Pergamon

Tetrahedron Letters, Vol. 37, No. 40, pp. 7213-7216, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01620-6

The Reaction of 4-Substituted Aroyl Azides with NaBH4/TFA

Douglas M. Krein, Pamela J. Sullivan[1] and Kenneth Turnbull*

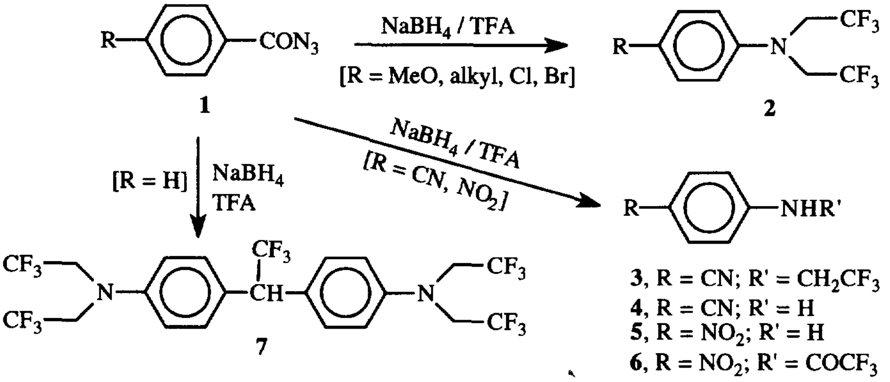
Department of Chemistry, Wright State University, Dayton, Ohio 45435, U.S.A.

Abstract: Treatment of 4-substituted aroyl azides (*cf.* **1a-e**) with $NaBH_4$ / TFA leads to the corresponding, novel 4-substituted N,N-di(2,2,2-trifluoroethyl)aniline derivatives (**2a-e**) in excellent yield except where electron-withdrawing groups are present (*cf.* **1f-g**). Copyright © 1996 Elsevier Science Ltd

Reduction of alkyl, aryl and vinyl azides to the corresponding amines has been effected with a variety of reagents[2], however, the analogous transformation of acyl azides ($R\text{-}CON_3$) to primary amides has been little studied. Not surprisingly, from the limited data available, it appears that the carbonyl group can have a marked effect upon the reactivity of the azide moiety. Thus, Rao[3] has shown that acyl azides react with sodium borohydride to give the corresponding primary alcohols rather than the appropriate amides. In some cases, however, amide products did result from treatment of 4-substituted aroyl azides with $NaBH_4$ / $NiCl_2$.[4]

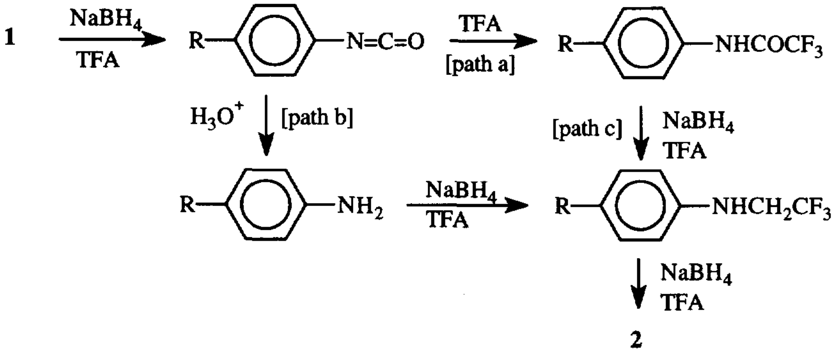
Our interest in this area stemmed from the prospect that an acyl azide could undergo **tandem** reduction to an aminomethyl (CH_2NH_2) functionality. It appeared that $NaBH_4$ in TFA might be an appropriate reagent for this purpose since $NaBH_4$ is known to reduce azides to amines[5] (and acyl azides to amides in the presence of $NiCl_2$, *vide infra*) and amides can be transformed to alkylamines using $NaBH_4$ in TFA.[6] However, it was likely that this approach would only be effective if initial reduction to an amide followed by carbonyl reduction occurred, rather than *vice versa* wherein the intact azido group could function as a leaving group. Complications could also arise if acid-induced acyl azide rearrangement preceded reduction.

To test these aspects, a series of 4-substituted aroyl azides **1** was prepared[7] and each azide was subjected to reduction with $NaBH_4$ (pellets) in TFA at room temperature. Where the *para* substituent was electron donating (*viz.* **1c-e**) or weakly electron withdrawing (*viz.* **1a-b**) slow (4 days), but efficient, transformation (72-91%) to the corresponding N,N-(di-2,2,2-trifluoroethyl)aniline derivatives **2** was observed.



3, R = CN; R' = CH_2CF_3
4, R = CN; R' = H
5, R = NO_2; R' = H
6, R = NO_2; R' = $COCF_3$

The mechanism of this novel transformation is unclear, but presumably involves acid catalyzed Curtius rearrangement to the isocyanate followed by either solvent induced transformation to the trifluoroacetamido species ($RNHCOCF_3$)[9] [path a] or cleavage to the primary amine by adventitious water [path b] (Scheme 1). The latter seems feasible since Gribble and coworkers have reported[10] the conversion of some primary amines to N,N-dialkyl derivatives using $NaBH_4$ / RCO_2H. However, one also can envisage a pathway involving reduction of a trifluoroacetamido species to a trifluoroethylamine ($RNHCH_2CF_3$) [path c] followed by the same acylation / reduction process as must be involved in the initial conversion of the primary amine to **2**.



Scheme 1 Possible mechanistic routes to N,N-di(2,2,2-trifluoroethyl)aniline derivatives **2**

It is possible that both mechanisms are operative and support for this conjecture comes from the results of the reactions with aroyl azides containing resonance withdrawing groups on the aryl ring. Thus, the corresponding reductions of 4-cyanobenzoyl azide (**1f**) and 4-nitrobenzoyl azide (**1g**) were much more sluggish than those for the other acyl azides **1a-e** examined; the nitro species **1g** took 2 weeks for complete conversion, and in neither case was the corresponding aniline **2** obtained. Correspondent to the electron withdrawing effects of the groups concerned, the major product from the 4-cyano species **1f**, *viz*. N-(2,2,2-trifluoroethyl)aniline (**3**) [56% yield] (4-cyanoaniline (**4**) also was formed in 39% yield), is clearly further along the path towards the ditrifluorethyl species **2** than from the 4-nitro azide **1g** where the major product is 4-nitroaniline (**5**) [62%], with a smaller amount (36%) of 4-nitro-N-trifluoroacetylaniline (**6**).

Interestingly, where the *para* position of the aroyl azide is open, further reductive acylation can occur. Thus, under the standard conditions, benzoyl azide **1h** gave 2,2-(bis (4-[N,N-(di-2,2,2-trifluoroethyl)anilino])-1,1,1-trifluoroethane (**7**) in 87% yield. A similar Friedel-Crafts alkylation / reductive acylation of indoline has been reported using the same reagents.[11]

The identities of the products (**2a-3, 7**) were ascertained from their satisfactory spectral (IR, ^{1}H and ^{13}C NMR, mass) and microanalytical data. The main features of their IR spectra were the strong absorptions at *ca.* 1100-1200 cm^{-1} for C-F stretch and the absence of the characteristic absorptions for the carbonyl and azido functionalities at around 1700 cm^{-1} and 2200 cm^{-1}, respectively. The proton NMR spectra for **2a-e**, in each case, displayed F-H coupling for the CF_3CH_2 group resulting in a quartet (~ 4δ) for the CH_2 moiety and a pattern of two 2H doublets (*ca.* 6.8 δ and *ca.* 7-7.4 δ) indicative of *para*-disubstitution. In their ^{13}C-NMR spectra, the most definitive signals were those for the CF_3 carbon (quartet, J = ~280 Hz, centered ~125 ppm) and the adjacent CH_2 carbon (quartet, J = ~33 Hz, centered ~52 ppm). Similar trends were observed for compounds **3** and **7**.

Overall, with the limitations described, we have developed a useful preparation of N,N-(ditrifluoroethyl)-anilines and related species (formally from carboxylic acids) and we plan to investigate further the scope and mechanism of these novel reactions.

Table 1. Reactions of 4-Substituted Aroyl Azides **1** with $NaBH_4$ / TFA

1	R	Product[a]	Yield (%)	mp(°C)
a	Br	**2a**	88	83.5-4.5
b	Cl	**2b**	91	73-4
c	Me	**2c**	87	72-3
d	MeO	**2d**	88	oil
e	^{t}Bu	**2e**	72	oil
f	CN	**3**	56	116-8
		4	39	85-6[12]
g	NO_2	**5**	62	150-1[12]
		6	36	147-9[13]
h	H	**7**	87	82-3

[a]All new compounds were fully characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and combustion analysis

General Procedure

To trifluoroacetic acid (25 mL) was added sodium borohydride (pellets, each ~0.4g) with stirring. After complete dissolution, the aroyl azide (0.001 mol) was added and, after 24 h, an additional pellet (broken into 4 pieces) was added and the mixture was stirred for a further 72 h. After cooling to 0°C the mixture was made basic with aqueous sodium hydroxide (15%, w/v) and extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo* to yield a slightly impure product which was purified by column chromatography (silica gel, hexane / dichloromethane (usually 80:20) as eluant).

Acknowledgement

The authors would like to thank Chris R. Gelvin for conducting some initial experiments and H.S.P. Rao for valuable discussions.

References and Notes

1. Current address: H.B. Fuller Company, Packaging Converting Group, 311 South Hicks Road, Palatine, IL 60067.
2. Scriven, E.F.V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.
3. Rao, H.S.P. *Synth. Commun.* **1990**, *20*, 45.
4. Rao, H.S.P.; Reddy, K.S.; Turnbull, K.; Borchers, V. *Synth. Commun.* **1992**, *22*, 1339.
5. Rolla, F. *J. Org. Chem.* **1982**, *47*, 4327.
6. Umino, N.; Iwakuma, T.; Itoh, M. *Tetrahedron Lett.* **1976**, 763.
7. Munch-Peterson, J. *Org. Synth., Coll. Vol.* **1963**, *4*, 715.
8. Smith, P.A.S. *Org. Reactions* **1947**, *3*, 337.
9. Pfister, J.R.; Wymann, W.E. *Synthesis* **1983**, 38.
10. Gribble, G.W.; Jasinski, J.M.; Pellicone, J.T.; Panetta, J.A. *Synthesis* **1978**, 766.
11. Gribble, G.W.; Nutaitis, C.F.; Leese, R.M. *Heterocycles* **1984**, *22*, 379.
12. Identical to an authentic sample obtained from the Aldrich chemical company.
13. Staab, H.A.; Walther, G. *Chem. Ber.* **1962**, *95*, 2070.

(*Received in USA* 28 *June* 1996; *accepted* 1 *August* 1996)