Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2022, **32**, 218–220

Mendeleev Communications

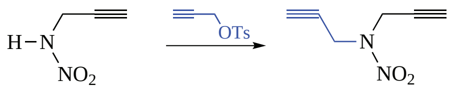
Di(propargyl)nitramine: synthesis and reactivity

Pavel S. Gribov,[a] Maria V. Mikhailova,[a,b] Tatiana S. Kon'kova,[c]
Yurii N. Matyushin[c] and Aleksei B. Sheremetev*[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: sab@ioc.ac.ru*
[b] *Mendeleev University of Chemical Technology, 125047 Moscow, Russian Federation*
[c] *N. N. Semenov Federal Research Center for Chemical Physics, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2022.03.021

An improved synthesis of (propargyl)nitramine and its pioneering conversion to di(propargyl)nitramine involve the alkylation of *NH* nitramines with propargyl halides or tosylate as the key steps. The standard ($p° = 0.1$ MPa) molar enthalpy of formation at 298.15 K for di(propargyl)nitramine was determined from the experimental standard molar energy of combustion in oxygen, measured by static bomb combustion calorimetry. Propargyl nitramines are suitable substrates for 1,3-dipolar cycloaddition reactions with azides, nitrile oxides and diazo compounds.



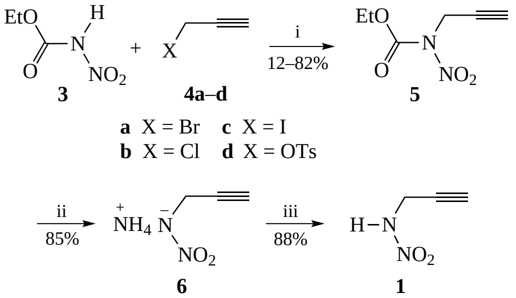
Keywords: propargylation, nitramines, click reactions, alkynes, azides, 1,2,3-triazoles, nitrile oxides, isoxazoles, diazoacetates, pyrazoles.

The nitramino group has long been recognized as a useful structural moiety for the design and synthesis of promising energetic compounds.[1–3] For these syntheses, the basic strategy is a combining of various explosophoric groups and auxiliary units on different frameworks into a target molecule. The ever-growing variety of structural motifs in the architecture of nitramines allows them to be used in a wide variety of fields due to the unique properties exhibited by them. Indeed, both explosives and propellant components such as oxidizers, fillers, polymers, plasticizers or combustion modifiers were created on the basis of nitramines. Evidently, the development of synthetic methods for combining the nitramino group with other useful groups and moieties is of considerable interest.

However, although the combination of various groups and frameworks with nitramino moiety has been documented,[4–8] very few examples have been reported on the synthesis of propargyl nitramines.[9–13] A bibliographical search in the Reaxys database revealed three articles and two patents containing information on only 12 compounds, only a few of them having been characterized by ^{1}H NMR spectra with neither ^{13}C or ^{14}N NMR nor X-ray data.

In 1964, (propargyl)nitramine was first patented by Cohen *et al*. as a liquid monopropellant for rocket engines.[9] In the next twenty years, two other approaches were described. Existing synthetic protocols to this rarely encountered combination of functional groups can be categorized as follows. (1) Nitration of *N*-propargyl urethane with HNO_3/Ac_2O mixtures at –20 °C followed by deprotection of the nitramine function (two examples[9,12]); (2) ring-opening solvolysis of *N*-(2,2-dibromocyclopropyl)-*N*-methyl-*N*-nitroamine in ethanol in the presence of KF with prolonged reflux (one example[11]); (3) *N*-alkylation of nitramines with propargyl halides in the presence bases (five examples[10,12,13]). However, due to safety and reproducibility concerns, protocols (1) and (2) are not suitable for scaling. In general, *N*-monosubstituted *N*-nitramines readily dissociate in polar solvents to form ambident anions whose alkylation affords isomeric products of N- and O-attacks.[4–8,10,12] In all cases, laborious procedures were required to obtain propargyl nitramines, while dipropargyl analogues were unknown.

Herein we report an improved procedure for access to parent (propargyl)nitramine **1** and its use as a building block for the first synthesis of di(propargyl)nitramine **2**, as well as describe their participation in some 1,3-dipolar cycloaddition reactions. We turned attention at readily available ethyl nitrocarbamate **3**[14] as the starting material promising for sequential introduction of two propargyl moieties. Our synthesis of monopropargyl nitramine **1** is depicted in Scheme 1. The alkylation of compound **3** with various alkyl halides is well-documented; it typically proceeds selectively at the N atom under various conditions, including the use of ammonium salt of **3** in acetone,[15] with its silver salt in acetonitrile at reflux,[16,17] with the lithium salt in methanol,[18] and in the presence of triethylamine in CH_2Cl_2.[12] The avoidance of



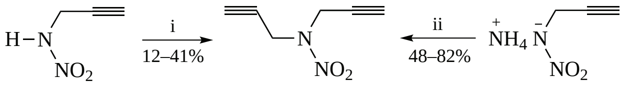
Scheme 1 *Reagents and conditions*: i, different solvents, base, 20–80 °C; ii, NH_3/Et_2O; iii, H^+.

the special preparation of compound **3** salts looks attractive. Therefore, initially conditions identical to those employed by Unterhalt *et al.*[19] (CH_2Cl_2 as the solvent and NEt_3 as the base at 40 °C) were tested; however, the reaction of compound **3** with propargyl bromide **4a** gave only a 12% yield of product **5**. A screen of other solvents revealed that the alkylation proceeded at room temperature in benzene, THF, MeOH, DMSO, and MeCN. The highest yield (71%) of **5** was achieved in DMF at room temperature for 96 h (for details, see Online Supplementary Materials, Table S1). Replacing NEt_3 with K_2CO_3 resulted in a similar yield of **5**. Using catalytic amounts of KI had a minimal impact on the yield of **5**. One common way to shorten the reaction time is to heat. An increase in temperature to 80 °C provided 100% conversion of nitrocarbamate **3** within 2 h, however the yield of compound **5** dropped to 63%; with the prolongation the reaction the yield decreased even more.

Finally, we examined the effects of the nature of four different propargylic reagents, $HC{\equiv}CCH_2{-}X$ **4a–d** (see Scheme 1). We found that employment of propargyl tosylate **4d** afforded the highest yield (82%) when using DMF as the solvent and NEt_3 as the base at room temperature for 96 h (see Table S1). To the best of our knowledge, this is the second example of the alkylation of nitramines with alcohol tosylates.[20] For comparison, the application of propargyl chloride **4b** or iodide **4c** brought about complex mixtures requiring lingering silica gel chromatography for isolation of product **5**.

When compound **5** was treated with an excess of gaseous ammonia in diethyl ether, the ester group was readily removed to provide ammonium salt **6** in 85% yield (see Scheme 1), while the same reaction in a mixture of diethyl ether and chloroform (1 : 1) gave salt **6** in quantitative yield with analytical purity. After acidification with 1 equiv. of H_3PO_4 at 0 °C, (propargyl)-nitramine **1** was obtained in good yield (88%) when extracted with diethyl ether and purified by passing through a short silica gel column. As a result, the reaction sequence shown in Scheme 1 produces compound **1** in overall 72% yield, which is more than double that of the previously developed approach.[9]

Having optimized conditions for propargylation of nitrocarbamate **3**, we looked to extend them to (propargyl)-nitramine **1** (Scheme 2, Table 1, entry 1). Using a shorter reaction time, since the anion generated from compound **1** is more nucleophilic than that from **3**, the conditions turned to be suitable providing the desired (dipropargyl)nitramine **2** in moderate yield (entry 2). The use of propargyl bromide **4a** as the alkylating agent is less effective than tosylate **4d** (31 *vs.* 43%). Variation of the temperature, reaction time, or the use of inorganic bases all failed to offer any further improvement in yield (see Table 1).



1 **2** **6**

Scheme 2 *Reagents and conditions*: i, $HC{\equiv}CCH_2X$ (**4a**,**d**), base, DMF, 20–80 °C; ii, $HC{\equiv}CCH_2X$ (**4a**,**d**), 20–80 °C.

Table 1 Optimization of the reaction[a] between (propargyl)nitramine **1** and propargylation agents **4a**,**d**.

Entry	Reagent	Base	*T*/°C	*t*/h	Yield[b] of **2** (%)
1	**4d**	NEt_3	20	96	35
2	**4d**	NEt_3	20	48	43
3	**4a**	NEt_3	20	48	31
4	**4d**	Li_2CO_3	20	48	12
5	**4d**	Na_2CO_3	20	48	18
6	**4d**	K_2CO_3	20	48	23
7	**4d**	NEt_3	40	48	41
8	**4d**	NEt_3	40	60	34
9	**4a**	Na_2CO_3	40	48	19

[a] Reactions were run with 10 mmol of **1**, 11 mmol of **4a**,**d**, and 1 equiv. of base in DMF (10 ml) for 96 h. [b] Isolated yields.

Surprisingly, when ammonium salt **6** was treated with propargyl bromide **4a** in DMF, TLC analysis showed complete consumption of the starting material within 12 h at room temperature, and the reaction gave the desired product **2** in 51% yield (Table 2, entry 1). Screening of various parameters provided an additional increase in the yield; the stoichiometry between the reactants, temperature and reaction time had an important influence on the reaction outcome. The reaction proceeded more efficiently in the presence of 1.5 equiv. of bromide **4a** (entry 3). The use of tosylate **4d** instead of bromide **4a** resulted in a noticeable increase in the yield of **2** (see Table 2, entries 1 and 6). The reaction time for this transformation could be reduced from 12 to 0.5 h by heating to 60 °C (entries 4 and 7), and the yield is increased by more than 20%. Notably, we observed no *O*-propargylation product in all of the above reactions; the other reaction components were composed of easily separable polar waste. The best reaction conditions (entry 7) gave 82% yield of (dipropargyl)nitramine **2** using ammonium salt **6** as the nucleophile. The practical applicability of the protocol is illustrated in the efficient 1 mole preparation of this compound, and only filtration through a pad of silica gel was necessary to obtain the desired product in pure form.

(Dipropargyl)nitramine **2** is a slightly yellow oil with an ambient temperature density of 1.155 g cm^{-3} and a boiling point of 75 °C at 1.5 mbar and 186 °C at atmospheric pressure. Compound **2** was found to have an enthalpy of formation of $+92.0 \pm 0.4$ kcal mol^{-1} by combustion calorimetry (see Online Supplementary Materials).

All compounds were characterized by IR, ^1H, ^{13}C and ^{14}N NMR spectroscopy as well as CHN analysis (see Online Supplementary Materials). For example, the δ values (in $CDCl_3$) for terminal H (2.42 ppm) and C (74.7 ppm) and the methylene group (^1H 4.67 and ^{13}C 39.7 ppm) of compound **2** conform well with the published values[21] for same atoms (^1H 2.44, ^{13}C 75.1 and ^1H 4.29, ^{13}C 37.2 ppm, respectively) of relative *N*,*N*-di(propargyl)triflamide. In the ^{14}N NMR spectra (with respect to $MeNO_2$ as external standard), the nitrogen atom of the nitro group resonated at –30.8 ppm.

With propargyl nitramines in hand, we wanted to quickly determine if typical [3+2] cycloaddition reactions could be performed using alkynes **2** and **5** as dipolarophiles to access heterocyclic adducts, aiming to assess whether this chemistry could be compatible with the nitramino group, since this topic has not been previously discussed. Under conventional (unoptimized) conditions,[22–25] model azide, nitrile oxide and diazo compound were tested in this study (Scheme 3). Azide

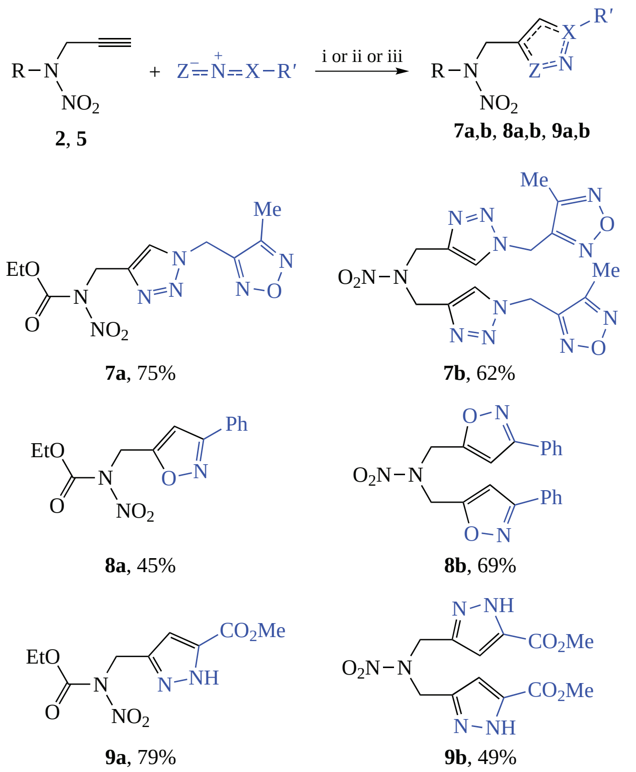
Table 2 Optimization of the reaction[a] between ammonium salt **6** and propargylating reagents **4a**,**d**.

Entry	Reagent	**6**/**4** ratio	*T*/°C	*t*/h	Yield[b] of **2** (%)
1	**4a**	1:1	20	12	48
2	**4a**	1:1.1	20	12	51
3	**4a**	1:1.5	20	12	66
4	**4a**	1:1.5	60	0.5	60
5	**4a**	1:1.5	60	1	56
6	**4d**	1:1	20	12	68
7	**4d**	1:1	60	0.5	82
8	**4d**	1:1	40	1	81
9[c]	**4d**	1:1	60	6	63

[a] Reactions were run with 10 mmol of **6**, 10–15 mmol of **4a,d** in DMF (10 ml) for 96 h. [b] Isolated yields. [c] The reaction was carried out in MeCN.

group of 3-azidomethyl-4-methylfurazan formed 1,2,3-triazoles **7a**,**b** in good yields under classical CuAAC conditions. Nitrile oxide (generated by *in situ* dehydrohalogenation of *N*-hydroxybenzenecarboximidoyl chloride) underwent cycloaddition with these alkynes to generate isoxazoles **8a**,**b**, and, in parallel, dimerized to form 3,4-diphenylfuroxan. When monoalkyne **5** reacted with methyl diazoacetate, the successful formation of 1*H*-pyrazole **9a** was observed indicating a tolerance for the nitramine functionality. However, in case of dialkyne **2**, the reaction gave a *ca*. 3 : 2 mixture (relative ratio from crude NMR analysis) of inseparable 3,3- and 3,4-regioisomers (see Scheme 3, only the main 3,3-regioisomer **9b** is presented; also see Online Supplementary Materials). Although the yields for the cycloaddition products remain to be optimized further, this approach appears to be a viable pathway for the synthesis of various *N*-(hetarylmethyl)nitramines. It should be noted that compounds **7b–9b** are exceedingly rare examples of dimethylnitramine derivatives bearing C-attached (het)aromatic rings.[18,26,27]

In conclusion, we have developed a safe, facile, efficient and fast synthetic route to propargyl nitramines *via* the alkylation reaction of a nitramine anion. Propargyl tosylate has been most efficient reagent for this purpose. Propargyl nitramines proved to be versatile building blocks for the construction of diverse heterocycles, including 1,2,3-triazoles, isoxazoles, pyrazoles, and should be useful in the syntheses considering the transformation of acetylene unit. The use of these building blocks is evidently an attractive strategy for the development of target-oriented nitramine syntheses. Future work will look at extending the scope of reagents employed in this study to create energetic materials.



Scheme 3 *Reagents and conditions*: i, 3-azidomethyl-4-methylfurazan, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, DMF, room temperature, 24 h; ii, Ph–C(=NOH)Cl, NEt_3, CH_2Cl_2, 0→20 °C; iii, $MeO_2C–CHN_2$, $ClCH_2CH_2Cl$, reflux, 110 h.

This work was supported by the Russian Foundation for Basic Research (grant no. 20-03-00514a).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.021.

References

1 J. P. Agrawal and R. D. Hodgson, *Organic Chemistry of Explosives*, Wiley, Hoboken, 2007.
2 S. G. Zlotin, A. M. Churakov, M. P. Egorov, L. L. Fershtat, M. S. Klenov, I. V. Kuchurov, N. N. Makhova, G. A. Smirnov, Yu. V. Tomilov and V. A. Tartakovsky, *Mendeleev Commun*., 2021, **31**, 731.
3 J. Zhou, J. Zhang, B. Wang, L. Qiu, R. Xu and A. B. Sheremetev, *FirePhysChem*, 2022, **2**, doi: 10.1016/j.fpc.2021.09.005.
4 A. L. Fridman, V. P. Ivshin and S. S. Novikov, *Russ. Chem. Rev.*, 1969, **38**, 640 (*Usp. Khim*., 1969, **38**, 1448).
5 S. V. Sysolyatin, G. V. Sakovich and V. N. Surmachev, *Russ. Chem. Rev.*, 2007, **76**, 673 (*Usp. Khim*., 2007, **76**, 724).
6 A. N. Gafarov and G. T. Shakirova, *Russ. Chem. Bull*., 2009, **58**, 2001 (*Izv. Akad. Nauk, Ser. Khim*., 2009, 1939).
7 U. Jahn, *Sci. Synth.*, 2010, **41**, 371.
8 A. E. Paromov and S. V. Sysolyatin, *Chem. Heterocycl. Compd*., 2017, **53**, 630.
9 M. S. Cohen, D. D. Perry and P. J. Keenan, *Patent US 3120566*, 1964.
10 B. Cross and D. H. Dawe, *Patent US 4130645*, 1978.
11 V. P. Ivshin, M. S. Komelin, G. B. Sofronova and T. V. Zykova, *J. Org. Chem. USSR*, 1982, **18**, 86 (*Zh. Org. Khim*., 1982, **18**, 101).
12 L. I. Vereshchagin, L. P. Kirillova, G. M. Luzgina and G. A. Gareev, *J. Org. Chem. USSR*, 1984, **20**, 29 (*Zh. Org. Khim*., 1984, **20**, 34).
13 V. P. Ivshin, T. N. Ivshina and K. I. Bakhtin, *J. Org. Chem. USSR*, 1984, **20**, 449 (*Zh. Org. Khim*., 1984, **20**, 498).
14 O. A. Luk'yanov, I. K. Kozlova, O. P. Shitov, Yu. V. Konnova, I. V. Kalinina and V. A. Tartakovsky, *Russ. Chem. Bull*., 1996, **45**, 863 (*Izv. Akad. Nauk, Ser. Khim*., 1996, 908).
15 J. Denkstein and V. Kadeřábek, *Coll. Czech. Chem. Commun*., 1966, **31**, 2904.
16 O. A. Luk'yanov, A. A. Onishchenko, G. V. Pokhvisneva and V. A. Tartakovskii, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1979, **28**, 1492 (*Izv. Akad. Nauk SSSR, Ser. Khim*., 1979, 1615).
17 O. A. Luk'yanov, T. G. Mel'nikova and E. G. Kashirskaya, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1982, **31**, 2420 (*Izv. Akad. Nauk SSSR, Ser. Khim*., 1982, 2738).
18 V. P. Tverdokhlebov, I. V. Tselinskii and B.V. Gidaspov, *Zh. Org. Khim*., 1976, **12**, 359 (in Russian).
19 B. Unterhalt and H. Bagherzadeh, *Pharmazie*, 2001, **56**, 745.
20 V. P. Tverdokhlebov, I. V. Tselinskii, B. V. Gidaspov and L. A. Fedorova, *Zh. Org. Khim.*, 1976, **12**, 362 (in Russian).
21 B. A. Shainyan and Yu. S. Danilevich, *Russ. J. Org. Chem*., 2015, **51**, 601 (*Zh. Org. Khim*., 2015, **51**, 623).
22 L. I. Belen'kii, in *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 2nd edn., ed. H. Feuer, Wiley, Hoboken, NJ, 2008, pp. 1–128.
23 T. V. Baiju and I. N. N. Namboothiri, *Chem. Rec*., 2017, **17**, 939.
24 E. A. Zakharova, O. I. Shmatova and V. G. Nenajdenko, *Russ. Chem. Rev.*, 2018, **87**, 619.
25 P. K. Mykhailiuk, *Chem. Rev*., 2020, **120**, 12718.
26 K. Yoshida, T. Nabeshima and Y. Yano, *J. Chem. Res., Synop*., 1991, 192.
27 G. Zhao, P. Yin, R. Staples and J. M. Shreeve, *Chem. Eng. J*., 2021, **412**, 128697.

Received: 18th October 2021; Com. 21/6727