic intermediates for the construction of more complex compounds. These studies are ongoing and will be disclosed in due course.[17]

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Supporting Information Available: Selected experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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