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ARYNIC SPECIES II; TOSYL AND TRIAZENE AS LEAVING GROUP IN THE GENERATION OF ARYNES FROM POLYMER-BOUND REAGENTS

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Abstract - o-Benzyne and its 4-methyl, 4-chloro and 4-bromo-derivatives were generated in the thermal decomposition of two new kinds of polymer-bound precursors: 1(2-carboxyaryl)triazenes and 2-carboxyaryl-sulphonates. New kinds of trapping polymers for these elusive species are also presented.

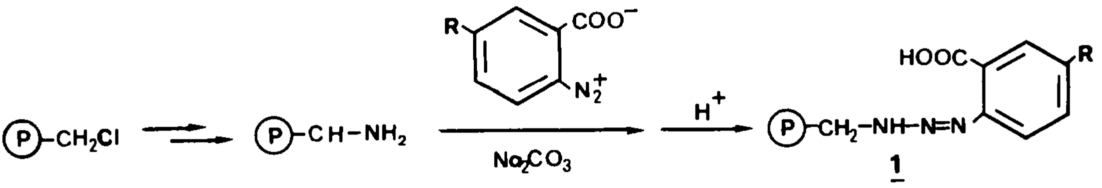
Recently[1] we have described the use of the three-phase test for studying the reactivity of monosubstituted o-arynes. These elusive species were generated in solution via decarboxylative heterolytic fragmentations, where a polymer-bound aryliodonium was the nucleofugal leaving group. In aryne chemistry a number of other non-polymeric leaving groups, like diazonium[2], halogen[3], triazene[4] etc have been used in generating processes. In the present work, we report the use of two new polymer-bound nucleofugal leaving groups for the generation of o-arynic species. The appearance of these intermediates has been unambiguously demonstrated by the three-phase test. A new arynic intermediate, 3-methyl-benzyne, has been studied in this way. Its lifetime determination by the modified three-phase method[1,5] is in good agreement with the former results for 4-substituted o-benzynes[1].

Methods and results

Polymeric 1-(2-carboxyaryl)triazenes. Thermal treatment of aryldiazonium-2-carboxylates has been one of the most usual methods described for the generation of o-arynes[2]. The triazene group acts like the diazonium group in some reactions. Also, the generation of several o-arynes and o-hetarynes from different 3-substituted 1-(2-carboxyaryl)triazenes has been reported[4].

Suitable polymer supported 1-(2-carboxyaryl) triazenes (IR 1680 cm^{-1}) were prepared as shown in Scheme I. This was done by condensation of diazotized anthranilic acids with a polymer supported benzylamine prepared from a Merrifield resin (3.5 mequiv Cl/g, 2% crosslinked) through a Gabriel synthesis[6].

Degrees of substitution for 1, calculated by titration of acidic groups in the usual way, are given in Table I, along with the overall yields from Merrifield's



SCHEME I

resin. Thermogravimetric analysis of polymers 1 (Figure 1) showed the presence of retained substances in the polymeric beads and a partial decomposition of functional groups below 190ºC. IR analysis of polymers 1 after heating under different conditions and thermogravimetry, suggested that heterolytic fragmentation is accompanied by other processes, mainly esterification[4c]. This is shown by the appearance of an ester C=O band at about 1720 cm^{-1} and the isolation of anthranilic acid by hydrolysis of the polymer which formed after heating 1a.

Table I. Polymeric triazenes degrees of functionalization

Polymers 1	R	Degree of functionalization (mequiv/g)	Yields from Merrifield's resin (%)
a	H	1.70	63
b	CH_3	0.58	27
c	Cl	0.63	30
d	Br	0.68	35

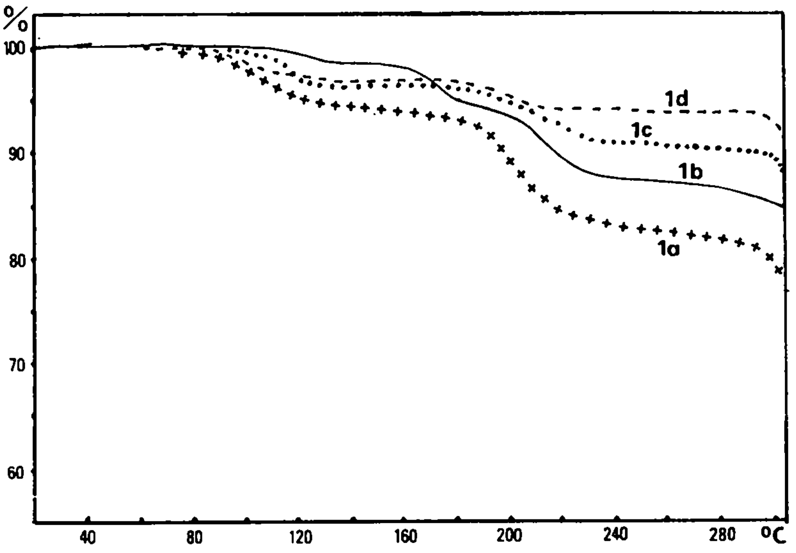
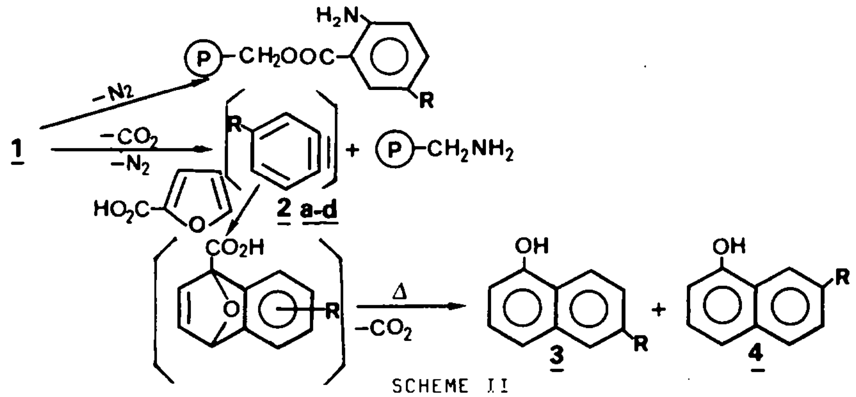


Fig. 1

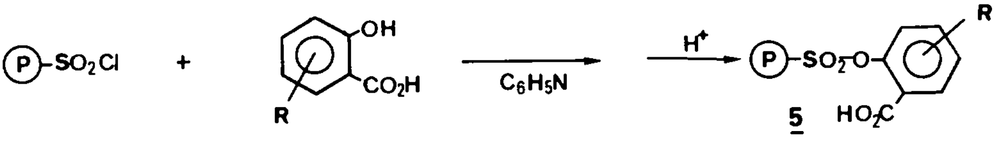


SCHEME II

When polymers 1 were refluxed in dioxane for 72 h in the presence of furoic acid (Scheme II), a mixture of 6- and 7-substituted 1-naphthols (3 and 4 a-d; R=H, CH_3, Cl and Br respectively) was obtained via the intermediacy of an arynic species, 2, and the initial adduct, the substituted 1,4-epoxy-1,4-dihydro-1-naphthoic acid[1]. However, yields (c.a. 10 %) were lower than when polymeric diaryliodonium-2-carboxylates were the precursors (20 - 30 %).

Polymeric 2-carboxyphenyl-sulphonates - Benzenesulphonate and related groups have been very useful leaving groups in heterolytic fragmentation[7]. In our own studies on reactive intermediates by the three phase test, we have found that polymeric tosyl and toluene p-sulphonate groups act efficiently as nucleofugals in the generation of diimine[8] and cyclopentadienones[5,9]. Also the generation of o-arynes from ortho-metallated aryl benzenesulphonates has recently been reported[10] However, the possibility of o-arynes production from 2-carboxyaryl benzenesulphonates has not yet been explored.

Polymer-bound 2-carboxyaryl-sulphonates were prepared by reaction of salicylic acids with a chlorosulphonated macroreticular resin[11] in basic media, then acidification (IR c.a. 1700 cm^{-1}) (Scheme III). Degrees of substitution for resins 5 (Table II) were below 0.6 mequiv/g, showing that only about 10 % of the initial



5

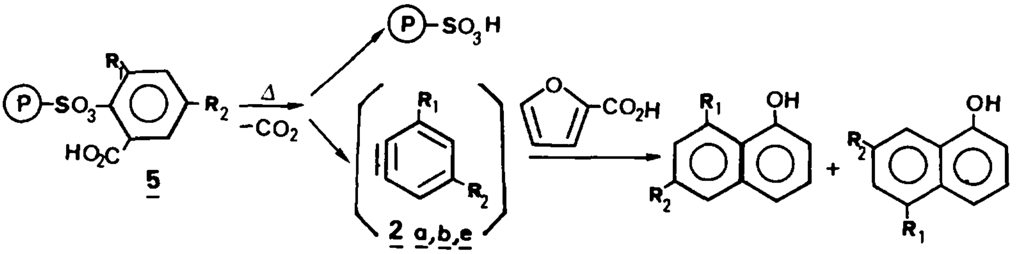
SCHEME III

chlorosulphonic groups reacted with the salicylic acids. Hence polymers 5 must be considered as having two different functional groups: 2-carboxyphenyl sulphonate (0.3-0.6 mequiv/g) and sulphonic (the principal one, c.a. 3.5-4.0 mequiv/g). Thermogravimetric analysis of these resins revealed that thermal decomposition of functional groups in 5 starts at about 100ºC, but a quantitative approach[12] cannot be easily applied bacause sulphonic groups also show thermal decomposition with weight loss in a broad range of temperatures[13]. However, for 5a, a kinetic analysis could be accomplished through the use of IR spectroscopy. This technique uses the direct relationship between the loading of the functional groups in the polymer and the absorbance ratio between a characteristic band of the group (for instance, the C=O band) and one characteristic of the polymer backbone (for instance the band at 1600 cm^{-1}). For a simple decomposition process like that indicated in Scheme IV, the general equation: $A_r = A_r^o e^{-kt}$ can be used, where A_r and A_r^o are the absorbance ratio and its initial value, respectively. In this way, for 5a at 120ºC, a value of $(5.4 \pm 0.2)\times10^{-4}$ s^{-1} could be stated by a graph of $\ln A_r$ in function of time. This value shows that thermal decomposition takes place with an appreciable rate at lower temperatures for these compounds than for polymeric diaryliodonium-2-carboxylates. Nevertheless, for 5b and 5e, which have lower degrees of substitution an accurate kinetic analysis could not be accomplished, because of the greater interference of overlapping between the C=O band and the characteristic absorption of sulphonic resins above 1600 cm^{-1}.

Table II. Polymeric 2-carboxyphenyl-sulphonates Degrees of substitution

Polymers 5	R	Degree of substitution (mequiv/g)
a	H	0.55
b	4-CH_3	0.28
e	6-CH_3	0.40

When polymers 5 were decomposed in the presence of furoic acid (Sscheme IV), the expected 1-naphthols were again obtained in yields below 10 %.

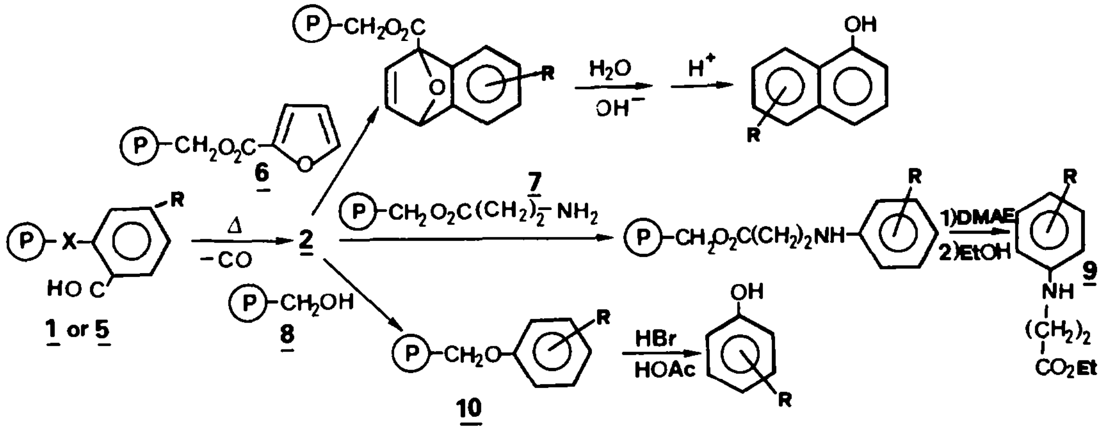


a) $R_1 = R_2 = H$; b) $R_1 = H$, $R_2 = CH_3$; e) $R_1 = CH_3$, $R_2 = H$

SCHEME IV

The three-phase test. Besides the polymeric ester of 2-furancarboxylic acid (6)[1], two new resin-bound nucleophilic trapping agents were also tested in our work. The first one was the polymeric benzyl ester of β-alanine (7), which was prepared from t-BOC-β-alanine and a Merrifield's resin (3.5 mequiv Cl/g) in the usual way for these compounds[14]. The other was the polymeric benzyl alcohol, 8, easily obtained by hydrolysis of polymeric benzyl esters[15].

Three phase experiments were carried out by heating and stirring a suspension of the polymeric precursor and the trapping resin (Scheme V). For the unsubstituted o-benzyne (R=H), different three phase tests were accomplished by using each one of the precursors (1a, 5a and the previously described polymeric diaryliodonium 2-carboxylate[1]) and each one of the trapping agents (6, 7 and 8). 1-Naphthol was always isolated from the solution (after basic hydrolysis and acidification) when polymer-bound furoate was used, showing that o-benzyne was generated from the three precursors. Transesterification of the polymers resulting from the trapping resin 7 after three phase tests with dimethylamino ethanol produced, when R=H, the ethyl ester of the 3(N-phenylamino)-propanoic acid (9a). This was identical with an authentic sample. An interesting side reaction with resin 7 was found to be the interaction at high temperatures of functional groups in 7 to form amide linkages, as shown by the appearance in the IR of a new C=O band at c.a. 1650 cm^{-1}. This behaviour reduces the effective loading of the nucleophile in the polymeric beads. The formation of the polymeric adduct 10, when using 8 was revealed by the appearance in the solution of phenol after treatment of this resin with HBr/AcOH.



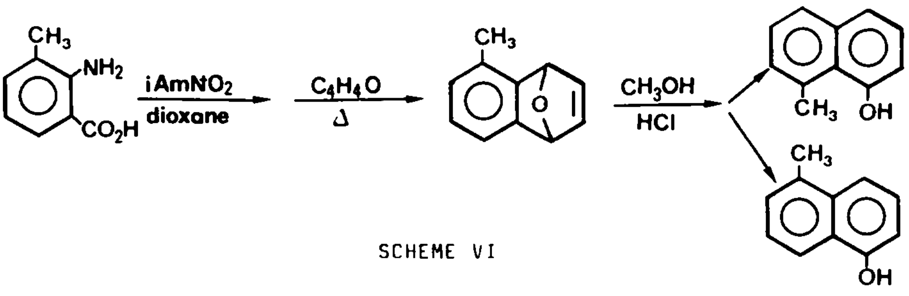
SCHEME V

These experiments showed that polymeric furoate was the best trapping agent of the three tested, as a result of the better yields and the easier work-up for adduct isolation. So, 6 was chosen as the trapping agent in three phase tests for substituted o-arynes (R≠H). In this way, when polymers 1b, c, d and 5b, e were used as precursors, the expected mixtures of substituted 1-naphthols were identified after the usual work-up (6- and 7-methyl-1-naphthol were formed either from 1b or 5b, 6- and 7-chloro-1-naphthol obtained from 1c, 6- and 7-bromo-1-naphthol from 1d and 5- and 8-methyl-1-naphthol from 5e).

When comparing our results of o-arynes generation from polymers 1 or 5 with the ones obtained by using polymeric diaryliodonium-2-carboxylates, the latter seem to be better precursors, giving much better yields. However, 1 and 5 are able of o-aryne generation at lower temperatures. Low yields in these resins can be atributed to the possibility of decomposition through different routes, without o-aryne generation (specially in polymeric benzyl triazenes 1) and to side reactions of the formed intermediate with functional groups into the precursor resin.

Lifetime measurement. Because in this work a new monosubstituted o-benzyne, 3-methyl-o-benzyne (2e), was studied by the three phase test, lifetime determinations for this reactive species were attempted. The method (a modified three phase test) has been thoroughly described. It requires the separation of precursor and trapping resins to a constant distance and the use of a variable flow of solution ("Polyphasic Dynamic Reactor")[5]. In the same conditions used in lifetime measurements for 4-substituted o-benzynes[1], transference of the 3-methyl-o-benzyne moiety, from 5e to polymeric furoate could not be detected even with the shortest run-time obtained in our conditions (3.4 s). Because the trapping of 2e on the three phase test, without using PDR, implies that its lifetime is at least in the range of some tenths of a second[17], a value of 0.2-3.4 s can be stated for this lifetime. This result is in a very close concordance with the one obtained for 4-methylbenzyne[1], and seems to confirm the destabilizing effect of methyl group on the kinetic stability of the o-arynic species.

Reference compounds. Preparation of 6- and 7-substituted 1-naphthols (3 and 4) has been described previously[1]. By the same procedure, starting from 2-amino-3-methylbenzoic acid (Scheme VI), 5- and 8-methyl-1-naphthol were prepared for



SCHEME VI

comparative purposes. Proton NMR analysis of methyl groups in the mixture showed in this case that the ratio between 5- and 8-methyl isomers was 6/1. A pure sample of the 5-isomer could be separated by fractional crystalization in ethanol.

A sample of the ethyl ester of 3-(N-phenylamino)-propionic acid was prepared as described by Thayer and McElvain[18].

Conclusions

Benzoic acids with polymeric triazene or sulphonate as leaving groups are able to generate monosubstituted o-benzynes by thermal decomposition. However, the formerly prepared analogous compounds with aryliodonium as a leaving group seem to be better precursors for these species.

Polymeric amino or hydroxyl group can act as trapping agents for o-arynes, but a dienic trapping agent like furoate affords better yields in every case.

Lifetime determination for 3-methyl-o-benzyne seems to confirm the substituent effect on the kinetic stability of o-arynic species, for which electron releasing groups have destabilizing effects.

EXPERIMENTAL SECTION

Preparation of polymeric 1-(2-carboxyaryl)-triazenes (1). General Method

The appropiate anthranilic acid (12.5 mmol) was dissolved in 20 mL of dioxane containing 50 mg (0.3 mmol) of trichloroacetic acid. A solution of 14.8 mmol of isoamyl nitrite was added dropwise over a period of 1 h at 2ºC and the mixture was stirred for another hour. Then a solution of Na_2CO_3 (4g) in 30 mL of water and 1.5 g (4.3 mmol) of polymeric benzylamine[6] were added and the suspension was stirred at r.t. for 22 h. The resin was filtered, washed with water, dioxane, methanol, acetone and ether, then treated with 69 mL of a 4N solution of HCl in water/ /dioxane 1/1 (v/v) at room temperature for half an hour. After washing and drying, resins 1 showed a C=O band at c.a. 1680 cm^{-1} and N-H bands at c.a. 3400 cm^{-1}. Degrees of substitution were calculated by tiration of acidic groups in the usual way[15]. Yields were estimated from the theoretical maximum degree of substitution of the initial Merrifield´s resins (Table I)

Preparation of polymeric 2-carboxyaryl-sulphonates (5). General Method

A chlorosulphonated macroreticular polystyrene-divinylbenzene resin (200-400 mesh, 2% cross-linked)(2.5 g, 10.5 mequiv) was stirred at room temperature for 72 h in a solution of the substituted salicylic acid (25 mmol in 15 mL of dry pyridine and 60 mL of dioxane). After being filtered and washed with ethanol, chloroform and acetone until the filtrate was colourless, the pyridinium salts of polymers 5 were obtained. IR (KBr, cm^{-1}): 3060, 1620, 1480, 1180, 1030, 1000, 745.

Treatment with 95 mL of 5N HCl in water/dioxane (1/1) at r.t. for 0.5 h, gave, after filtering and washing with water, chloroform, ethanol and acetone, polymers 5. IR (KBr, cm^{-1}): 1680, 1160, 1115.

Basic hydrolysis of resins 5 with a 25 solution of NaOH in water/dioxane (1/1) for 24 h, yielded back the salicylic acids. Degrees of substitution were calculated from the weight of recovered acids.

Thermal decomposition of polymeric 1-(2-carboxyaryl)-triazenes (1) or polymeric 2-carboxyarylsulphonates (5)in the presence of furoic acid

0.8 Mequiv of either triazene (1) or sulphonate (5) were suspended in a solution of furoic acid (0.27 g, 2.4 mmol) in 50 mL of dioxane and refluxed for 72 h. The resin was washed with dioxane, methanol and acetone and the filtrates were evaporated to dryness. The residue was dissolved in chloroform, washed with a dilute aqueous solution of $NaHCO_3$ and chromatographed on silica-gel. It gave then either 1-naphthol (from 1a or 5a) or mixtures of 6- and 7-substituted 1-naphthols (from 1b, c, d and 5b) or 5- and 8-methyl-1-naphthol (from 5e) identical with authentic samples. Yields were in the range of 10 %.

Three-Phase Tests

a) o-Benzyne transfer from polymeric precursors to polymeric β-alanine. Polymeric diaryliodonium-2-carboxylate (0.8 mequiv) and resin 7 (0.50 g, 1.8 mequiv) separeted by porous plates and suspended in diglyme, were heated at 140-150ºC for 30 h. Both polymers were separated and washed with ethanol, acetone and ether and vacuum dried at room temperature. The trapping polymer was then stirred at 25ºC for 64 h with a dry mixture of Dimethylaminoethanol/Dimethylformamide (1/1) After filtering, the solution was evaporated, the residue being stirred with anhydrous ethanol at r.t. for 24 h. By vacuum distillation of the solvent an oil was obtained, from which the ethyl ester of the 3-(N-phenylamino)-propanoic acid (9a) was isolated after chromatography on silica-gel (ether/hexane 1/1) IR (KBr, cm^{-1}): 3380, 2950, 2920, 1726, 1660, 1600, 1495, 742. ^{1}H NMR (CCl$_4$) δ 1.15 (t, 3H), 2.45 (t, 2H), 3.3 (t, 2H), 3.55 (t, 1H), 4.05 (q, 2H), 6.4-7.3 (m, 5H). Yield 28 %. It was identical with an authentic sample[18].

When polymers 1a or 5a were used as precursors (0.9 mequiv ea in refluxing dioxane) ethyl 3-(N-phenylamino)-propanoate was again isolated in the same way. Yields were in the range of 5 - 7 %.

b) o-Benzyne transfer from polymeric precursors to hydroxybenzylic resin(8) Polymeric diaryliodonium-2-carboxylate (0.8 mequiv) and hydroxybenzylic resin 8 (c.a. 3.8 mequiv) separated by porous plates and suspended in diglyme were heated at 140-150ºC for 30 h. The trapping polymer was washed with ethanol, acetone and ether and then refluxed for 48 h with a saturated solution of hydrogen bromide in acetic acid. After work-up, phenol could be obtained from the solution.(25% yield)

For polymers 1a or 5a, the procedure was the same, but refluxing dioxane was used.

c)o-Aryne transfer from polymers 1 or 5 to 6.Polymeric triazenes (1) or 2-carboxyarylsulphonates (5) (c.a. 0.8 mequiv) and polymeric furoate, 6 (0.6 g, 1.7 mequiv) separated by porous plates and suspended in dioxane, were refluxed for 72 h. The trapping polymer was filtered and washed with dioxane, ethanol, acetone and ether, then refluxed with a 5% solution of NaOH in H_2O/EtOH 1/1 (v/v) for 48 h. The liquid was filtered from the resin, concentrated and acidified, giving furoic acid and the respective substituted 1-naphthols. Yields were in the range of 7-8 %.

Preparation of 5- and 8-methyl-1-naphthol

By using the same experimental procedure as that for 6- and 7-substituted 1-naphthols, 7 mL of furan, 5 mL (0.037 mol) of isoamyl nitrite and 3 g (0.020 mol) of 3-methylanthranilic acid gave 1,4-epoxy-1,4-dihydro-5-methylnaphthalene. Treatment with MeOH/HCl of this compound afforded 1 g (30% yield) of a mixture of 5- and 8-methyl-1-naphthol. IR: (KBr, cm^{-1}): 3300, 3080, 2875, 1575, 1402, 1375, 1355, 1255, 1230, 1132, 890, 765. ^{1}H NMR (CDCl$_3$) δ: 2.7 (s, 2.6 H), 3.0 (s, 0.4 H) 5.3 (s, 1H), 6.8-8.2 (m, 6H). MS m/e, 158, 157, 130, 128, 115. A pure sample of the 5-methyl isomer could be separated by fractional crystalyzation in ethanol, m.p. 98 ± 0.5ºC (identical to the given in literature[20])

PDR lifetime measurements

Lifetime measurements for 3-methylbenzyne were made as has been described[5] by using polymeric 2-carboxy-6-methyl sulphonate as precursor and polymeric furoate as trapping agent. Diethylbenzene as solvent and reaction times of 7 h were used. No transference of 3-methylbenzyne could be detected for the shortest run-time(3.4 s).

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