Synthetic Equivalents

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4-Substituted *tert*-Butyl Phenylazocarboxylates—Synthetic Equivalents for the *para*-Phenyl Radical Cation**

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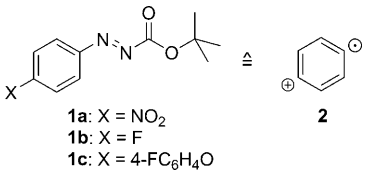
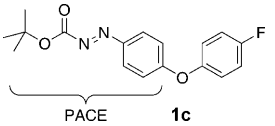
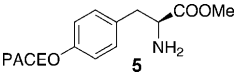
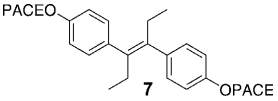
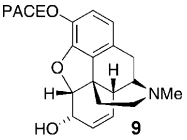
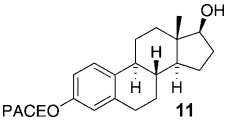
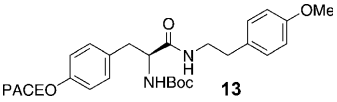
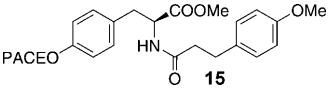
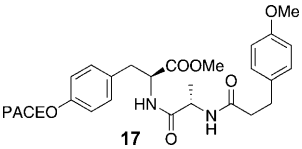
Dedicated to Professor Samir Z. Zard on the occasion of his 55th birthday

Broadly applicable bifunctional synthetic building blocks are of high value not only for the preparation of single molecules but also for the modular assembly of structurally diverse compound libraries.[1] Along the lines of our recent work in the field of aryl radical chemistry,[2,3] we turned our interest towards derivatives of benzene, in which the aromatic core could be selectively modified by a nucleophilic substitution[4–7] as well as by a radical reaction. Herein we present the results of our first investigation concerning 4-substituted *tert*-butyl phenylazocarboxylates (**1a–c**) as synthetic equivalents of the *para*-phenyl radical cation (**2**).



The azocarboxylates **1a** and **1b** were prepared in two steps from 4-nitro- and 4-fluorophenylhydrazine, respectively, by reaction with di-*tert*-butyl dicarbonate and subsequent oxidation with manganese dioxide.[8,9] To our knowledge, no examples have been reported for the selective nucleophilic substitution of **1a–c** or analogous esters. Importantly, under the given reaction conditions the nucleophilic attack should not occur at either the N=N bond[10] or at the carbonyl moiety of the aryl azocarboxylate.[11–13] In a first study, we therefore investigated the reactivity of different nucleophiles towards the nitro compound **1a**.[14,15] It became apparent that phenolates are particularly suitable reagents for the selective substitution of the nitro group. The desired diphenyl ethers were obtained as reaction products under surprisingly mild conditions (Table 1). Comparably simple nucleophilic substitutions were observed for aliphatic amines in combination with Sanger's reagent[16] and with activated Fukuyama-type protecting groups.[17,18]

Table 1: Synthesis of 4-phenylazocarboxylic acid *tert*-butyl ester (PACE) phenyl ethers from **1a** and phenolates.

Entry	Phenol	PACE ether	Yield [%]
1	4-fluorophenol (**3**)	 **1c**	74[a]
2	L-tyrosine methyl ester (**4**)	 **5**	61[b]
3	diethylstilbestrol (**6**)	 **7**	45[a]
4	morphine (**8**)	 **9**	81[b]
5	estradiol (**10**)	 **11**	quant.[a]
6	tyrosine derivative (**12**)	 **13**	70[a]
7	tyrosine derivative (**14**)	 **15**	quant.[a]
8	tyrosine derivative (**16**)	 **17**	66[b]

[a] Reaction conditions: Cs_2CO_3 (5.0 equiv), K_2CO_3, DMF, RT. [b] K_2CO_3 (5.0 equiv), [18]crown-6 (5.0 equiv), DMF, RT.

Because the products are colored, the reactions summarized in Table 1 could be monitored easily by thin-layer chromatography. At room temperature, the formation of the diphenyl ethers was usually complete within a few hours. The conversion of morphine (**8**) to its diphenyl ether derivative **9** was possible by changing the standard conditions (Cs_2CO_3 in DMF) to potassium carbonate in the presence of [18]crown-6. Several control experiments revealed that primary or secon-

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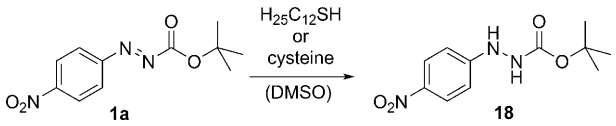
dary amines do not interfere with the phenyl ether synthesis (Table 1, entry 2). As an example, azo compound **1a** remained stable in the presence of *n*-butyl amine for more than 24 h. With thiols, in contrast, **1a** was readily reduced to hydrazine **18** (Scheme 1).[19] The unique influence of the nitro

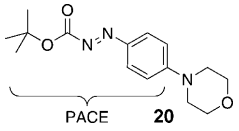
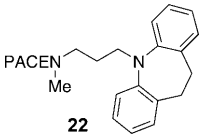
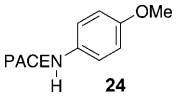
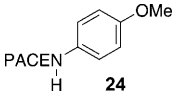
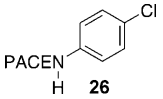


Scheme 1. Selective reduction of nitro compound **1a**. The fluoro compound **1b** does not react under these conditions.

group further became evident by the observation that only **18** was formed from a 1:1 mixture of **1a** and **1b** in the presence of dodecane thiol or cysteine while the fluorinated compound **1b** remained unchanged. Thiols can therefore be used to selectively remove an excess of reagent **1a** after completion of a diphenyl ether synthesis.

Besides the nitro compound **1a**, the fluorinated phenylazocarboxylate **1b** were successfully substituted by aliphatic amines such as morpholine (**19**) and desipramine (**21**). (Table 2, entries 1 and 2). In comparison to known reagents[16] the azocarbonyl moiety in **1** again proved to be a highly activating substituent for nucleophilic aromatic substitutions.[20]

Table 2: Nucleophilic substitution of **1b** and **1c** with aliphatic and aromatic amines.

Entry	Reactants	Product	Yield [%]
1	**1b** + morpholine (**19**)	 PACE **20**	90[a]
2	**1b** + desipramine (**21**)	 PACEN, Me **22**	92[a]
3	**1b** + *p*-anisidine (**23**)	 PACEN, OMe **24**	0[a]
4	**1c** + *p*-anisidine (**23**)	 PACEN, OMe **24**	74[b]
5	**1c** + *p*-chloroaniline (**25**)	 PACEN, Cl **26**	53[c]

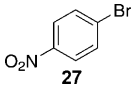
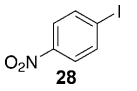
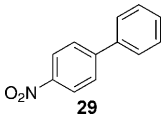
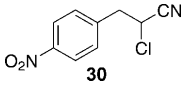
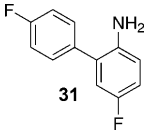
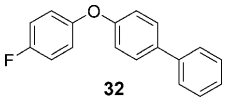
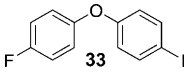
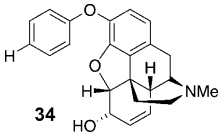
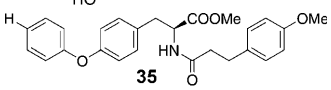
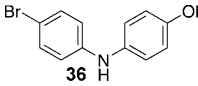
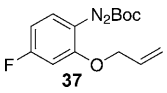
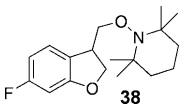
[a] Reaction conditions: DMF, RT. [b] CF_3COOH, CH_3CN, 80°C. [c] CF_3COOH, CH_3CN, RT.

The aromatic amine *para*-anisidine (**23**), however, did not react with **1b** under the conditions that had been suitable for the reactions of **19** and **21** (Table 2, entry 3). The preparation of the desired diaryl amine **24** was instead achieved using diphenyl ether **1c** (Table 1, entry 1) in combination with the trifluoroacetate salt of **23**.[21] Even the salt of *para*-chloroaniline (**25**) reacted with **1c**.

We then turned to investigate the generation of aryl radicals from the previously prepared azocarboxylates. In this context, only a few reports exist on arylazo ketones,[11a,12] arylazo succinates,[11c] and arylazo carboxylates.[22] These substrates, however, would not be suited for nucleophilic substitutions since they are less stable than **1a–c**.[23] The results of our experiments are summarized in Table 3.

At temperatures above 60°C, trifluoroacetic acid reliably induced the cleavage of the *tert*-butyloxycarbonyl (Boc) group. In this way, the azo compounds were probably first converted to aryl diazenes. This assumption is supported by the remarkable influence of ambient oxygen on the reaction

Table 3: Products from radical reactions of 4-substituted *tert*-butyl phenylazocarboxylates.

Entry	PACE compound	Product	Yield [%]
1	**1a**	 **27**	57[a]
2	**1a**	 **28**	89[b]
3	**1a**	 **29**	64[c,h]
4	**1a**	 **30**	58[d,h]
5	**1b**	 **31**	40[e]
6	**1c**	 **32**	59[c]
7	**1c**	 **33**	67[b]
8	**9**	 **34**	73[f]
9	**15**	 **35**	57[f]
10	**24**	 **36**	42[a]
11	 **37**	 **38**	53[g]

[a] Reaction conditions: CF_3COOH, $BrCCl_3$, CH_3CN, 80°C. [b] CF_3COOH, I_2, CH_3CN, 80°C. [c] CF_3COOH, benzene, 80°C. [d] CF_3COOH, $H_2C{=}CHCN$, $CuCl_2$, MnO_2, CH_3CN, 65°C. [e] 4-Fluoraniline, NaOH, H_2O_2, $(H_3C)_2NCOCH_3$, RT. [f] CF_3COOH, CH_3CN, EtOH, H_2O, 90°C. [g] CF_3COOH, TEMPO, CH_3CN, 65°C. [h] Reactions on a 2 mmol scale.

course. As reported by Kosower[24] for phenyl diazene (Ph-N=NH), the decomposition of this type of compound occurs instantly in the presence of oxygen ($k_2 \approx 10^3\ L\,mol^{-1}\,s^{-1}$). Although quite unusual for radical reactions,[25] comparative experiments proceeded best when they were conducted under air instead of under argon. We therefore assume that aryl diazenyl radicals (Ar-N=N$^{\bullet}$) were first generated from the aryl diazenes by hydrogen-atom transfer, and these were then transformed into aryl radicals with loss of nitrogen. Under argon, the aryl diazenes have an increased lifetime in the reaction mixture and were therefore able to undergo side reactions.[26] These observations are also in agreement with mechanistic studies on the decomposition of alkyl diazenes (alkyl-N=NH) in the presence of oxygen or the tetramethylpiperidin-1-oxyl radical (TEMPO).[27]

The aryl radicals were used for the preparation of brominated,[28a] iodinated,[28b,c] and arylated compounds[28a] (Table 3, entries 1–3, 6, 7, and 10), among which the halogenated products are well suited for further transformations.[29] Moreover, a Meerwein arylation could be achieved employing acrylonitrile, copper(II) chloride, and manganese dioxide as reagents (Table 3, entry 4).[2c,30] Under strongly basic conditions[31] and in the presence of hydrogen peroxide,[32] the difficult radical arylation of an unprotonated aniline derivative was realized using 4-fluoroaniline as a sample substrate (Table 3, entry 5).[3a,33] By treatment with trifluoroacetic acid and ethanol, we obtained the previously unknown phenylated morphine **34** from azocarboxylate **9** without observing the apomorphine rearrangement as side reaction (Table 3, entry 8).[34] The tyrosine derivative **15** was reduced under comparable conditions (Table 3, entry 9). The allyl ether **37** was converted in the presence of TEMPO to the dihydrobenzofuran **38** by a 5-*exo* cyclization typical for radicals. This result provides further support for the proposed radical reaction mechanism (Table 3, entry 11).[35,36]

In summary, 4-substituted *tert*-butyl phenylazocarboxylates such as **1a**, **1b**, and **1c** can be employed as versatile synthetic building blocks. After a mild and selective nucleophilic substitution of these compounds with phenolates and aliphatic and aromatic amines, various substituents can be introduced by a radical reaction as a second step. In our study the *tert*-butyloxycarbonylazo group was employed for the first time as a highly activating but also rather inert substituent in nucleophilic aromatic substitutions. At the same time, the carbonyl azo moiety allows the metal-free generation of aryl radicals. Further results on the application of phenylazocarboxylates in biochemistry and in combinatorial synthesis will be reported in due course.

Experimental Section

For the synthesis of the diphenyl ethers (Table 1), Cs_2CO_3 (5.0 equiv) was added to a solution of the phenol (1.2 equiv) in DMF (0.1 M) under argon, and the reaction mixture was stirred for 1 h. Azo compound **1a** (1.0 equiv) was added and after the reaction was complete (monitored by TLC), the mixture was diluted with water at 0 °C and was then extracted several times with ethyl acetate. The combined organic phases were washed with saturated aqueous NaCl and dried over Na_2SO_4. After removal of the solvents under reduced pressure, the crude product was purified by column chromatography.

For the radical reactions (Table 3), the 4-substituted *tert*-butyl phenylazocarboxylate and the substrate (30 equiv) were dissolved in acetonitrile (0.03 M), and the resulting mixture was heated to 80 °C and stirred under air. At this temperature, the required amount of trifluoroacetic acid (see individual products in the Supporting Information) was added and, the reaction was monitored by TLC. After cooling to room temperature, the reaction mixture was diluted with water (for some substrates, the pH was adjusted to 9 by the addition of saturated aqueous Na_2CO_3) and extracted with ethyl acetate. The combined organic phases were washed with saturated aqueous NaCl and dried over Na_2SO_4. After removal of the solvents under reduced pressure, the crude product was purified by column chromatography.

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