N-(2-Tetrahydrofuranyl)azole Nucleoside Analogs by Reactions of Azoles with Dihalomethanes in Tetrahydrofuran

Jerzy Zadykowicz and Pierre G. Potvin*

Department of Chemistry, York University,
4700 Keele Street, North York, Ontario, Canada M3J 1P3
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The reactions of the mono-*N*-substututed bispyrazolylpyridine 2-(1-methyl-4,5,6,7-tetrahydroindazol-3-yl)-6-(2*H*-4,5,6,7-tetrahydroindazol-3-yl)pyridine, 3,5-dimethylpyrazole and benzimidazole with sodium hydride and diiodomethane or dibromomethane in tetrahydrofuran produced the unexpected *N*-tetrahydrofuran-2-yl adducts as well as the expected diazolylmethanes. These side-reactions are thought to involve the 2-halo tetrahydrofuran derivative resulting from a free-radical halogenation by the dihalomethane.

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Introduction.

In the course of earlier work aimed at the preparation of polytopic heterocyclic ligands for transition metals [1], we discovered a new reaction that resulted in the formation of a tetrahydrofuran adduct of an indazole. In view of the potential importance of such adducts as nucleoside analogs or as protected forms of azoles, we engaged in a limited study of the scope of this reaction and report herein our findings and a discussion of its mechanism.

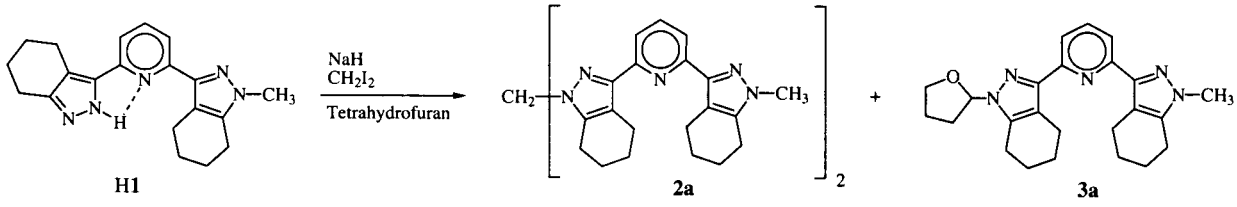
Results.

The reaction of the diindazolylpyridine **H1** [1] with sodium hydride (1.2 equivalents) and diiodomethane (0.53 equivalent) in tetrahydrofuran at reflux unexpectedly produced a mixture of products. Chromatography led to the isolation, in reverse order of elution, of unreacted **H1** (16%), the desired **2a** (50%) and a new product later identified as the *N*-tetrahydrofuran-2-yl adduct **3a** (26%). The structure of **3a** was deduced from several pieces of information. The aromatic region of the ^{1}H-nmr spectrum contained no new signals and was typical of an unsymmetrically *out,out-* or 1',1"-disubstituted 2,6-bis(tetrahydroindazol-3-yl)pyridine which was, moreover, in the *anti,anti* conformation expected of an *N,N'*-disubstituted product, according to our previous experience with such materials [1,2]. The aliphatic region contained several new coupled multiplets, including a characteristic doublet of doublets at 5.97 ppm which was eventually assigned to H-2 of the tetrahydrofuran portion. COSY, ^{13}C-nmr, HMQC and DEPT spectra confirmed the connectivity and the multiplicities in the tetrahydrofuran moiety of **3a**. The ms (EI) showed the highest mass peak at *m/z* 403 corresponding to **3a** and, in accord with the ready loss of *N*-alkyl substitutents noted earlier [1,2], fragments corresponding to $\mathbf{1}^+$ and to the tetrahydrofuran cation. Finally, elemental analysis confirmed the formulation as **3a**.

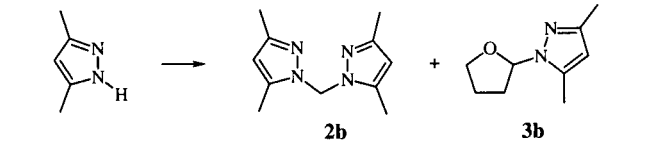
The alternate use of dibromomethane led to the same result. An analogous reaction maintained at or below 40° led to a 76% yield of **2a** free of **3a**. The use of dichloromethane or dibromomethane as solvents led to high yields of pure **2a**. This and the characterization of **2a** have been reported elsewhere [1]. The use of significant excesses of sodium hydride reduced the yields of both products and produced a complex mixture of unidentified materials.

Similar reactions of 3,5-dimethylpyrazole and benzimidazole, which suffer no regiochemical ambiguity, were also carried out to verify the generality of this occurence. Under the same conditions as with **H1**, 3,5-dimethylpyrazole produced the known methylene-bridged dimer **2b** [3] and the new tetrahydrofuran adduct **3b** in 24% and 17% yields, respectively, after chromatography. The crude yield of **3b** was higher, as measured by ^{1}H-nmr, but volatility and a sensitivity toward hydrolysis lowered the isolated yields. In fact, nearly pure **2b** can be isolated by leaving the crude mixture out in the open.

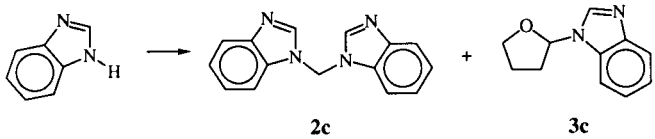
The same reaction with benzimidazole and diiodomethane was more variable in outcome. One instance produced the known **2c** [3] and the new tetrahydrofuran adduct **3c** in about 10:1 ratio, according to ^{1}H-nmr, and they were isolated in 81% and 4% yields, respectively. Volatility was also a problem with **3c** and it was an



even more sensitive material. With 2.5 equivalents of diiodomethane, the ratio of crude **3c**:**2c** increased to about 3:2. At room temperature, there resulted a clean reaction producing only **2c**. Other instances resulted in the isolation of little or no **3c**. The best isolated yields of **3c** were obtained when the diiodomethane was added last, after an overnight incubation at reflux of the other ingredients. No detectable amount of **2c** was then produced and the isolated yield of **3c** grew to 28%. Some benzimidazole, which was absent in the crude mixture, arose during chromatography as a contaminant, of which only a portion was actually isolated (6% yield). The true yield of **3c** was therefore significantly higher. An important secondary product (23% isolated yield) was *N*-methylbenzimidazole (see below). Much diiodomethane remained unreacted. Reactions replacing diiodomethane by iodine, with or without irradiation, were not clean and failed to provide useful products.



2b **3b**



2c **3c**

The structures of **3b** and **3c** were confirmed by spectral similarities with **3a** as well as by ms (EI). This revealed common fragmentation patterns, including the loss of the tetrahydrofuran 2-radical and the loss of formaldehyde. Elemental analysis confirmed the formulation of **3b**. That of the fragile **3c** yielded the expected C/N ratio but, not suprisingly, partial hydrolysis in transit resulted in slightly high H/C and H/N ratios.

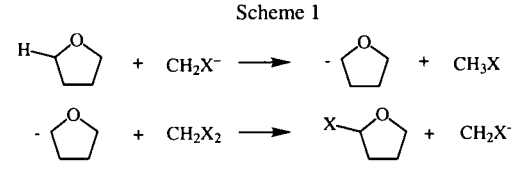
Discussion.

Similar adducts have been reported by other groups. Alcohols form tetrahydrofuran and tetrahydrothiophene adducts under basic conditions in the presence of sulfuryl chloride [4,5] or tosyl chloride [6], with the presumed intermediacy of 2-chloro derivatives formed by radical or ionic processes. Such α-halogenations of ethers and thioethers are well established [4,7] and Kruse *et al.* [8] have used 2-chlorotetrahydrofuran directly in alcohol protection. Peroxydisulfate ion [9] or Ce(IV) in tetrahydrofuran [10] also convert alcohols to their tetrahydrofuran ethers, presumably *via* the tetrahydrofuran 2-radical. Thiols and the N-H compounds pyridone, pyrazole and 1,2,4-triazole, but not imidazole, also form tetrahydrofuran adducts with sulfuryl chloride [5]. Tetrahydrofuran adducts can also arise by the addition of 2-oxacarbenes across O-H, S-H and N-H bonds [11].

On the assumption that all three azoles tested here react in the same way, a few observations are mechanistically relevant. First, the reactions of **H1** are regioselective with respect to the pyrazole ring. This is consistent with the intermediacy of a Na^+ chelate serving to protect the *inner* pyrazole N (N-2) during the reaction of the anion, an effect that we have witnessed in ordinary alkylations and arylations [1,2], and eliminates mechanisms involving *N*-centred radicals. Secondly, the product distribution in the reaction of **H1** implied the consumption of one equivalent of diiodomethane in producing **3a**. Thirdly, the fact that reactions with all three azoles are regioselective with respect to the tetrahydrofuran ring is consistent with the intermediacy of a 2-halo derivative arising from the tetrahydrofuran 2-anion or 2-radical. A related, earlier instance of a dihalomethane acting as a halogen source is the peroxide-initiated formation of cyclopropanes from alkenes and diiodomethane [12], where iodine radical transfer from diiodomethane to a carbon radical was probably involved. Finally, because significant excesses of sodium hydride were detrimental, whereas excess dihalomethane was not, mechanisms in which more sodium hydride is consumed than is needed for the deprotonation of the azole can be discounted. Indeed, excess sodium hydride complicated the reactions, possibly by deprotonating the putative 2-halo derivatives or by causing elimination to dihydrofuran [4]. One can write a mechanism involving the tetrahydrofuran 2-carbene, which might add azole anions much as carbanions add to difluoromethylene [13,14] but, because such a 2-carbene would presumably arise by α-elimination of a 2-halo derivative, the direct reaction with the 2-halo derivative provides a more parsimonious explanation.

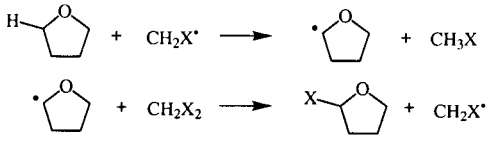
In principle, the requisite 2-halo derivative could arise by halogenation of deprotonated tetrahydrofuran, with dihalomethane acting as a source of halonium ions. The halomethyl anion by-product could then deprotonate tetrahydrofuran to propagate the reaction (Scheme 1). The alternative decomposition of halomethyl anion to halide and methylene would result in a net consumption of sodium hydride. Certainly, the deprotonation of tetrahydrofuran with organolithiums is facile, but decomposition of the 2-lithio product to the acetaldehyde enolate is faster [15]. Further, one would expect that much of the tetrahydrofuran anion would become methylated or iodomethylated, resulting in a net consumption of base and diiodomethane.

Scheme 1



We favour instead a radical pathway (Scheme 2), in which dihalomethane halogenates the tetrahydrofuran 2-radical, leaving behind halomethyl radical to propagate the reaction. In support of this, the iodination of carbon radicals with alkyl iodides is known to be very fast [16] (the competing transfer of hydrogen radicals would be much slower [17]). As well, we can calculate from known heats of formation and bond dissociation energies [18] that the first step in Scheme 2 is exothermic by 12 kcal/mol, and the AM1-calculated heat of formation of 2-iodotetrahydrofuran (-35.5 kcal/mol) allows one to predict that the second step is also exothermic by 7.9 kal/mol.

Scheme 2



The process could be initiated by an electron transfer [14] from sodium hydride to dihalomethane, followed by loss of halogen radical to provide the halomethyl radical. Indeed, sodium hydride in tetrahydrofuran is known to reduce *gem*-dibromocyclopropanes in the presence of sodium amylate, a process said to occur *via* one-electron transfer from sodium hydride to the substrate and expulsion of bromide ion to leave the monobromo radical [19] in analogy to the reductions of *gem*-dihalides by lithium aluminum hydride [20]. Related reductions of aryl iodides [21] and benzylic halides [22] by sodium hydride are also known. The decomposition of iodomethyl radical to iodine radical and methylene is too endothermic to viably compete [12]. The direct formation of iodomethyl radical by photoinduced homolysis of dihalomethane is an unlikely initiatiation step because the photolysis of diiodomethane preferentially forms molecular iodine and methylene [23] and requires light of wavelength ≤290 nm [24]. An alternative initiator is the tetrahydrofuran radical, but this is unlikely because electron transfer directly to tetrahydrofuran leads to ring cleavage and requires a potent reductant [25].

By either anionic or radical routes, there is a halomethane by-product which should then produce *N*-methylated products, albeit in competition with the more reactive 2-halo tetrahydrofuran derivative. *N*-Methylbenzimidazole was indeed isolated in significant amounts in the benzimidazole reaction.

Further experiments would be required to conclusively determine the mechanism of this interesting reaction, but no attempts were made to use this reaction in a useful protection of azoles nor as a general route to nucleoside analogues because competing *N*-methylation and a sensitivity toward hydrolysis would be possible limitations and because the conversion of diiodomethane does not seem to be efficient.

EXPERIMENTAL

General procedures were as before [1] except for the following. Diiodomethane was purified by drying over anhydrous calcium chloride and distillation under reduced pressure. It was stored in the refrigerator in a dark glass bottle containing a copper wire. The nmr spectra were obtained on a 400 MHz instrument in deuteriochloroform. Elemental analyses were carried out by Guelph Chemical Laboratories, Guelph, Ontario, Canada. The heat of formation of 2-iodotetrahydrofuran was estimated using the *Spartan v3.1.2* suite of programs (Wavefunction Inc., 18401 Von Karman, Suite 370, Irvine CA 92715) on a Silicon Graphics Indigo R4000 workstation.

2-(1-Methyl-4,5,6,7-tetrahydroindazol-3-yl)-6-(1-(Tetrahydrofuran-2-yl)-4,5,6,7-tetrahydroindazol-3-yl)pyridine (**3a**).

Solid sodium hydride (0.011 g, 0.47 mmole) was added to a solution of 0.096 g (0.29 mmole) of *N*-methylbis(pyrazolyl)pyridine **H1** [1] in dry tetrahydrofuran. Hydrogen evolution was immediate and the solution became milky-white. The mixture was stirred under argon for 2 hours and then treated with diiodomethane (0.041 g, 0.152 mmole). After heating to reflux overnight, tetrahydrofuran was removed and the light yellow oily residue was dissolved in chloroform and washed with water. After the removal of the chloroform, the resulting oil was purified by column chromatography on alumina, using 1:1 ethyl acetate-light petroleum ether as eluent, to yield the tetrahydrofuran adduct **3a** as a white solid, 0.030 g (26%), mp 121-123°; ^{1}H nmr: δ 1.76 (m, 4H), 1.89 (m, 4H), 2.08 (m, 1H), 2.28 (m, 1H), 2.48 (m, 1H), 2.63 (m, 2H), 2.73 (m, 1H), 2.80 (m, 1H), 2.95 (m, 5H), 3.81 (s, 3H), 3.97 (ddd, 1H), 4.12 (ddd, 1H), 5.97 (dd, 1H), 7.70 (m, 1H), 7.84 (m, 2H) ppm; ^{13}C nmr: δ 21.7, 22.5, 22.9, 23.3, 23.4, 25.2, 30.2, 35.7, 68.7, 86.4, 115.7, 116.4, 119.0, 119.3, 136.3, 140.0, 147.3, 148.0, 153.2, 153.4; ms: *m/z* (%) 403 (79), 373 (31), 346 (43), 332 (100), 318 (48), 304 (68), 197 (22), 69 (16), 55 (11).

Anal. Calcd. for $C_{24}H_{29}N_5O$: C, 71.44; H, 7.24; N, 17.36. Found: C, 71.75; H, 7.39; N, 17.15.

A second fraction contained **2a**, isolated as a white solid, 0.049 g (50%). Its spectral data were in agreement with those previously published [1]. A third fraction consisted of unreacted **H1**, 0.015 g (16%).

1-(Tetrahydrofuran-2-yl)-3,5-dimethylpyrazole (**3b**).

A mixture of 3,5-dimethylpyrazole (0.385 g, 4 mmoles) in dry tetrahydrofuran was treated with solid sodium hydride (0.106 g, 4.4 mmoles) and treated with freshly distilled diiodomethane (0.536 g, 2 mmoles). After heating to reflux for two days, the reaction mixture became clear. The solvent was removed and the crude yellow oily mixture was purified by column chromatography on alumina, using ethyl acetate-petroleum ether (20:80) as eluent, to yield the tetrahydrofuran adduct **3b** as a liquid, 0.111 g (17%), bp 245-248°; ^{1}H nmr: δ 2.03 (m, 1H), 2.23 (s, 3H), 2.26 (m, 1H), 2.32 (s, 3H), 2.38 (m, 1H), 2.81 (m, 1H), 3.91 (ddd, 1H), 4.06 (ddd, 1H), 5.83 (s, 1H), 5.88 (dd, 1H); ^{13}C nmr: δ 11.0, 13.7, 25.4, 30.1, 68.5, 85.8, 106.2, 139.9, 148.0; ms: *m/z* (%) 166 (41), 135 (10), 97 (100), 71 (50), 57 (15), 43 (20).

Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.08; H, 8.33; N, 17.07.

A second fraction was **2b**, a white solid, 0.095 g (24%), whose spectral data were in agreement with those previously reported by Elguero *et al.* [3].

1-(Tetrahydrofuran-2-yl)benzimidazole (**3c**).

A suspension of solid sodium hydride (0.115 g, 4.8 mmoles) in 50 ml of dry tetrahydrofuran was treated with freshly distilled diiodomethane (2.68 g, 10.0 mmoles) and heated to reflux overnight. Then 0.473 g (4.00 mmoles) of benzimidazole was added to the resulting yellow mixture and reflux was prolonged for another 2 days. Thin layer chromatography (tlc) showed that no benzimidazole remained and that no **2c** was detectable. After removal of the tetrahydrofuran, the crude mixture was purified on a column of alumina, using 5% methanol in ethyl acetate as eluent. The mixed fractions were rechromatographed on silica gel using 15% methanol in ethyl acetate. The total yield of **3c** was 0.210 g (28%), isolated as a yellowish oil, bp 188-190°; ^{1}H nmr: δ 2.16 (m, 2H), 2.48 (m, 2H), 4.09 (ddd, 1H), 4.22 (ddd, 1H), 6.22 (dd, 1H), 7.32 (m, 2H), 7.49 (m, 1H), 7.83 (m, 1H), 8.05 (s, 1H) ppm; ^{13}C nmr: δ 24.3, 31.9, 69.0, 86.1, 110.5, 120.5, 122.5, 123.1, 132.7, 140.3, 144.4; ms: *m/z* (%) 188 (52), 157 (6), 118 (99), 71 (100), 43 (43).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 67.99; H, 6.67; N, 14.33.

A later fraction contained a white solid, later identified as 1(*N*)-methylbenzimidazole, 0.120 g (23%), and a third contained benzimidazole, 0.030 g (6%).

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REFERENCES AND NOTES

* Telephone: (416) 736-2100 ext 66140. FAX: (416) 736-5936. E-mail: pgpotvin@yorku.ca

[1] J. Zadykowicz and P. G. Potvin, *J. Org. Chem.*, **63**, 235 (1998).

[2] R. Dash and P. G. Potvin, *Can. J. Chem.*, **70**, 2249 (1992); Y. Luo and P. G. Potvin, *J. Org. Chem.*, **59**, 1761 (1994); P. van der Valk and P. G. Potvin, *J. Org. Chem.*, **59**, 1766 (1994).

[3] J. Elguero and C. Ochoa, *J. Heterocyclic Chem.*, **25**, 1797 (1960).

[4] C. G. Kruse, E. K. Poels, F. L. Jonkers and A. van der Gen, *J. Org. Chem.*, **43**, 3548 (1978).

[5] C. G. Kruse, N. L. J. M. Broekhof and A. van der Gen, *Tetrahedron Letters*, 1725 (1976).

[6] B. Yu and Y. Hui, *Synth. Commun.*, **25**, 2037 (1995).

[7] E. Vilsmeier, *Liebigs Ann. Chem.*, **728**, 12 (1969); E. Vilsmeier and R. Westernacher, *Liebigs Ann. Chem.*, **757**, 170 (1972); W. Middlebos, B. Zwanenburg and J. Strating, *Rec. Trav. Chim. Pays-Bas*, **90**, 435 (1971); F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955); D. L. Tuleen and R. H. Bennett, *J. Heterocyclic Chem.*, **6**, 115 (1969); G. E. Wilson and R. Albert, *J. Org. Chem.*, **38**, 2156 and 2160 (1973); M. A. Vasijanina and V. K. Khairullin, *J. Org. Chem. USSR (Engl. Transl.)*, **10**, 2175 (1976); W. E. Truce, G. H. Birum and E. T. McBee, *J. Am. Chem. Soc.*, **74**, 3594 (1952); D. L. Tuleen and V. C. Marcum, *J. Org. Chem.*, **32**, 204 (1967); D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34**, 31 (1969); J. S. Grossert, W. R. Hardstaft and R. F. Langler, *Can. J. Chem.*, **55**, 425 (1977); G. Allegra, G. E. Wilson, Jr., C. Pedone, E. Benedeth and R. Albert, *J. Am. Chem. Soc.*, **92**, 4002 (1970).

[8] C. G. Kruse, F. L. Jonkers, V. Dert and A. van der Gen, *Recl. Trav. Chim. Pays-Bas*, **98**, 371 (1979).

[9] J.-C. Jung, H.-C. Choi and Y.-H. Kim, *Tetrahedron Letters*, 3581 (1993).

[10] A. M. Maione and A. Romeo, *Synthesis*, 250 (1987).

[11] M. C. Pirrung and C. V. DeAmicis, *Heterocycles*, **25**, 189 (1987); M. C. Pirrung and C. V. DeAmicis, *Tetrahedron Letters*, 159 (1988); M. C. Pirrung, V. K. Chang and C. V. DeAmicis, *J. Am. Chem. Soc.*, **111**, 2824 (1989); E. Lee-Ruff, I. I. E. Hayes and L. Jandrisits, *Can. J. Chem.*, **67**, 2057 (1989); E. Lee-Ruff, W.-Q. Wan and J.-L. Jiang, *Tetrahedron Letters*, 261 (1993); E. Lee-Ruff, J.-L. Jiang and W.-Q. Wan, *J. Org. Chem.*, **59**, 2114 (1994); E. Lee-Ruff, F. Xi and J. H. Qie, *J. Org. Chem.*, **61**, 1547 (1996).

[12] L. Kaplan, *J. Am. Chem. Soc.*, **89**, 4566 (1967).

[13] V. Franzen and L. Fikentscher, *Chem. Ber.*, **95**, 1958 (1962).

[14] T. S. Everett, S. T. Purrington and C. L. Bumgardner, *J. Org. Chem.*, **49**, 3702 (1986); P. Bey, J.-P. Vevert, V. Van Dorsselaer and M. Kolb, *J. Org. Chem.*, **44**, 2732 (1979); I. Rico, D. Cantacuzene and C. Wakselman, *J. Org. Chem.*, **48**, 1979 (1983) and *J. Chem. Soc., Perkin Trans. 1*, 1063 (1982), and references cited therein.

[15] R. B. Bates, L. M. Kroposki and D. E. Potter, *J. Org. Chem.*, **37**, 560 (1972) and references cited therein.

[16] F. W. Evans, R. J. Fox and M. Szwarc, *J. Am. Chem. Soc.*, **82**, 6416 (1960).

[17] J. Fossey, D. Lefort and J. Sorba, Free Radicals in Organic Chemistry, Wiley, New York, 1995, p 129.

[18] D. M. Golden and S. W. Benson, *Chem. Rev.*, **69**, 125 (1969).

[19] J. Moreau and P. Caubere, *Tetrahedron*, **27**, 5741 (1971).

[20] E. C. Ashby, A. K. Deshpande and F. Doctorovich, *J. Org. Chem.*, **59**, 6223 (1994).

[21] R. B. Nelson and G. W. Gribble, *J. Org. Chem.*, **39**, 1425 (1974).

[22] P. Caubere and J. Moreau, *Tetrahedron*, **25**, 2469 (1969); *Bull. Soc. Chim. France*, 1986 (1970); S. Bank and M. C. Prislopski, *J. Chem. Soc., Chem. Commun.*, 1624 (1970).

[23] D. C. Blomstrom, K. Herbig and H. E. Simmons, *J. Org. Chem.*, **30**, 959 (1965).

[24] K. Kimura and S. Nagakura, *Spectrochim. Acta*, **17**, 166 (1961).

[25] B. Mudryk and T. Cohen, *J. Am. Chem. Soc.*, **113**, 1866 (1991); J. J. Eisch, *J. Org. Chem.*, **28**, 707 (1963); W. J. Bailey and F. Marktscheffel, *J. Org. Chem.*, **25**, 1797 (1960).