ISSN 0012-5008, Doklady Chemistry, 2010, Vol. 432, Part 1, pp. 133–135. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © A.B. Koldobskii, N.P. Tsvetkov, V.N. Kalinin, 2010, published in Doklady Akademii Nauk, 2010, Vol. 432, No. 2, pp. 188–190.

CHEMISTRY

Universal Method for the Functionalization of β-Bromovinyl Trifluoromethyl Ketones of Cyclobutene Series

A. B. Koldobskii, N. P. Tsvetkov, and V. N. Kalinin

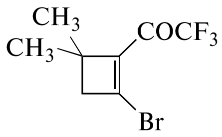
Presented by Academician Yu.N. Bubnov October 14, 2009

Received November 10, 2009

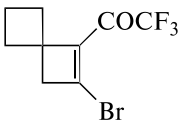
DOI: 10.1134/S0012500810050046

Unsaturated trifluoromethyl ketones are a new extremely promising class of compounds whose properties in recent two decades have been intensively studied in medicine [1], biochemistry [2], and molecular biology [3]. Moreover, these compounds are widely used in organic synthesis [4]. It is of special synthetic interest to use unsaturated trifluoromethyl ketones containing a leaving group in the β position, whose structural features provide a possibility to carry out functionalization reactions and to synthesize different fluorine-containing heterocyclic compounds [4]. However, these transformations have hitherto been studied only for the simplest acyclic β-substituted fluorine-containing enones [5], whereas similar enones with the C=C bond being incorporated into a strained small ring have been unknown until recently.

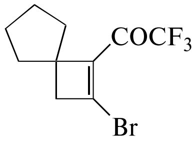
Very recently, we found an unusual reaction of [2+2] cycloaddition of 1-trifluoroacetyl-2-haloacetylenes to simple alkenes that proceeded in the absence of light and catalyst to give β-halovinyl trifluoromethyl ketones of cyclobutene series [6, 7]. With the use of corresponding bromides **1a–1f**, we attempted to develop a general method for the displacement of bromine atom by different aryl and hetaryl substituents to form new β-arylvinyl trifluoromethyl ketones of cyclobutene series.



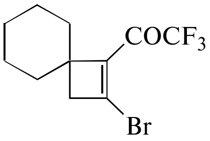
1a



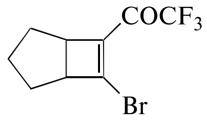
1b



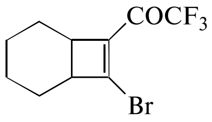
1c



1d



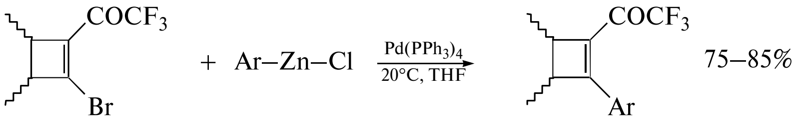
1e



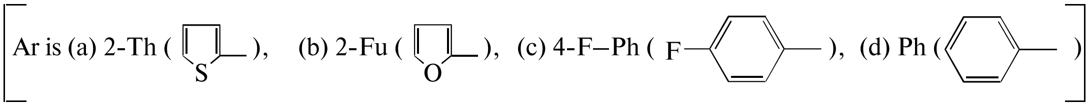
1f

At the first stage of research, we established that organolithium compounds and Grignard reagents bind mainly at the carbonyl group of unsaturated ketones **1** to yield corresponding tertiary alcohols, the C=C bond and the halogen atom being intact. Reactions with arylzinc chlorides (2-thienyl-, 2-furyl-, 4-fluorophenyl-, and phenylzinc chlorides) are very slow and lead to a complex mixture of products in low yield. We have found, however, that the addition of catalytic amounts of tetrakis(triphenylphosphine)palladium (the Negishi reaction) considerably accelerates the process and allows preparation in high yields of corresponding cross-coupling products **2–7** where bromine atom is displaced by an aryl group.

Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, Moscow, 119991 Russi

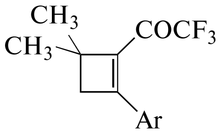


1 **2–7**

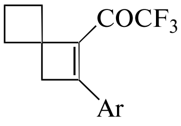

Ar is (a) 2-Th (S), (b) 2-Fu (O), (c) 4-F–Ph (F), (d) Ph ( )

It is worth noting that, in spite of the very high carbonyl activity of the trifluoroacetyl group in ketones **1**, the careful analysis of reaction products showed the complete absence of tertiary alcohols that could result from the addition of organozinc compounds to the C=O bond.

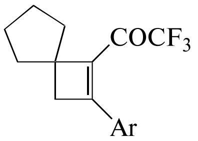
The revealed transformation seems to have a general character: all vinyl bromides **1** react with different arylzinc compounds under mild conditions to give corresponding β-arylvinyl trifluoromethyl ketones **2–7** retaining the cyclobutene fragment.



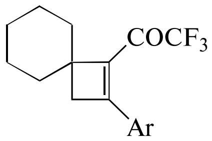
2a–2d



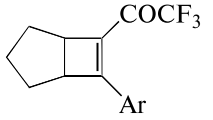
3a–3d



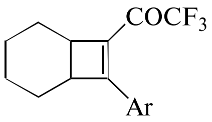
4a–4d



5a–5d



6a–6d



7a–7d

[Ar is (a) 2-Th, (b) 2-Fu, (c) 4-F–Ph, (d) Ph]

It should be noted that substituted cyclobutenes are of great interest as biologically active compounds [8]; in addition, they are universal reagents in organic synthesis due to high reactivity [9]. However, until now, neither the general method for the preparation of cyclobutenes containing trifluoroacetyl group nor the methods for the introduction of substituents in the β position of the strained endocyclic C=C bond have been available and the conjugated trifluoroacetylcyclobutenes have been unknown. The present work offers broad access to this new class of compounds and comprehensive study of its properties.

EXPERIMENTAL

The synthesis of all organozinc compounds and cross-coupling reactions were carried out in an argon atmosphere with the use of anhydrous solvents. Initial bromocyclobutenes **1a–1f** were obtained by the [2 + 2] cycloaddition of 1-trifluoroacetyl-2-bromoacetylene to appropriate alkenes [6, 7]. In all experiments, the structure of cross-coupling products **2–7** was confirmed by elemental analysis data, ^{1}H and ^{13}C NMR, and IR spectra.

General Procedure for the Synthesis of Adducts **2–7**

(a) Synthesis of 2-thienyl-, 2-furyl-, and 4-fluorophenylzinc chlorides. A solution of butyllithium in hexane (6.2 mL of 1.6 M solution, 0.01 mol) was added dropwise to a solution of 0.012 mol of thiophene or 0.012 mol of furan in 10 mL of anhydrous THF with stirring under an argon atmosphere and cooling to 0°C. The reaction mixture was stirred for 0.5 h at 0°C. (Under these conditions, 2-thienyllithium and 2-furyllithium form in quantitative yield [10].) 4-Fluorophenyllithium and phenyllithium were obtained by the addition of 6.2 mL of a 1.6 M solution of butyllithium in hexane (0.01 mol) to a stirred solution of *p*-fluorobromobenzene or bromobenzene (0.011 mol) in 10 mL of THF at –70°C followed by stirring of the reaction mixture for 1 h at –70°C. A solution of 1.57 g (0.012 mol) of anhydrous $ZnCl_2$ in 15 mL of THF was added dropwise to the prepared solution or suspension of organolithium compound with stirring and cooling to –70°C, the reaction mixture was allowed to warm to 20°C, and the resultant organozinc compounds were further used in the cross-coupling reactions.

(b) Cross-coupling reactions of cycloadducts 1a–1f with organozinc compounds. One of compounds **1a–1f**

(0.01 mol) and 0.01 g (0.002 mol) of $Pd(PPh_3)_4$ were added to a stirred solution of organozinc compound at 20°C in one portion. After an exothermic reaction completed, the mixture was stirred for 18 h at 20°C, and 30 mL of a saturated solution of ammonium chloride was added. The organic layer was separated, and the aqueous layer was extracted with ether (4 × 20 mL). The combined organic extracts were washed with 20 mL of a saturated solution of ammonium chloride, dried with sodium sulfate, and concentrated in a vacuum. The residue was diluted with 30 mL of hexane, catalyst decomposition products were separated by filtration, and the filtrate was concentrated in a vacuum. The residue was passed through a thin layer of silica gel in a hexane–ethyl acetate (2 : 1) solution, and the solution was concentrated. Adducts **2–7** were isolated by column chromatography on silica gel with hexane–ethyl acetate (2 : 1) as an eluent.

REFERENCES

1. Ashour, M.B. and Hammock, B.D., *Biochem. Pharm.,* 1987, vol. 36, pp. 1869–1873.
2. Szekacs, A., Hammock, B.D., Abdel-Aal, Y.A.I., and Halarnkar, S.J., *Pestic. Biochem. Physiol.,* 1989, vol. 33, pp. 112–120.
3. Allen, K.N. and Abeles, R.N., *Biochemistry*, 1989, vol. 28, pp. 135–148.
4. Druzhinin, S.V., Balenkova, E.S., and Nenajdenko, V.G., *Tetrahedron*, 2007, vol. 63, pp. 7753–7808.
5. Nenajdenko, V.G., Druzhinin, S.V., and Balenkova, E.S., Chemistry of *α,β-Unsaturated Trifluoromethyl Ketones*, New York: Nova Sci. Publ., 2007.
6. Tsvetkov, N.P., Koldobskii, A.B., and Kalinin, V.N., *Dokl. Chem.,* 2005, vol. 404, part 1, pp. 174–177 [*Dokl. Akad. Nauk*, 2005, vol. 404, no. 2, pp. 201–204].
7. Koldobskii, A.B., Tsvetkov, N.P., Verteletskii, P.V., et al., *Izv. Akad. Nauk, Ser. Khim.,* 2009, no. 7, pp. 1390–1396.
8. Lee-Ruff, E., *Adv. Strain Org. Chem.,* 1991, vol. 1, pp. 167–213.
9. Lee-Ruff, E. and Mladenova, G., *Chem. Rev.*, 2003, vol. 103, pp. 1449–1483.
10. Brandsma, L. and Verkruijsse, H.D., *Preparative Polar Organometallic Chemistry*, New York: Springer, 1988, vol. 1.