ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2016, **26**, 226–227

Mendeleev Communications

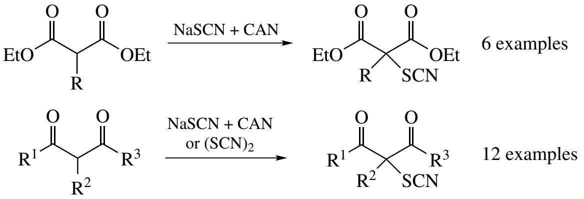
Difference in α-thiocyanation of malonates, β-oxo esters and β-diketones with sodium thiocyanate and cerium(IV) ammonium nitrate

Alexander O. Terent'ev,*[a,b] Mikhail Yu. Sharipov,[a,b] Alexey P. Glinuskin,[c] Igor B. Krylov,[a] Darya V. Gaidarenko[b] and Gennady I. Nikishin[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: terentev@ioc.ac.ru*
[b] *D. I. Mendeleev University of Chemical Technology of Russia, 125047 Moscow, Russian Federation*
[c] *All-Russian Research Institute of Phytopathology, 143050 B.Vyazyomy, Moscow Region, Russian Federation*

DOI: 10.1016/j.mencom.2016.05.001

β-Diketones and β-oxo esters are thiocyanated with the NaSCN/$(NH_4)_2Ce(NO_3)_6$ system or with pre-generated dirhodanogen. Malonates undergo thiocyanation only with the NaSCN/$(NH_4)_2Ce(NO_3)_6$ system.



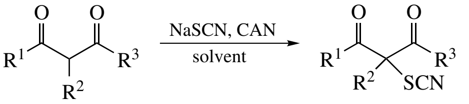
Thiocyanates prepared from carbonyl compounds are known as intermediates in the synthesis of thymidine,[1] triazole,[2] thiazolidine and cyclic thiourea derivatives,[3] some of which possess herbicidal activity.[4] Thiocyanates are of interest due to their antitumor, antiasthmatic and insecticidal activity.[5]

Here, were prepared thiocyanates from β-dicarbonyl compounds that differ significantly in their ability to undergo enolization. This reaction is characteristic of β-diketones and is less typical of β-oxo esters, whereas diesters (malonates) are virtually not enolized. Thiocyanomalonates are mainly obtained by the replacement of a halogen atom with a thiocyanate anion including one-pot halogenation followed by the replacement of a halogen atom.[4(a),6] Thiocyanation of diketones and oxo esters is usually carried out using metal thiocyanates and oxidizing agents, such as hypervalent iodine compounds,[4(a),7] potassium persulfate and copper(II) salts[8] or bromodimethylsulfonium bromide.[9] Another method commonly employed in the synthesis of thiocyanates from diketones and oxo esters is based on the substitution of a halogen atom in 2-halo-1,3-dioxo derivatives on treatment with metal thiocyanates.[6(a),(c),10]

In the present study, the thiocyanation of α-substituted β-dicarbonyl compounds **1a**–**r** with cerium(IV) ammonium nitrate (CAN) and sodium thiocyanate affords thiocyanates **2a**–**r** (Scheme 1).[†]

The reactivity of malonates in the thiocyanation with NaSCN/CAN system is essentially different from that of diketones and oxo esters. Optimization was performed using model diethyl benzylmalonate **1a** treated with NaSCN and CAN. The effect of the solvent nature, reagent ratio and synthesis procedure on the yield of diethyl 2-benzyl-2-thiocyanomalonate **2a** is outlined in Table 1.

The experiments were carried out by two different procedures. In runs 1–5, the thiocyanation was performed by mixing malonate **1a** and NaSCN followed by the addition of the oxidizing agent CAN, which provided the presence of all three reagents in the mixture in the beginning of the reaction. In runs 6–9, malonate **1a** was added to dirhodanogen pre-generated from NaSCN and



1a–**r** **2a**–**r**

	R^1	R^2	R^3	Yield of **2** (%)
a	OEt	CH_2Ph	OEt	96
b	OEt	Me	OEt	95
c	OEt	Et	OEt	95
d	OEt	Bu	OEt	96
e	OEt	$CH_2CH{=}CH_2$	OEt	96
f	OEt	Ph	OEt	90
g	Me	hexyl	Me	83
h	Me	$(CH_2)_2COOEt$	Me	95
i	Me	$(CH_2)_2CN$	Me	87
j	Me	CH_2Ph	Me	98
k	Me	$4\text{-}ClC_6H_4CH_2$	Me	95
l	Me	$4\text{-}BrC_6H_4CH_2$	Me	85
m	Me	$4\text{-}NO_2C_6H_4CH_2$	OEt	80
n	Me	$4\text{-}MeC_6H_4CH_2$	OEt	80
o	Me	Bu	OEt	88
p	Me	hexyl	OEt	85
q	$(CH_2)_4$		OEt	89
r	Me	$(CH_2)_2CN$	OEt	85

Scheme 1

[†] *General procedure.* Diethyl malonate **1a** (0.50 g, 2.0 mmol) and NaSCN (0.162–0.648 g, 2.0–8.0 mmol) were mixed with EtOAc (10 ml), and then CAN (1.096–4.386 g, 2.0–8.0 mmol) was added with stirring. The reaction mixture was stirred for 3 h at 20–25 °C, then CH_2Cl_2 (10 ml) was added, and the mixture was poured into water (30 ml) and extracted with CH_2Cl_2 (3×15 ml). Combined organic extracts were successively washed with a saturated $NaHCO_3$ solution (30 ml) and water (30 ml), dried over $MgSO_4$ and filtered. The solvent was evaporated under water-jet pump vacuum. Product **2a** was isolated by column chromatography on silica gel using light petroleum–ethyl acetate as the eluent with an increasing ethyl acetate gradient from 0 to 20%.

For more details and characteristics of compounds **2a**–**r**, see Online Supplementary Materials.

Table 1 Thiocyanation of model malonate **1a** and β-diketone **1j**.

Run	Substrate	Molar ratio **1**:NaSCN:CAN	Solvent	Product	Yield of **2** (%)
1[a]	**1a**	1:2:3	EtOAc	**2a**	82
2[a]	**1a**	1:3:2	EtOAc	**2a**	86
3[a]	**1a**	1:3:3	EtOAc	**2a**	96
4[a]	**1a**	1:3:4	EtOAc	**2a**	84
5[a]	**1a**	1:4:3	EtOAc	**2a**	84
6[b]	**1a**	1:3:3	EtOAc	**2a**	traces
7[b]	**1a**	1:3:3	Acetone	**2a**	traces
8[b]	**1a**	1:3:3	AcOH	**2a**	traces
9[b]	**1a**	1:1:1	AcOH	**2a**	traces
10[a]	**1j**	1:3:3	AcOH	**2j**	96
11[a]	**1j**	1:3:3	Acetone	**2j**	97
12[a]	**1j**	1:3:3	EtOH	**2j**	91
13[a]	**1j**	1:3:3	EtOAc	**2j**	98
14[b]	**1j**	1:3:3	EtOAc	**2j**	95

[a] CAN was added to a mixture of NaSCN and **1**, 20–25 °C, 3 h. [b] Compound **1** was added 10 min after the mixing of NaSCN and CAN, 20–25 °C, 3 h.

CAN. In the second case, thiocyanation product **2a** was virtually not detected. In runs 1–5, the reagent ratio was varied. The best results were achieved using **1a**:NaSCN:CAN in a ratio of 1:3:3. The unusual feature of the thiocyanation of malonates is that it occurs only when CAN, NaSCN and **1a** are simultaneously present in the starting reaction system. This is apparently attributed to the principally different reaction mechanism, which involves the transfer of the thiocyanate moiety from the cerium coordination sphere to malonate.[11]

The optimum reaction conditions for the synthesis of thiocyanates from β-diketones and β-oxo esters were determined using the reaction of 3-benzylpentane-2,4-dione **1j** with NaSCN and CAN (Table 1).

In runs 10–13, the conditions of the mixing of reactants provide the presence of all three reagents in the mixture in the beginning of the thiocyanation. In run 14, diketone **1j** was thiocyanated with pre-generated dirhodanogen. Product **2j** was synthesized in 91–98% yield regardless of the mixing mode. Apparently, the pre-generated $(SCN)_2$ adds at the enol form of the β-diketone.

The optimum reaction conditions given in Table 1 for run 3 were used to synthesize thiocyanates **2a–r** from α-substituted β-dicarbonyl compounds in yields indicated in Scheme 1.

In summary, the method proposed for the synthesis of thiocyanates using the NaSCN/CAN system is suitable for the thiocyanation of various α-substituted β-dicarbonyl compounds containing alkyl, benzyl or phenyl substituents in the α-position. The main achievements of the work are the development of one-step experimental procedure, application of available cerium(IV) ammonium nitrate and sodium thiocyanate, and simplicity of product isolation.

This work was supported by the Russian Foundation for Basic Research (grant no. 15-29-05820).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.05.001.

References

1 (*a*) T. T. Nikiforov and B. A. Connolly, *Tetrahedron Lett.*, 1992, **33**, 2379; (*b*) T. T. Nikiforov and B. A. Connolly, *Tetrahedron Lett.*, 1991, **32**, 2505.

2 J. B. Metzer, in *Comprehensive Heterocyclic Chemistry*, ed. A. Katritzky, Pergamon, Oxford, 1984, vol. 6, p. 235.

3 T. R. Kelly, M. H. Kim and A. D. M. Curtis, *J. Org. Chem.*, 1993, **58**, 5855.

4 (*a*) O. Prakash, H. Kaur, H. Batra and N. Rani, *J. Org. Chem.*, 2001, **66**, 2019; (*b*) *Chemistry and Biochemistry of Thiocyanic Acid and its Derivatives*, ed. A. A. Newman, Academic Press, London, New York, San Francisco, 1975.

5 (*a*) A. H. El-Sebae, R. L. Metcalf and T. R. Fukuto, *J. Econ. Entomol.*, 1964, **57**, 478; (*b*) P. S. Hewlett, *Ann. Appl. Biol.*, 1969, **63**, 477.

6 (*a*) F. Eiden and G. Gauglitz, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, 1969, **302**, 297; (*b*) Y. Tanabe, T. Makita and K. Mori, *Chem. Lett.*, 1994, **23**, 2275; (*c*) E. F. Atkins, S. Dabbs, R. G. Guy, A. A. Mahomed and P. Mountford, *Tetrahedron*, 1994, **50**, 7253; (*d*) Y. Suzuki and M. Kodomari, *Chem. Lett.*, 1998, **27**, 1091; (*e*) H. M. Meshram, P. B. Thakur, B. M. Babu and V. M. Bangade, *Tetrahedron Lett.*, 2012, **53**, 1780.

7 (*a*) O. Prakash, H. Kaur and R. Pundeer, *Synth. Commun.*, 2003, **33**, 4037; (*b*) J. S. Yadav, B. S. Subba Reddy, U. V. Subba Reddy and A. D. Krishna, *Tetrahedron Lett.*, 2007, **48**, 5243.

8 A. Kumar, P. Ahamd and R. A. Maurya, *Tetrahedron Lett.*, 2007, **48**, 1399.

9 D. S. Bhalerao and K. G. Akamanchi, *Synth. Commun.*, 2010, **40**, 799.

10 (*a*) H. L. Wheeler and G. S. Jamieson, *J. Am. Chem. Soc.*, 1902, **24**, 743; (*b*) W. D. Malmberg, J. Voß and S. Weinschneider, *Liebigs Ann. Chem.*, 1983, **10**, 1694; (*c*) A. O. Abdelhamid, H. M. Hassaneen, I. M. Abbas and A. S. Shawali, *Tetrahedron*, 1982, **38**, 1527.

11 (*a*) B. L. Kalsotra, R. K. Multani and B. D. Jain, *J. Inorg. Nucl. Chem.*, 1972, **34**, 2265; (*b*) F. A. Hart and F. P. Laming, *J. Inorg. Nucl. Chem.*, 1964, **26**, 579.

Received: 19th October 2015; Com. 15/4753