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Graphical Abstract



The triazolyl analogue of the trityl cation

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Abstract.

The formation of the tris(3-benzyl-triazol-5-yl)carbenium cation, a heterocyclic analogue of the trityl cation, from tris(3-benzyl-triazol-5-yl)methanol, itself generated by Cu(I)-catalyzed Huisgen reaction of benzyl azide with triethynylmethanol, in the presence of trifluoroacetic anhydride is evidenced through a selective S_N1 reactivity with various O-, N-, S- and C-nucleophiles, giving the corresponding triazolylmethane derivatives in moderate to high yields.

Key-Words. Carbenium, Trityl cation, Tris(1,2,3-triazolyl)methanol, Tris(triazolyl)methylium

Introduction

By virtue of their steric and electronic stabilization, trivalent triphenylmethyl -or "trityl"- centers could long be studied under radical,ⁱ anionic,ⁱⁱ or cationic state,ⁱⁱⁱ the latter having to be considered as the stable paradigm.^{iv} Associated to nonbonding anions such as hexafluorophosphate,^v tetrafluoroborate,^{vi} or trifluoroacetate,^{vii} the trityl cation is indeed currently used as a versatile electrophilic reagent, in particular towards alcohols for the reversible generation of hindered ethers (alternative to *tert*-butyl ethers), and towards C–H hydrides, e.g. in oxidative aromatization of cyclohexene derivatives.^{viii} Beyond this reference use as an alkoxide or hydride abstractor, the trityl cation has long been reported to react with other nucleophiles, in a stoichiometric or catalytic manner,^{ix} or even as an initiator of cationic polymerization.^x Chiral related functional triarylcarbenium ions were also used as catalysts for various organic transformations.^{xi} In spite of an obvious generalization principle (Scheme 1), functional variation of the trityl cation has been however limited to substituted or ethynylogous versions of the phenyl substituents,^{xii} e.g. with stabilizing anisyl^{xiii} or anilinyl substituents, such as in the classical triarylmethane dyes (with primary uses as pH indicators),^{xiv} or to trinaphthyl-^{xv} or triazulenyl-methyl analogues.^{xvii}



Scheme 1. Known structural types of trityl cation derivatives or analogues.

Heteroaromatic analogues of trityl salts have been mainly illustrated by trithienyl representatives,^{xvii} and a few other examples.^{xviii} In the aza-aromatic series, tripyridylmethyl^{xix} and tripyrrolylmethyl cations have been considered as putative or elusive species.¹⁸ The challenge is here resumed in the triazolyl series. The 1,2,3-triazole ring, in particular, is indeed an ubiquitous "clicking" motif resulting from Huisgen [2+3] cycloaddition reactions of alkynes with organic azides,^{xx} and its stability can be related to its weak basicity and strong aromaticity,^{xxi} which, in the topological scale, turns out to be essentially identical to that of benzene (Topological Resonance Energy, TRE = 0.274 β vs 0.273 β , where β is the assumed transferable Hückel resonance integral for C–C bonds).^{xxii}

Results and discussion

Reaction of tris(trimethylsilylethynyl)methanol **1**, prepared by a modified version of a previously described method (see Supplementary data, S.D.),^{**xxiii**} with three equivalents of benzyl azide under "Cu-AAC" (copper-mediated alkyne-azide cycloaddition) click-chemistry conditions afforded the triple Huisgen reaction product tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol **2** with simultaneous desilylation of the three terminal carbon atoms (Scheme 2). Although a slightly different procedure was employed (see S.D.), this alcohol was previously described by Pericas *et al.* and reported to act as an efficient ligand for further Cu-AAC reactions of various terminal alkynes with alkyl- and aryl-azides.^{**xxiv**}



Scheme 2. Cu-ACC access to the tris-N-benzyl derivative of triazolylmethanol.

The generation of the corresponding tris(triazolyl)carbenium 3, abreviated below as the "trizyl" cation for the sake of brevity, was tentatively carried out by treating a solution of 2 in dichloromethane (DCM) with trifluoroacetic anhydride, a treatment that resulted in the appearance of the same yellow color as that of the trityl cation. Evidences for the formation of the trizyl cation 3 were sought by trapping experiments consisting in the quenching of the solution with an excess of various nucleophilic reagents.



Scheme 3. Evidence of the generation of a tris(triazolyl)carbenium by trapping with nucleophiles.

Upon addition of methanol, the color faded away indeed rapidly, and after treatment with aqueous NaOH, the methyl ether **4a** was obtained in 77 % yield (Scheme 3, Nu = OMe), thus demonstrating the intermediacy of the trizyl cation **3**. It is noteworthy that tritylation of alcohols usually calls for the use of Ph₃CCl as the precursor.^{xxv} In the present case, attempt at chlorination of **2** with SOCl₂ in diethyl ether, or using the reported method for the conversion of Ph₃C–OH to Ph₃C–Cl (with acetyl chloride in refluxing toluene),^{xxvi} failed to convert the alcohol **2**. The straightforward use of the alcohol substrate **2** is however benefitial and could be generalized for the preparation of other ethers by reaction of the transient carbenium **3** with primary (EtOH), secondary (*i*-PrOH) and tertiary (*t*-BuOH) alcohols **4b**, **4c** and **4d** in 68 %, 74 % and 63 % yield, respectively (Table 1).

entry	Nu	Е	Yield (%)	$\delta_{13C}(2,4)^{a}$	$\delta_{13}C(Ph_3C-Nu)^b$
2	ОН	Н	quant.	68.0 (67.1) ^{24a}	82.0
4 a	OMe	Н	77	100.5	87.0
4b	OEt	Н	68	97.8	86.5
4 c	O ⁱ Pr	Н	74	82.2	88.5 ^{25c}
4d	O ^t Bu	Н	63	89.5	-
4e	^t BuNH	Н	54	55.5	- 0
4f	(R)-NHCHMePh	Н	75	57.1	-
4 g	NEt ₂	Н	75	78.7	(77.5: calcd)
4h	SC(S)OEt	K	75	64.3	$(73.0: calcd)^{28}$
4i	4-MeO-C ₆ H ₄	Н	86	69.9	64.3 ³⁰
4j	Et	ZnEt	48	42.5	61.0 ³²

Table 1. Reaction of *in-situ* generated tris(triazolyl)carbenium trifluoroacetate **3** (Scheme 3) with nucleophilic reagents Nu–E (0°C, DCM: see general procedure and S.D. for details). ^a ¹³C NMR chemical shifts of the triarylated quaternary carbon atom; spectra recorded in CDCl₃ solution, at 75 MHz and 293 K. ^b Chemical shifts for the trityl analogues, when available under the "spectra" rubric from *SciFinder* (<u>https://scifinder.cas.org/scifinder/</u>). References are also recalled for the specific cases **4c**, **4h-4j**.

The conditions were then applied to the trizylation of other nucleophilic heteroatoms. Primary amines such as *t*-BuNH₂ and (*R*)-MePhCHNH₂ were thus found to afford the trizylated products **4e** (whose analogous trityl derivative is known)^{**xxvii**} and **4f** in 54 % and 75 % yield, respectively. Likewise a secondary amine, Et₂NH, gave the corresponding highly hindered tertiary amine product **4g** in 75 % yield. Nevertheless treatment of **3** with a tertiary amine like NEt₃ failed to provide the corresponding quaternary amonium salt.

In contrast to the hard oxygen and nitrogen atoms, a soft sulfur atom was also found to undergo trizylation by **3**. Potassium O-ethyl xanthate thus led to the S-trizyl carbonodithioate **4h** in 75 % yield. Incidentally, just as the analogous S-trityl xanthate is the precursor of the trityl radical, ^{xxviii} the S-trizyl xanthate **4h** could behave as a precursor of the trizyl radical.^{xxix}

Generalization of the S_N1 reactivity of **3** to monoatomic nucleophiles was then investigated with halogen anions. Treatment of solutions of **3** with the soft bromide anion of $[n-Bu_4N][Br]$ was however found unproductive. The same absence of reactivity was observed with chloride ions of either the poorly soluble $[Et_4N][Cl]$ salt or the more soluble $[BnEt_3N][Cl]$ salt. Finally, no reaction occured with $[n-Bu_4N][F]$. A similar inertness was finally observed with the hard hydride ion in NaBH₄.

In view of generating novel quaternary carbon centers, the reactivity of **3** was finally envisaged with C nucleophilic centers. An efficient C-C bond formation process was found to occur with anisole, affording the *p*-trizylated product in high yield (86 %) and complete regioselectivity (the *o*-isomer was not observed). The p-anisylyl-trityl analogue was recently reported to be prepared by a similar S_N1 method from triphenylmethanol.^{xxx} Further attempts at C-trizylation were envisaged with sp^3 - and sp-hybridized carbon nucleophiles. In spite of its illustrated C-nucleophilic reactivity with carbenium centers under Friedel-Crafts conditions,^{xxxi} bis(trimethylsilyl)acetylene (Me₃Si–CC–SiMe₃) was found unreactive with the trizyl cation **3**. In contrast, the more reactive ethylide groups of diethylzinc led to the ethyltrizyl coupling product in 48 % yield. The analogous trityl-ethyl compound was prepared from Ph₃C-Cl and EtMgBr,^{xxxii} and this direct procedure for C-trizylation from **2** in acidic medium contrasts with the most used methods for C-tritylation: from isolated trityl salts (e.g. pre-associated to a PF₆⁻ anion),^{xxxiii} more frequently from trityl chloride,^{32,xxxiv} or in a quite original manner from lithium triphenylmethoxide in the presence of FeCl₃.^{xxxv}

Conclusion

The existence of the trizyl cation 3 has been appraised through its electrophilic properties towards an illustrative set of nucleophiles, showing both analogy and specificity with respect to classical tritylation reactions. The scope of chemical applications now deserves further investigations, in particular from a larger panel of trizyl N-substituents (a priori accessible thanks to the flexibility of the click chemistry), and with other nucleophiles and compatible solvents (different from DCM, e.g. for Grignard nucleophiles). Efforts for the crystallization of pure trizyl salts should also be pursued (attempts hitherto led to the isolation of tris(triazolyl)methanol 2 only, indicative a high hydrolytic sensitivity of 3). Regarding comparative physical properties, it is noteworthy that the range of the ¹³C NMR chemical shifts of the central quaternary carbon of trizylated compounds is wider (40-100 ppm) than in the corresponding trityl series (60-90 ppm, Table 1). The optical properties of trizyl cations with various N- and C-substituents, starting from their absorption and emission spectra, should also be the topics of further investigations for comparison with those of the trityl counterpart.¹⁴ Finally, biological properties of O-, N-, S- and C-trizyl derivatives, whose three triazole rings are known for their peptido-mimetic properties, also deserve to be examined by comparison to the corresponding trityl derivatives.^{xxxvi}

Typical tris(triazolyl)methylation procedure (Scheme 3). To a 0.1 M solution of tris(1benzyl-1*H*-1,2,3-triazol-4-yl)methanol **2** (0.1 g, 0.2 mmol) in DCM (2 mL) at 0°C under a nitrogen atmosphere, 1.2 equivalents of trifluoroacetic anhydride (0.03 mL, *ca* 45 mg, 2.1 mmol) are added dropwise. After stirring for 30 min., five equivalents of nucleophile (1 mmol) are added (e. g. 0.04 mL of MeOH), and stirring is continued for another 3 h at 0°C. The reaction medium is finally treated with aqueous NaOH (1 M), and the medium is extracted by DCM. The combined organic layers were dried and concentrated under vacuum,

and the residue is purified by chromatography on silicagel, using EtOAc/petroleum ether mixtures as eluting systems, to afford the trizylated product (usually as a pale yellow oil) in the specific yield given in Table 1.

Supplementary data. Experimental procedures and spectroscopical characterizations of the previously described compounds 1 and $2^{23,24}$ and of the 10 new compounds 4a-4j.

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