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Alkyl Nitrite–Metal Halide Deamination Reactions. 3. Arylation of Olefinic Compounds in the Deamination of Arylamines by Alkyl Nitrites and Copper(II) Halides. A Convenient and Effective Variation of the Meerwein Arylation Reaction[1]

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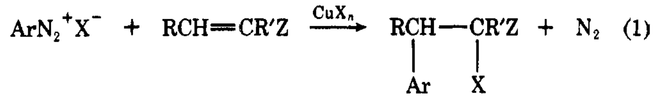
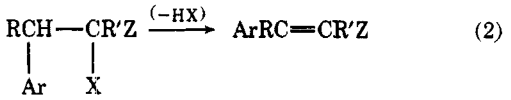
Arylation of olefinic substrates occurs when arylamines are treated with alkyl nitrites and copper(II) halides in acetonitrile or acetone solutions that contain the olefin. The corresponding β-aryl-α-halo derivatives are formed in high yields by this direct procedure. Results from direct arylation reactions of representative arylamines with acrylonitrile and styrene in the presence of copper(II) chloride are reported; isolated yields of arylation products from these reactions are comparable or superior to those obtained by the Meerwein procedure. The yields of α-chloro-β-arylpropionitriles from deamination reactions of arylamines in the presence of copper(II) chloride and acrylonitrile closely match those of substitution products that are formed by direct substitutive deamination of arylamines with *tert*-butyl nitrite and copper(II) chloride. This similarity indicates that neither the Sandmeyer reaction nor potentially competitive processes that involve arylation intermediates adversely affect this Meerwein reaction, and that reactions that compete with the Sandmeyer reaction are of comparable importance in the Meerwein reaction. Reactions with acrylonitrile that employ copper(II) bromide, however, are complicated by a preponderance of products that result from competing substitutive deamination and ring substitution by bromine. In arylation reactions that involve the deamination of *p*-nitroaniline in the presence of copper(II) chloride and selected olefins the importance of the competing Sandmeyer reaction is dependent on the nature of the olefinic substrate.

The Meerwein reaction is the copper salt catalyzed arylation of olefinic compounds by arenediazonium halides (eq 1).[3]



$$\mathrm{ArN_2{}^+X^-} + \mathrm{RCH{=}CR'Z} \xrightarrow{\mathrm{CuX}_n} \underset{\mathrm{Ar}}{\mathrm{RCH}}-\underset{\mathrm{X}}{\mathrm{CR'Z}} + \mathrm{N_2} \tag{1}$$

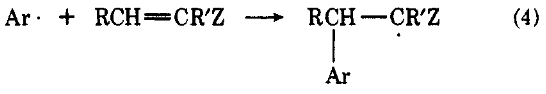
The olefinic components that are most suitable for this transformation are activated by electron-withdrawing groups or by conjugation with unsaturated functional groups (Z). Combination of the diazonium salt with the unsaturated compound and the copper salt results in the addition of the aryl component to the β carbon of the substituted olefin, with halide added to the α carbon. Elimination of hydrogen halide (eq 2) may occur under the reaction conditions of the Meerwein reaction or often results from a subsequent transformation.



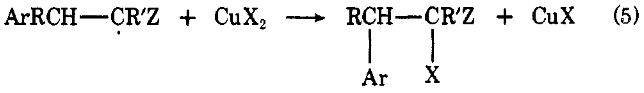
$$\underset{\mathrm{Ar}}{\mathrm{RCH}}-\underset{\mathrm{X}}{\mathrm{CR'Z}} \xrightarrow{(-\mathrm{HX})} \mathrm{ArRC{=}CR'Z} \tag{2}$$

Although cupric salts were promoted by Meerwein,[4] cuprous halides have been shown to be the effective catalysts for the arylation reaction.[5,6] However, both copper(I) and copper(II) oxidation states are utilized in the production of the Meerwein addition compound (eq 3–5).[7] Competing reactions, which in addition to formation of the Sandmeyer product include those processes that are most often associated with the Sandmeyer reaction, reinforce the widely held belief that the Meerwein reaction is initiated by copper(I)-catalyzed production of aryl radicals (eq 3).[3,7–9]

$$\mathrm{ArN_2{}^+} + \mathrm{CuX_2{}^-} \longrightarrow \mathrm{Ar\cdot} + \mathrm{N_2} + \mathrm{CuX_2} \tag{3}$$



$$\mathrm{Ar\cdot} + \mathrm{RCH{=}CR'Z} \longrightarrow \underset{\mathrm{Ar}}{\mathrm{RCH}}-\dot{\mathrm{C}}\mathrm{R'Z} \tag{4}$$



$$\mathrm{ArRCH}-\dot{\mathrm{C}}\mathrm{R'Z} + \mathrm{CuX_2} \longrightarrow \underset{\mathrm{Ar}}{\mathrm{RCH}}-\underset{\mathrm{X}}{\mathrm{CR'Z}} + \mathrm{CuX} \tag{5}$$

In the procedure normally employed for the Meerwein reaction[3] the arenediazonium halide is initially prepared in an aqueous halogen acid solution and then mixed with the unsaturated component in an appropriate solvent (water, acetone, or acetonitrile). Copper(II) halide is added to the homogeneous mixture and nitrogen evolution ensues, usually at temperatures at or below 25 °C. In this two-step procedure reaction variables, including the solution pH and the reaction solvent, are important determinants of the yield of the Meerwein arylation product. The Meerwein reaction is usually conducted in buffered solutions within the pH range of 2–4 to minimize side reactions.[10] Acetone is most often employed as the organic cosolvent but is reported to inhibit arylation in reactions with certain unsaturated compounds.[11]

The yields of arylation products are dependent on the structure of the diazonium salt and of the unsaturated compound, as well as on the previously mentioned reaction variables. For example, electron-donating substituents on the arenediazonium ion and the presence of ortho substituents generally adversely affect the yield of the Meerwein product.[3] Reactions that compete with the Meerwein reaction are often dominant and, consequently, the yield of the arylation product is low in many reactions.

Table I. Yields of α-Chloro-β-arylpropionitriles from Reactions of Arylamines and *tert*-Butyl Nitrite with Copper(II) Chloride and Acrylonitrile[a]

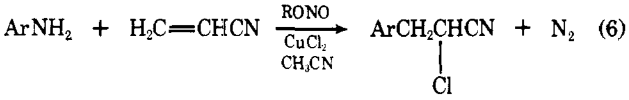
Registry no.	$ArNH_2$	Temp, °C	$ArCH_2CHClCN$	Isolated yield, %[b] (eq 6)	Reported yield, % (eq 7)
100-01-6	$p\text{-}NO_2C_6H_4NH_2$	25	$p\text{-}NO_2C_6H_4CH_2CHClCN$	(93)	48,[13] 83[14]
99-09-2	$m\text{-}NO_2C_6H_4NH_2$	25	$m\text{-}NO_2C_6H_4CH_2CHClCN$	74	38[13]
99-92-3	$p\text{-}CH_3COC_6H_4NH_2$	25	$p\text{-}CH_3COC_6H_4CH_2CHClCN$	83	
106-47-8	$p\text{-}ClC_6H_4NH_2$	25	$p\text{-}ClC_6H_4CH_2CHClCN$	78 (71)	76[5a]
62-53-3	$C_6H_5NH_2$	25	$C_6H_5CH_2CHClCN$	71	34[13]
106-49-0	$p\text{-}CH_3C_6H_4NH_2$	25	$p\text{-}CH_3C_6H_4CH_2CHClCN$	73	40[13]
104-94-9	$p\text{-}CH_3OC_6H_4NH_2$	65	$p\text{-}CH_3OC_6H_4CH_2CHClCN$	32	
		25		5	31[15]
634-93-5	$2,4,6\text{-}Cl_3C_6H_2NH_2$	25	$2,4,6\text{-}Cl_3C_6H_2CH_2CHClCN$	92	
88-05-1	$2,4,6\text{-}(CH_3)_3C_6H_2NH_2$	65	$2,4,6\text{-}(CH_3)_3C_6H_2CH_2CHClCN$	0	
		25		0	

[a] Reactions were performed by adding 10.0 mmol of the amine to 15.0 mmol of *tert*-butyl nitrite and 12.0 mmol of anhydrous copper(II) chloride in 20 mL (0.30 mol) of acrylonitrile and 20 mL of acetonitrile. [b] Absolute yield of the Meerwein product as determined by ^1H NMR analysis through comparison to an internal standard. From duplicate runs experimentally determined percentage yields were accurate to within ±2% of the reported values. Isolated yield after purification by distillation or recrystallization is given in parentheses.

In the accompanying paper[1] alkyl nitrites are reported to react with arylamines and copper(II) halides to effect direct substitutive deamination which is remarkably free of the side reactions that usually accompany the Sandmeyer reaction. The high product yields obtained by this direct procedure and the mechanistic similarity between the Sandmeyer and Meerwein reactions[6,7a] suggest that a similar direct procedure for the arylation of olefinic compounds should have comparable synthetic advantages. If reactions that compete with the Sandmeyer reaction are assumed to be of equal importance in the Meerwein reaction, and if these processes are significantly minimized in the direct substitutive deamination procedure, then only the Sandmeyer reaction and side reactions of the arylation intermediate (the β-arylalkyl radical formed in eq 4) are expected to be competitive with production of the Meerwein product. In this paper we report the results of our investigation of the arylation of olefinic compounds by deamination of arylamines with alkyl nitrites in the presence of copper(II) halide and olefinic substrates.

Results and Discussion

Addition of an arylamine to an acetonitrile solution containing alkyl nitrite, anhydrous copper(II) chloride, and an olefinic substrate results in the evolution of nitrogen and in the formation of the arylation product from vicinal addition of the aryl group and halogen to the carbon–carbon double bond. Use of acrylonitrile, one of the most reactive olefinic substrates employed in the Meerwein reaction,[6] results in the formation of α-chloro-β-arylpropionitriles (eq 6). Isolated



$$ArNH_2 + H_2C{=}CHCN \xrightarrow[\substack{CuCl_2\\CH_3CN}]{RONO} ArCH_2\underset{\substack{|\\Cl}}{C}HCN + N_2 \quad (6)$$

yields of α-chloro-β-arylpropionitriles in representative reactions of arylamines, *tert*-butyl nitrite,[12] and anhydrous copper(II) chloride with acrylonitrile are presented in Table I.

A relatively large molar excess of acrylonitrile (30-fold) relative to the arylamine was employed in these reactions. Lower yields of the arylation product were obtained when only a twofold excess of acrylonitrile was used. For example, the isolated yield of α-chloro-β-(*m*-nitrophenyl)propionitrile from deamination of *m*-nitroaniline was only 40% when the molar ratio of acrylonitrile to *m*-nitroaniline was 2:1, whereas this same product was isolated in 74% yield when acrylonitrile was used as a cosolvent with acetonitrile. Optimum conditions for these reactions were not investigated with the individual substrates that were employed in this study; instead, since unreacted acrylonitrile could be conveniently separated from Meerwein arylation products, a general procedure was developed in which reactivity differences in arylation reactions with acrylonitrile would be effectively minimized. Polymerization of acrylonitrile, which would effect lower yields of α-chloro-β-arylpropionitriles, was not an obvious disadvantage in the operation of this experimental procedure.

The yields of α-chloro-β-arylpropionitriles in Table I closely match the yields of substitution products previously obtained for direct substitutive deamination of arylamines by *tert*-butyl nitrite and copper(II) chloride.[1] This similarity indicates that neither the Sandmeyer reaction nor potentially competitive processes involving the arylation intermediate adversely affect this Meerwein process, and that reactions that compete with the Sandmeyer reaction are of comparable importance in the Meerwein reaction. Indeed, *p*-chlornitrobenzene is not observed in the direct arylation of acrylonitrile that occurs with *p*-nitroaniline, and the Sandmeyer products from deamination of *p*-chloroaniline and 2,4,6-trichloroaniline in the presence of acrylonitrile are formed in 3 and 4% yield, respectively.

Low product yields in the direct substitutive deamination process[1] forecast comparably low yields of Meerwein products from reactions with acrylonitrile. *p*-Anisidine, for example, forms *p*-chloroanisole in 32% yield by direct substitutive deamination and yields α-chloro-β-(*p*-anisyl)propionitrile in 32% yield by the process that involves acrylonitrile. Furthermore, the restriction placed upon substitutive deamination reactions regarding the use of arylamines possessing *p*-methyl substituents is also applicable to the Meerwein reaction: 2,4,6-trimethylaniline does not form the Meerwein product with acrylonitrile and the chloride substitution product, 2,4,6-trimethylchlorobenzene, is not observed as a side product in attempted arylation reactions with this amine.

Yields from the direct arylation of acrylonitrile are compared in Table I with reported yields of the same compounds by the usual two step Meerwein procedure in which the amine is first diazotized and then added to a buffered aqueous acetone solution containing copper(II) chloride and acrylonitrile (eq 7).[3] Although the reported yields for arylation reactions that employ this procedure are highly variable,[16] the comparative data in Table I show that the direct method (eq 6) is clearly superior to the procedure previously employed for the

Table II. Product Yields from Reactions of Arylamines and *tert*-Butyl Nitrite with Copper(II) Bromide and Acrylonitrile[a]

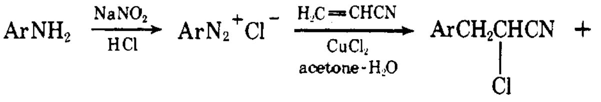
$ArNH_2$	Temp, °C	Isolated yield, %[b]				Recovered product
		ArBr	$ArBr_2$	$ArCH_2CHBrCN$	$BrArCH_2CHBrCN$	
$C_6H_5NH_2$	25	16	13[c]	57	7[e]	97[g]
p-$CH_3C_6H_4NH_2$	25	17	10[d]	39	16[f]	82
p-$CH_3C_6H_4NH_2$	5	25	9[d]	42	9[f]	84

[a] Reactions were performed as described in footnote *a* of Table I. [b] Absolute yield of products as determined by ^1H NMR and GLC analyses through comparison to an internal standard. [c] *p*-Dibromobenzene. [d] 3,4-Dibromotoluene. [e] α,*p*-Dibromo-β-(2-bromo-4-methylphenyl)propionitrile. [g] A 4% yield of 1,2,4-tribromobenzene was also obtained.

Table III. Yields of 2-Aryl-1-chloro-1-phenylethanes from Reactions of Arylamines and *tert*-Butyl Nitrite with Copper(II) Chloride and Styrene[a]

$ArNH_2$	$ArCH_2CHClC_6H_5$	Isolated yield, %[b] (eq 8)	Reported yield, % (eq 9)
p-$NO_2C_6H_4$-NH_2	p-$NO_2C_6H_4CH_2$-$CHClC_6H_5$	58	32[18]
p-ClC_6H_4-NH_2	p-$ClC_6H_4CH_2CHCl$-C_6H_5	57 (57)	41[18] (71)[19,c]
$C_6H_5NH_2$	$C_6H_5CH_2CHClC_6H_5$	53	23[18]
p-$CH_3C_6H_4$-NH_2	p-$CH_3C_6H_4CH_2$-$CHClC_6H_5$	51	

[a] Reactions were performed by adding 10.0 mmol of the amine to 15.0 mmol of *tert*-butyl nitrite and 12.0 mmol of anhydrous copper(II) chloride in 20 mL of styrene (0.175 mol) and 20 mL of acetonitrile. [b] Absolute yield of the Meerwein product as determined by ^1H NMR analysis through comparison to an internal standard. From duplicate runs experimentally determined percentage yields were accurate to within ±2% of the reported values. Isolated yield after purification by recrystallization is given in parentheses. [c] Yield of 2-(*p*-chlorophenyl)-1-chloro-1-phenylethane.



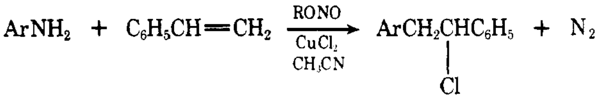
$$ArNH_2 \xrightarrow[HCl]{NaNO_2} ArN_2^+Cl^- \xrightarrow[\text{CuCl}_2,\ \text{acetone-H}_2\text{O}]{H_2C{=}CHCN} ArCH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCN + N_2 \qquad (7)$$

Meerwein reaction. The direct method shortcuts the preparation of the arenediazonium chloride, avoids the usual requirement for buffered solutions, and produces the Meerwein product in relatively high and predictable yield.

Use of the more reactive copper(II) bromide in place of copper(II) chloride for reactions of arylamines and *tert*-butyl nitrite with acrylonitrile gives mixtures of Sandmeyer and Meerwein products that include those from ring substitution by bromine.[1] Products and product yields from the arylation reactions that initiate from aniline and *p*-toluidine are given in Table II. In contrast to reactions that employ the anhydrous copper(II) chloride, those that use copper(II) bromide effect a high yield of Sandmeyer product and lead to substantial amounts of ring substitution products. Substitutive deamination is not effectively controlled by lowering the reaction temperature and, therefore, a general practical use of copper(II) bromide in arylation reactions by a direct procedure from arylamines and acrylonitrile is not presently feasible. However, the direct arylation procedure can be employed for deamination reactions of nitroanilines in the presence of copper(II) bromide and acrylonitrile; for example, *p*-nitroaniline yielded α-bromo-β-(*p*-nitrophenyl)propionitrile in 53% yield when reaction conditions identical with those described in Table I were used.

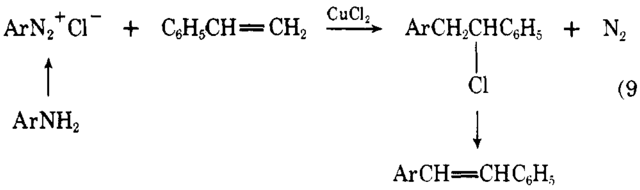
Variation of the reaction solvent from acetonitrile to acetone did not noticeably affect product yields in arylation reactions with acrylonitrile. In reactions run under conditions identical with those whose results are reported in Table I, but with acetone rather than acetonitrile as the solvent, aniline gave α-chloro-β-phenylpropionitrile in 65% yield and *p*-aminoacetophenone formed the corresponding Meerwein product in 78% yield.

Acrylonitrile is a reactive olefinic substrate and yields of the Meerwein products from arylations of acrylonitrile are generally high. Styrene, on the other hand, although not significantly affecting the rates of nitrogen evolution in the Meerwein reaction,[5b,6,7a] is a less reactive olefinic substrate. Product yields from arylation of styrene are significantly lower than those from arylation of acrylonitrile,[17,18] and this fact presents an identifiable synthetic challenge for the direct procedure of arylation. Reactions of arylamines with *tert*-butyl nitrite, copper(II) chloride, and styrene in acetonitrile at 25 °C result in the formation of 2-aryl-1-chloro-1-phenylethanes (eq 8). Isolated yields from representative reactions are presented in Table III. Noteworthy is the absence of stilbenes in these reactions; stilbenes are products normally obtained in the two-step Meerwein procedure.[18,19] Table III compares the yields of 2-aryl-1-chloro-1-phenylethanes (eq 8) with the



$$ArNH_2 + C_6H_5CH{=}CH_2 \xrightarrow[\text{CuCl}_2,\ \text{CH}_3\text{CN}]{RONO} ArCH_2\underset{\displaystyle Cl}{\underset{|}{C}}HC_6H_5 + N_2 \qquad (8)$$

corresponding yields of stilbene products that are formed from arylamines by the scheme outlined in eq 9.



$$\begin{array}{l} ArN_2^+Cl^- + C_6H_5CH{=}CH_2 \xrightarrow{CuCl_2} ArCH_2\underset{\displaystyle Cl}{\underset{|}{C}}HC_6H_5 + N_2 \\ \uparrow \\ ArNH_2 \qquad\qquad\qquad\qquad \downarrow \\ \qquad\qquad\qquad\qquad\qquad ArCH{=}CHC_6H_5 \end{array} \qquad (9)$$

Substitutive deamination is the major competing reaction in the direct process for arylation of styrene. The Sandmeyer products from deamination of *p*-nitroaniline (*p*-chloronitrobenzene, 23%) and *p*-chloroaniline (*p*-dichlorobenzene, 18%) in the presence of a 17.5 molar excess of styrene, for example, are the only compounds observed in greater than 3% yield. These data, when compared with similar results from arylation reactions with acrylonitrile, indicate that styrene is indeed a less reactive olefinic substrate than acrylonitrile. As was the case for reactions with acrylonitrile, polymerization of styrene does not occur in deamination reactions that employ anhydrous copper(II) chloride and *tert*-butyl nitrite.

Isolated yields of the Meerwein and Sandmeyer products from deamination reactions of *p*-nitroaniline in the presence of selected olefins are given in Table IV. The successful employment of acrylamide in the direct arylation procedure is notable since previous attempts to use this and related amides in the Meerwein procedure were unsuccessful.[3] These results indicate that the direct arylation procedure is potentially applicable to syntheses involving the wide range of olefinic substrates which have previously been successfully employed

Table IV. Product Yields from Reactions of *p*-Nitroaniline and *tert*-Butyl Nitrite with Copper(II) Chloride and Conjugated Olefins[a]

Registry no.	Olefin	Arylation product	Yield, %[b]	p-$NO_2C_6H_4Cl$ yield, %[c]
107-13-1	$H_2C{=}CHCN$	p-$NO_2C_6H_4CH_2CHClCN$	(93)	0
140-88-5	$H_2C{=}CHCOOCH_2CH_3$	p-$NO_2C_6H_4CH_2CHClCOOCH_2CH_3$	70	16
79-06-1	$H_2C{=}CHCONH_2$	p-$NO_2C_6H_4CH_2CHClCONH_2$	49[d]	18
100-42-5	$H_2C{=}CHC_6H_5$	p-$NO_2C_6H_4CH_2CHClC_6H_5$	58	23

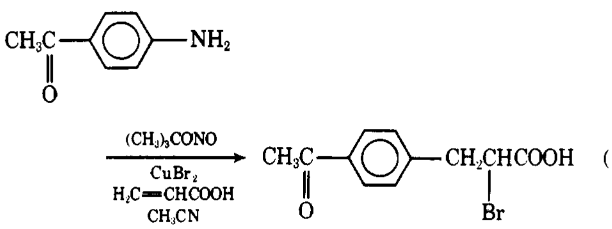
[a] Reactions were performed by adding 10.0 mmol of the amine to 15.0 mmol of tert-butyl nitrite and 12.0 mmol of anhydrous copper(II) chloride in 20 mL of the olefinic substrate and 20 mL of acetonitrile. [b] Absolute yield of the Meerwein product as determined by ^1H NMR analysis through comparison to an internal standard. From duplicate runs experimentally determined percentage yields were accurate to within ±2% of the reported values. Isolated yield after purification by recrystallization is given in parentheses. [c] Absolute yield of the Sandmeyer product as determined by GLC analysis through comparison to an internal standard. [d] Product recrystallized from chloroform, mp 143.0–144.5 °C.

Table V. ^1H NMR Absorptions of Meerwein Products Formed by the Direct Arylation Procedure

Registry		Chemical shift, δ[a]			
no.	$ArCH_2CHXZ$	Ar	CH_2	CH	Z
17849-31-9	p-$NO_2C_6H_4CH_2CHClCN$	8.40–8.15 (m, 2 H) 7.70–7.45 (m, 2 H)	3.47 (d)	4.72 (t)	
62448-25-3	p-$NO_2C_6H_4CH_2CHBrCN$	8.40–8.15 (m, 2 H) 7.70–7.45 (m, 2 H)	3.53 (d)	4.57 (t)	
17849-30-7	m-$NO_2C_6H_4CH_2CHClCN$	8.40–8.00 (m, 2 H) 7.80–7.30 (m, 2 H)	3.40 (d)	4.72 (t)	
62448-26-4	p-$CH_3COC_6H_4CH_2CHClCN$[b]	8.15–7.85 (m, 2 H) 7.60–7.30 (m, 2 H)	3.40 (d)	4.68 (t)	
17849-64-8	p-$ClC_6H_4CH_2CHClCN$	7.55–7.15 (m, 4 H)	3.28 (d)	4.58 (t)	
17849-62-6	$C_6H_5CH_2CHClCN$	7.45–7.30 (m, 5 H)	3.32 (d)	4.59 (t)	
62448-27-5	$C_6H_5CH_2CHBrCN$[c]	7.38 (s, 5 H)	3.38 (d)	4.42 (t)	
62448-28-6	p-$BrC_6H_4CH_2CHBrCN$[c]	7.70–7.10 (m, 4 H)	3.25 (d)	4.40 (t)	
3909-19-1	p-$HH_3C_6H_4CH_2CHClCN$[d]	7.22 (s 4 H)	3.17 (d)	4.48 (t)	
62448-29-7	p-$CH_3C_6H_4CH_2CHBrCN$[c,e]	7.21 (s, 4 H)	3.32 (d)	4.38 (t)	
62448-30-0	2-Br, 4-$CH_3C_6H_3CH_2CHBrCN$[c,d]	7.55–7.15 (m, 3 H)	3.48 (d)	4.75–4.45 (m)	
17849-23-9	p-$CH_3OC_6H_4CH_2CHClCN$[f]	7.40–6.80 (m, 4 H)	3.19 (d)	4.48 (t)	
27916-99-0	2,4,6-$Cl_3C_6H_2CH_2CHClCN$	7.43 (s, 2 H)	3.88–3.58 (m)	4.83 (t)	
4781-42-4	p-$NO_2C_6H_4CH_2CHClC_6H_5$	8.20–7.95 (m, 2 H) 7.45–7.20 (m, 2 H)	3.38 (d)	5.07 (t)	7.31 (s, 5 H)
4714-17-4	p-$ClC_6H_4CH_2CHClC_6H_5$	7.30–6.85 (m, 4 H)	3.28 (d)	5.00 (t)	7.31 (s, 5 H)
4714-14-1	$C_6H_5CH_2CHClC_6H_5$	7.50–7.30 (m, 5 H)	3.29 (d)	4.99 (t)	7.37 (s, 5 H)
4714-15-2	p-$CH_3C_6H_4CH_2CHClC_6H_5$[g]	7.41 (s, 4 H)	3.32 (d)	5.02 (t)	7.33 (s, 5 H)
57460-34-1	p-$NO_2C_6H_4CH_2CHClCOOCH_2CH_3$	8.30–8.00 (m, 2 H) 7.45–7.25 (m, 2 H)	3.45–3.25 (m)	4.38 (t)	OCH_2, 4.25 (g) CH_3, 1.27 (t)
18166-61-5	p-$NO_2C_6H_4CH_2CHClCONH_2$[h]	8.35–8.05 (m, 2 H) 7.75–7.45 (m, 2 H)	3.50–3.15 (m)	4.85–4.50 (m)	NH_2, 7.37 (broad δ)
18910-19-5	p-$CH_3COC_6H_4CH_2CHBrCOOH$[b]	8.05–7.85 (m, 2 H) 7.50–7.30 (m, 2 H)	3.55–3.25 (m)	4.47 (t)	

[a] Relative to internal Me_4Si in $CDCl_3$; temperature 37 °C. [b] CH_3CO at δ 2.58 (s). [c] Product isolated by GLC separation. [d] p-CH_3 at δ 2.33 (s). [e] p-CH_3 at δ 2.35 (s). [f] CH_3O at δ 3.83. [g] p-CH_3 at δ 2.29 (s). [h] Spectrum taken in Me_2SO-d_6.

in the Meerwein reaction.[3]



(10)

The synthesis of *p*-acetyl-α-bromohydrocinnamic acid was performed by the direct arylation procedure (eq 10) in order to provide a critical comparison of this method to that of the tested Meerwein procedure.[20] Use of 2 molar equiv of acrylic acid relative to *p*-aminoacetophenone resulted in the formation of *p*-acetyl-α-bromohydrocinnamic acid in 32% yield by the direct arylation procedure. However, when a 14.7-fold molar excess of acrylic acid was employed, the Meerwein product was isolated in 59% yield (55% yield after recrystallization). This same compound was prepared in 61–67% yield by sequential diazotization and reaction with copper(I) bromide and a 14.7-fold molar excess of acrylic acid (the Meerwein procedure).[20] Although results were presented earlier that showed copper(II) bromide to be inferior to copper(II) chloride in direct arylation reactions, and no attempt was made to optimize reaction conditions for the synthesis described by eq 10, the yields of *p*-acetyl-α-bromohydrocinnamic acid by these two procedures were comparable.

If copper(I) chloride is substituted for copper(II) chloride in the procedure for direct arylation, the Meerwein product is not obtained. In contrast, copper(I) halides have been successfully employed for Meerwein reactions that are performed in acetone.[5,6,21] However, for reactions of *p*-toluidine with *tert*-butyl nitrite in equal volumes of acrylonitrile and acetonitrile under conditions identical with those reported in Table I, the use of copper(I) chloride did not result in the formation of the corresponding Meerwein product. Similarly, the Meerwein product is not obtained from reactions in which an aliphatic amine is substituted for an arylamine; benzylamine, for example, yields only those products that were previously observed in reactions with *tert*-butyl nitrite and copper(II) chloride that occurred in the absence of acrylonitrile.[22]

Experimental Section

General. Instrumentation has been previously described.[1] Anhydrous cupric chloride and cupric bromide were obtained commercially and were dried in an oven at 110 °C prior to use. Anhydrous cuprous chloride was prepared from cupric chloride dihydrate.[23] Aniline and *p*-anisidine were purified prior to use. *tert*-Butyl nitrite was prepared from *tert*-butyl alcohol according to the procedure of Noyes.[24] Reagent grade acetonitrile was distilled from calcium hydride prior to its use as a reaction solvent. Acetone, acrylonitrile, and acrylic acid were distilled prior to use.

Direct Arylation of Olefins. General Procedure. In the procedure employed for the reactions that were run on a small scale anhydrous copper(II) halide (12 mmol), *tert*-butyl nitrite or isopentyl nitrite (15 mmol), the olefinic substrate (20 mL), and anhydrous acetonitrile (20 mL) were added to a three-necked round-bottom flask that was equipped with a reflux condenser, addition funnel or solid inlet tube, and a gas outlet tube. The resulting mixture was rapidly stirred at room temperature (23 ± 2 °C). The amine in 2 mL of acetonitrile (for liquid or acetonitrile-soluble amines) or as a solid was slowly added over a period of 5 min to the reaction solution. During the amine addition the reaction temperature remained below 30 °C and the reaction solution turned completely black from the initial green ($CuCl_2$) or black ($CuBr_2$) color as nitrogen was evolved. Total gas evolution was measured on the closed system by water displacement from a calibrated gas buret; with the exception of 2,4,6-trimethylaniline, the yield of gaseous products in these reactions was 220 ± 20 mL (based on 10 mmol of the limiting reagent). Gas evolution was generally complete within 15 min following the additon of the amine. After complete gas evolution the reaction solution was poured into 200 mL of 20% aqueous hydrochloric acid and extracted with 200 mL of ether, and the organic layer was washed once with 200 mL of 20% aqueous hydrochloric acid. The resulting ether solution was dried over anhydrous magnesium sulfate and the ether and excess of low-boiling olefinic substrate were removed under reduced pressure. Styrene was fractionally distilled through a 12.5-cm Vigreux column under reduced pressure.

Product Analyses. Reactions of copper(II) chloride with a two- to fourfold molar excess of *p*-nitroaniline or aniline, *tert*-butyl nitrite, and a corresponding excess of acrylonitrile produced a black, granular powder having a light green tint. The reaction mixtures were filtered following complete gas evolution and prior to workup in aqueous acid. The isolated solids were washed with benzene and then dried in an oven for 2 h at 110 °C. The resulting powders were subjected to x-ray powder analysis which gave no evidence for the presence of either of the structurally defined copper oxides or copper chlorides. No further attempt to define the structure of the copper product was made.

Structural assignments for the Meerwein products produced in reactions of arylamines with alkyl nitrites and copper(II) halides in the presence of olefinic substrates were made on the reaction solutions by ^1H NMR spectral analyses (Table V). Product yields for Meerwein products were determined through the use of either dibenzyl ether or 1,2-dibromoethane as the internal standard in ^1H NMR analyses. Absolute yields were calculated from integrations of the individual and characteristic absorption signals of the reaction products and of the internal standard; the average values of at least five integrations were utilized in these yield determinations.

Structural assignments for aryl halides produced in these arylation reactions were generally made on the reaction solutions by GLC retention time and peak enhancement comparisons with authentic samples.[1] *p*-Bromotoluene and 3,4-dibromotoluene were isolated by GLC separations and their identity was confirmed by ^1H NMR spectral analyses. The yields of aryl halides were determined by GLC analyses through the use of an internal standard. Absolute yields were calculated with the use of experimentally determined thermal conductivity ratios.

α-Chloro-β-(*p*-nitrophenyl)propionitrile. *p*-Nitroaniline (13.8 g, 0.100 mol) dissolved in 100 mL of anhydrous acetonitrile was added dropwise over a 30-min period to a rapidly stirred mixture of anhydrous copper(II) chloride (16.0 g, 0.120 mol) and *tert*-butyl nitrite (15.5 g, 0.150 mol) in 125 mL of acetonitrile and 125 mL of freshly distilled acrylonitrile (1.9 mol). The rate of addition of *p*-nitroaniline to the stirred mixture at room temperature was determined by the rate of gas evolution; gas evolution was complete within 30 min following the last addition of the amine to the reaction mixture. After complete gas evolution the black reaction mixture was poured into 400 mL of 20% aqueous hydrochloric acid and extracted twice with 200-mL portions of ether. The combined ether solution was dried over anhydrous magnesium sulfate and the organic layer was concentrated under reduced pressure to yield 21.9 g of a yellow-brown solid. Recrystallization from methanol gave 19.5 g of colorless needles of α-chloro-β-(*p*-nitrophenyl)propionitrile (0.093 mol, 93% yield) having mp 118–119 °C (lit.[13] mp 111–112 °C).

α,*p*-Dichloro-β-phenylpropionitrile. *p*-Chloroaniline (12.75 g, 0.100 mol) dissolved in 30 mL of anhydrous acetonitrile was added dropwise over a 30-min period to a rapidly stirred mixture of anhydrous copper(II) chloride (16.1 g, 0.120 mol) and *tert*-butyl nitrite (15.5 g, 0.150 mol) in 60 mL of acetonitrile and 100 mL of freshly distilled acrylonitrile (1.5 mol). The reaction flask was cooled by means of an ice bath during the addition in order to prevent the reaction temperature from rising above 30 °C. Gas evolution was complete within 10 min following the last addition of *p*-chloroaniline. After complete gas evolution the black reaction mixture was poured into 400 mL of 20% aqueous hydrochloric acid and extracted with 400 mL of ether. The organic layer was washed once with 400 mL of 20% aqueous hydrochloric acid, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 17.5 g of a brown liquid. Distillation of this liquid at 0.3 Torr yielded 0.6 g of *p*-dichlorobenzene (bp 60 °C) and 14.2 g (0.071 mol, 71% yield) of the yellow liquid α,*p*-dichloro-β-phenylpropionitrile, bp 130–135 °C (lit.[5a] bp 128–132 °C at 5 Torr).

2-(*p*-Chlorophenyl)-1-chloro-1-phenylethane. *p*-Chloroaniline (12.8 g, 0.100 mol) dissolved in 20 mL of anhydrous acetonitrile was added dropwise over a 30-min period to a rapidly stirred mixture of anhydrous copper(II) chloride (16.1 g, 0.120 mol) and *tert*-butyl nitrite (15.5 g, 0.150 mol) in 60 mL of acetonitrile and 150 mL of styrene (1.3 mol). The previous procedure was followed and, after removal of the ether and distillation of the excess styrene, 24.6 g of an orange liquid was obtained. Crystallization from pentane yielded 14.3 g of crystalline 2-(*p*-chlorophenyl)-1-chloro-1-phenylethane (0.057 mol, 57% yield),[25] mp 73–75 °C (lit.[5a] mp 75–76 °C).

***p*-Acetyl-α-bromohydrocinnamic Acid.** *p*-Aminoacetophenone (13.57 g, 0.100 mol) dissolved in 60 mL of anhydrous acetonitrile was added dropwise over a 30-min period to a rapidly stirred mixture of anhydrous copper(II) bromide (27 g, 0.120 mol) and *tert*-butyl nitrite (15.5 g, 0.150 mol) in 50 mL of acetonitrile and 100 mL of freshly distilled acrylic acid (1.47 mol). The reaction flask was cooled by means of an ice bath during the addition in order to maintain a reaction temperature of 25–26 °C. Gas evolution was complete within 10 min following the last addition of *p*-aminoacetophenone. After complete gas evolution the reaction mixture was poured into 500 mL of 20% aqueous hydrochloric acid and extracted with 500 mL of a 1:1 ether–benzene combination. The organic layer was washed twice with 200-mL portions of 20% aqueous hydrochloric acid and then was dried over anhydrous magnesium sulfate. The organic solvent was removed under reduced pressure to yield 36 g of an orange-yellow solid. This precipitate was filtered under vacuum and then recrystallized from a 2:3 (v/v) formic acid–water mixture to yield 15.0 g of light yellow needles of *p*-acetyl-α-bromohydrocinnamic acid (0.055 mol, 55% yield), mp 152–156 °C (lit.[20] mp 159–161 °C). The ^1H NMR spectrum of this solid (Table V) corresponded to the reported spectrum of *p*-acetyl-α-bromohydrocinnamic acid in trifluoroacetic acid.[20] An additional 1.7 g of impure product was obtained after concentration of the filtrate but was not further purified.

A similar reaction was performed using only 16 g of acrylic acid (0.22 mol) in 200 mL of anhydrous acetonitrile. However, only 8.3 g of the white, crystalline Meerwein product (32% yield) could be obtained when the above reaction procedure was employed.

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Registry No.—*tert*-Butyl nitrite, 540-80-7; copper(II) chloride, 7447-39-4; acrylonitrile, 107-13-1; copper(II) bromide, 7789-45-9.

References and Notes

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Design of Chiral Derivatizing Agents for the Chromatographic Resolution of Optical Isomers. Asymmetric Synthesis of Some Chiral Fluoroalkylated Amines

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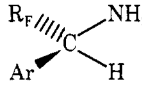
A general approach for the asymmetric synthesis of type **1** fluoroalkylated amines is described and an assignment of absolute configuration is made for 2,2,2-trifluoro-1-phenylethylamine (**2**). Amine **2** is obtained in high yield and >80% ee by reducing chiral imine **5** with sodium bis(2-methoxyethoxy)aluminum hydride with subsequent catalytic hydrogenolysis over palladium on charcoal. Catalytic hydrogenolysis of secondary amine **6** proceeds with complete regioselectivity owing to the retarding effect of the α-trifluoromethyl group upon the rate of hydrogenolysis of benzylamine. Fluoro amine **2** is evaluated as a chiral derivatizing agent (CDA) for the chromatographic resolution of racemic alcohols. Relative to the diastereomeric carbamates derived from menthol or 2-octanol and the nonfluorinated analogues of **2**, those derived from **2** show greater chromatographic separability and an inverted elution order.

Recently, we reported the resolution of 2,2,2-trifluoro-1-(1-naphthyl)ethanol via the multigram chromatographic separation of diastereomeric carbamate derivatives[1] and in a subsequent paper elaborated a rationale which provides insight into the reasons underlying the chromatographic separability of diastereomeric carbamates.[2] On the basis of this rationale, we are endeavoring to design chiral derivatizing agents (CDA) that will confer still greater chromatographic separability upon the diastereomeric adducts of racemates. Although chiral type 1 fluoroalkylamines are of general interest in this context, we specifically desired 2,2,2-trifluoro-1-phenylethylamine (**2**), since the aforementioned chromatographic rationale suggests strongly that diastereomeric carbamates derived from this amine should show greater chromatographic separability and inverted elution order when compared to those derived from nonfluorinated analogues, such as 1-phenylethylamine (**3**) or 1-(1-naphthyl)ethylamine (**3a**).[3]



1

We presently describe the asymmetric synthesis, assignment of absolute configuration, and preliminary chromatographic evaluation of **2** as a CDA and demonstrate that the synthetic scheme utilized is applicable for a series of structurally related amines.

Initial efforts to prepare racemic **2** from phenyl trifluoromethyl ketone (**4**) by Leuckart reductive amination or through the use of sodium cyanoborohydride and ammonium acetate in methanol[4] were fruitless. While ammonia readily adds to this ketone to afford the carbinolamine, the latter is very resistant to dehydration to the imine. Nevertheless, lithium aluminum hydride converts the carbinolamine to racemic **2** in ca. 30% yield. In an alternate approach, the tosylate of 2,2,2-trifluoro-1-phenylethanol was found to react with ammonia at 130 °C and 6 kbar pressure although it is resistant to aminolysis at ordinary pressures. The Curtius sequence on 3,3,3-trifluoro-2-phenylpropionic acid also affords **2**; however, the effort required, as well as the low overall yield (from **4**), makes this route unattractive.

A more direct approach to chiral **2** is shown in Scheme I and involves asymmetric reduction of imine **5**, derived from ketone **4** and the readily available chiral 1-phenylethylamine (**3**). This approach is similar to that of Overberger et al.,[5] who showed