Chemistry of Heterocyclic Compounds, Vol. 44, No. 9, 2008

NEW APPROACH TO THE FORMATION OF AZEPINE RING: SYNTHESIS OF 2-METHYL-6-(5-METHYL-2-THIENYL)-3H-AZEPINE FROM 2-METHYL-5-PROPARGYLTHIOPHENE AND ISOTHIOCYANATE*

N. A. Nedolya, O. A. Tarasova, O. G. Volostnykh, and A. I. Albanov

The first representative of thienyl-substituted 3H-azepines has been synthesized starting from dilithiated 2-methyl-5-propargylthiophene and isopropyl isothiocyanate. It was shown that N-(1-methylethylidene)-2-(5-methyl-2-thienyl)-1-(methylthio)-1,3-butadiene-1-amine (2-aza-1,3,5-triene) formed as a result of this reaction is readily converted into 2-methyl-6-(5-methyl-2-thienyl)-3H-azepine under the action of super bases.

Keywords: azatrienes, 3H-azepines, deprotonation, isothiocyanates, propargylthiophene, electrocyclization.

The reaction of dilithiated 2-methyl-5-propargylthiophene **1** with isothiocyanates leads, depending on the structure of the latter, with a high degree of selectivity to an exotic bicyclic systems, *viz.* poly-substituted 2,3'-bithiophenes **2**, 1-(2-thienyl)cyclobutenes **3**, and 3-(2-thienyl)thietane **4** [1].

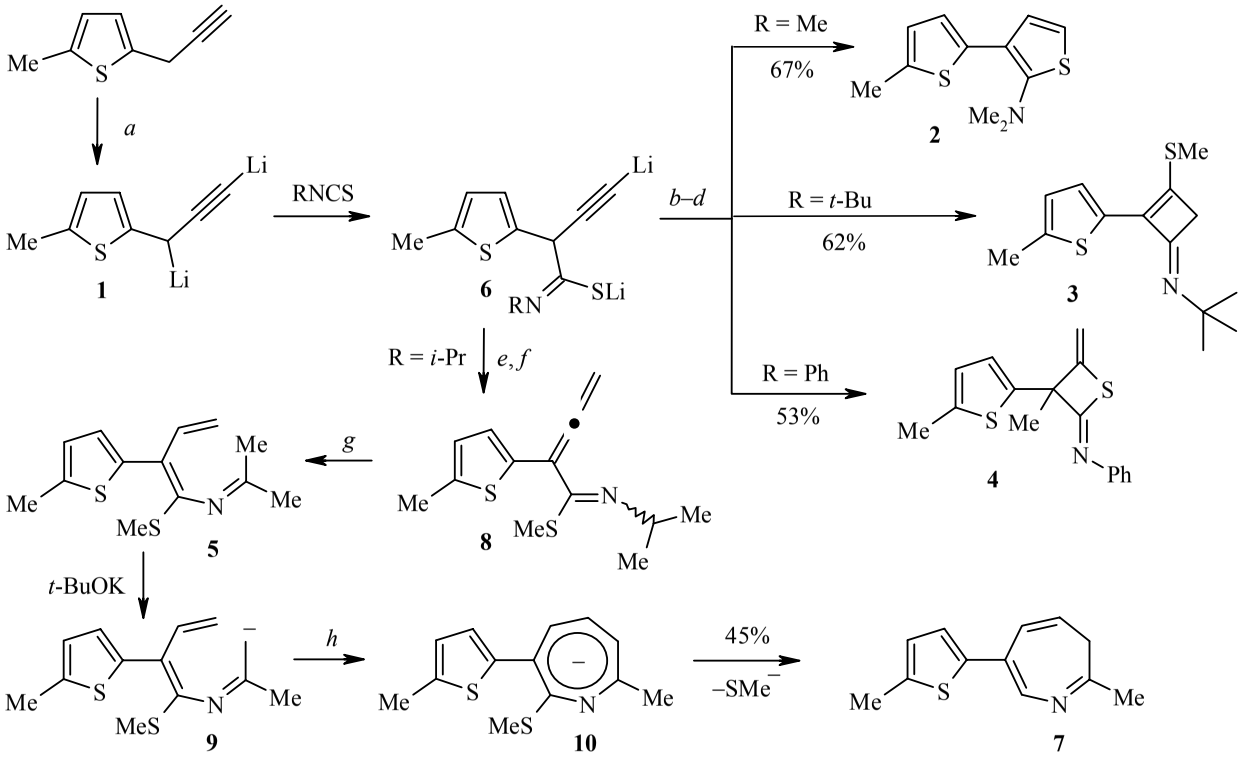
While continuing these investigations we have found that the conjugated 2-aza-1,3,5-triene **5**, readily obtained from the adduct of dilithiated 2-methyl-5-propargylthiophene with isopropyl isothiocyanate (intermediate **6**, R = *i*-Pr), interacts with potassium *tert*-butoxide (THF–DMSO, 4.5:1, -30°C, 30 min) with the formation of the previously unknown and unavailable 2-methyl-6-(5-methyl-2-thienyl)-3H-azepine (**7**), the nonoptimized yield of which was 45%.

The structure of azepine **7** was established on the basis of data of elemental analysis and ^{1}H and ^{13}C NMR spectra. Heteronuclear (HSQC and HMBC) two-dimensional correlation methods were used to assign the carbon atom signals in the ^{13}C NMR spectra.

The whole process, from lithiation of the available 2-methyl-5-propargylthiophene [2] to formylation of the azepine nucleus, was carried out in three preparative stages: 1) one-pot synthesis of 1-aza-1,3,4-triene **8**; 2) thermally induced isomerization of 1-aza-1,3,4-triene **8** into 2-aza-1,3,5-triene **5** (through a [1,5]-H sigmatropic shift); 3) rapid transformation of 2-aza-1,3,5-triene **5** into azepine **7** under the action of *t*-BuOK (through intermediates **9** and **10**).

* Dedicated to Academician B. A. Trofimov of the Russian Academy of Sciences on his 70th jubilee.

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, Irkutsk 664033; e-mail: nina@irioch.irk.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1380-1383, September, 2008. Original article submitted July 3, 2008.



a – 2 BuLi–THF–hexane; *b* – *t*-BuOH; *c* – *t*-BuOK–DMSO; *d, f* – MeI; *e* – *t*-BuOH; *g* – [1,5]-H shift; *h* – [1,7]electrocyclization

2-Aza-1,3,5-trienes, obtained from monolithiated allenic acetals, are subject to highly selective reorganization under the action of superbases into structural isomers of the azacycloheptadiene series, *viz*. 2-(methylsulfanyl)-4,5-dihydro-3H-azepines [3].

It is evident that the implication into this reaction of other isothiocyanates containing *sec*-alkyl and cycloalkyl substituents like other propargylthiophenes offers an effective synthetic approach to previously unknown azepine–thiophene ensembles as promising basic compounds for the construction of new medicinal agents and materials for critical technology [4-8].

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra (400 and 100 MHz respectively) and the experiments on heteronuclear correlation were carried out on Bruker DPX 400 and AV-400 instruments in $CDCl_3$, internal standard was HMDS.

N-(1-Methylethylidene)-2-(5-methyl-2-thienyl)-1-(methylsulfanyl)-1,3-butadienylamine (2-Aza-1,3,5-triene 5). A solution of BuLi (102 mmol) in hexane (64 ml) was added with vigorous stirring at –100°C in an atmosphere of argon to a solution of 2-methyl-5-propargylthiophene (6.81 g, 50 mmol) in dry THF (110 ml). The mixture was stirred for 10 min at 10-12°C, then cooled to -90°C, and isopropyl isothiocyanate (5.05 g, 50 mmol) added. The mixture was stirred for 15 min at about -30°C, cooled to -55°C, and *t*-BuOH (3.7 g, 50 mmol) added. The temperature was allowed to rise to -40°C, the mixture cooled to -80°C, MeI (23 g, 16 mmol) was added, and the cooling removed. The mixture was stirred for 2 h at ~20°C, cooled to -80°C, saturated aqueous NH_4Cl solution (100 ml) was added, and the organic layer separated. The products from the aqueous fraction were extracted with ether (4×30 ml), the combined organic fraction was washed with water (2×50 ml), and dried over $MgSO_4$. The solvents were removed at ~20°C under reduced pressure. The residue (15.57 g) was chromatographed on a column of neutral Al_2O_3 [eluent petroleum ether (40-70°C)], methyl N-isopropyl-2-(5-methyl-2-thienyl)-2,3-butadieneimidothioate (1-aza-1,3,4-triene **8**, mixture of *syn* and *anti* isomers) mixed with 2-aza-1,3,5-triene **5** in a ratio of 88:12 was obtained (7.41 g, 59%) . ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 (6H, d, ^{3}J = 6.24, $(C\underline{H}_3)_2CH$); 2.35 (3H, s, SCH_3); 2.41 (3H, s, 5'-CH_3); 3.86 (1H, hept, ^{3}J = 6.24, $Me_2C\underline{H}$); 5.21 (2H, s, CH_2=); 6.62, 6.58 (2H, two d, ^{3}J = 2.68, H-3',4' thienyl) – *major isomer*; 1.23 (6H, d, ^{3}J = 6.24, $(C\underline{H}_3)_2CH$); 2.33 (3H, s, SCH_3); 2.41 (3H, s, 5'-CH_3); 3.92 (1H, hept, ^{3}J = 6.24, $Me_2C\underline{H}$); 5.31 (2H, s, CH_2=); 6.78, 6.58 (2H, two d, ^{3}J = 2.68, H-3',4' thienyl) – *minor isomer*; ratio 61:39.

The quantitative isomerization of 1-aza-1,3,4-triene **8** into 2-aza-1,3,5-triene **5** was effected by rotating a sample in a rotary evaporator at 74-82°C (bath temperature) for 10 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.94, 2.01 (6H, two s, $(CH_3)_2C$=): 2.22 (3H, s, SCH_3); 2.48 (3H, s, 5'-CH_3); 4.77 (1H, dd, J_{trans} = 17.05, J_{gem} = 1.4, CH_2=); 4.84 (1H, dd, J_{cis} = 10.64, J_{gem} = 1.4, CH_2=); 6.36 (1H, dd, J_{cis} = 10.64, J_{trans} = 17.05, CH=); 6.68 (2H, s, H-3',4' thienyl). ^{13}C NMR spectrum, δ, ppm: 13.94 (SCH_3); 15.44 (5'-CH_3); 21.60, 27.57 (($\underline{C}H_3)_2C$=)); 112.13 (CH_2=); 113.41 (C-2); 124.82, 133.74 (C-3', C-4' thienyl); 128.66 (CH=); 135.81 (C-1); 140.24 (C-2' thienyl); 145.61 (C-5' thienyl); 172.47 (C=N).

2-Methyl-6-(5-methyl-2-thienyl)-3H-azepine (7). A mixture of DMSO (10 ml) and THF (10 ml) and then *t*-BuOK (3.81 g, 34 mmol) were added to a solution of 2-aza-1,3,5-triene **5** (7.13 g, 28 mml) in THF (35 ml) at -65°C. The mixture was stirred at ~-30°C for 30 min, cooled to -60°C and water (100 ml) added. After separating the layers the products of the aqueous fraction were extracted with ether (4×40 ml), the combined organic fraction was washed with water (3 times), dried over $MgSO_4$, and the solvents removed under reduced pressure. The residue was purified by column chromatography [through a 3-4 cm layer of neutral Al_2O_3, eluent was petroleum ether (40-70°C)–Et_2O, 10:1]. Azepine **7** (2.59 g, 45%) was obtained as fine, light- brown crystals, mp 56°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.15 (3H, s, 2-CH_3); 2.44 (3H, s, 5'-CH_3); 5.39 (1H, dt, $^{3}J_{4,5}$ = 8.83, $^{3}J_{4\text{-}CH2\text{-}3}$ = 6.91, H-4); 6.45 (1H, dd, $^{3}J_{5,4}$ = 8.83, $^{4}J_{5,7}$ = 1.66, H-5); 6.64 (1H, dq, $^{3}J_{4',3'}$ = 3.58,

$^4J_{4',Me}$ = 1.02, H-4' thienyl); 6.81 (1H, d, $^3J_{3',4'}$ = 3.58, H-3' thienyl); 7.65 (1H, br. s, H-7). ^{13}C NMR spectrum, δ, ppm: 15.31 (5'-CH_3); 26.21 (2-CH_3); 38.35 (C-3); 116.61 (C-4); 123.14 (C-6); 123.62 (C-3' thienyl); 125.83 (C-4' thienyl); 127.0 (C-5); 136.69 (C-7); 138.76 (C-5' thienyl); 141.76 (C-2' thienyl); 149.90 (C-2). Found, %: C 71.36; H 6.55; N 6.94; S 16.49. $C_{12}H_{13}NS$. Calculated, %: C 70.89; H 6.45; N 6.86; S 15.77.

The work was carried out with the financial supportof the Russian Foundation for Fundamental Investigations (RFFI) (grant No. 05-03-32578a).

REFERENCES

1. O. A. Tarasova, L. Brandsma, N. A. Nedolya, and G. V. Dmitrieva, in: *International Conference on the Chemistry of Heterocyclic Compounds. Dedicated to the 90th Birthday of Professor A. N. Kost, Abstracts,* Moscow, 2005, p. 316.
2. L. Brandsma, *Best Synthetic Methods. Synthesis of Acetylenes, Allenes, and Cumulenes: Methods and Technique*, Acad. Press, Elsevier, Amsterdam, Boston, Heidelberg, London, New York, Oxford, Paris, San Diego, San Francisco, Sydney, Tokyo, 2004, p. 254.
3. N. A. Nedolya, O. A. Tarasova, A. I. Albanov, O. G. Volostnykh, L. Brandsma, and B. A. Trofimov, *Mendeleev Commun.*, **18**, 164 (2008).
4. D. J. Le Count in: A. R. Katritzky, C. W. Rees, and E. F. V. Scriven (editors), *Comprehensive Heterocyclic Chemistry II,* Vol. 9, Elsevier, Oxford, (1996), p. 1.
5. R. J. Knapp, R. Goldenberg, C. Shuck, A. Cecil, J. Watkins, C. Miller, G. Crites, and E. Malatynska, *Eur. J. Pharmacol.*, **440**, 27 (2002).
6. O. Levy, M. Erez, D. Varon, and E. Keinan, *Bioorg. Med. Chem. Lett.*, **11**, 2921 (2001).
7. M. Gill, *Nat. Prod. Rep.*, **20**, 615 (2003).
8. J. Schatz, T. Brendgen, and D. Schühle, in: A. R. Katritzky, C. A. Ramsden, E. F. V, Scriven, and R. J. K. Taylor (editors), *Comprehensive Heterocyclic Chemistry III. A Review of the Literature 1995-2007*, Vol. 3, Elsevier, Amsterdam, Boston, Heidelberg, London, New York, Oxford, Paris, San Diego, San Francisco, Singapore, Sydney, Tokyo, (2008), p. 931.