Synthesis of novel benzo[1,3]oxazines based on monoterpenoid (–)-isopulegol and study of their analgesic activity

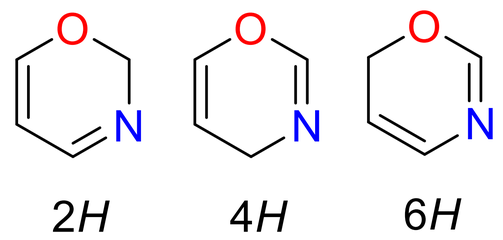
Nikolai Li-Zhulanov[1,2], A. Pavlova[1], D. Korchagina[1], Y. Gatilov[1], K. Volcho[1,2], T. Tolstikova[1], N. Salakhutdinov[1,2]

[1]N.N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, SB RAS, 9 Lavrentiev Ave., Novosibirsk 630090, Russia

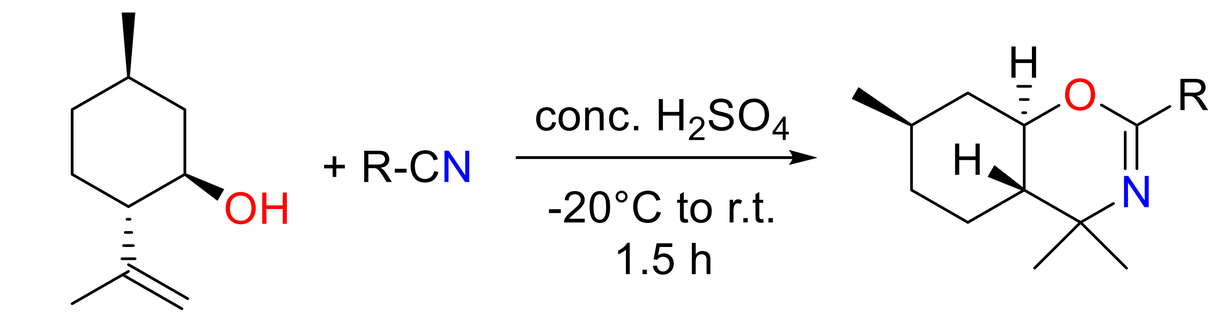
[2]Novosibirsk State University, 2 Pirogova St., Novosibirsk 630090, Russia

Oxazines are heterocyclic compounds containing one nitrogen and one oxygen atom in a six-membered ring, have been of great interest to medicinal chemists in recent decades[1]. This is especially true for compounds containing the 1,3-oxazine moiety due to the wide range of biological activity they exhibit, including anticancer, antibacterial, antifungal and etc. The aim of this work was the synthesis of chiral 1,3-oxazines based on the monoterpenoid (–)-isopulegol commercially available in optically pure form.

1,3-oxazine moieties



2H *4H* *6H*



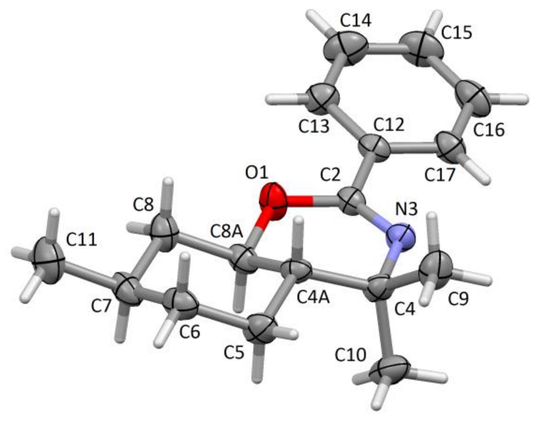
(-)-Isopulegol **1-6**

We found that the Ritter reaction between monoterpenoid (–)-isopulegol and a number of aliphatic and aromatic nitriles in the presence of concentrated sulfuric acid led to a series of chiral 1,3-oxazine derivatives with 35–80 % yields[2].

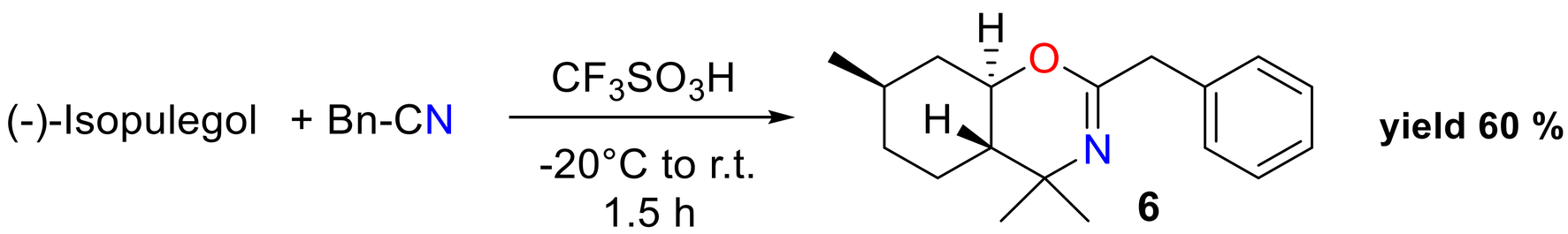
R	1	2	3	4	5	6
	CH_3	$(CH_2)_3CH_3$	$(CH_2)_6CH_3$	$(CH_2)_2OCH_3$	Ph	Bn
Yield, %	80	60	45	35	40	40

All synthesized compounds were tested for analgesic activity in the hot plate test for thermal irritation. Compound **6** at a dose of 10 mg/kg exhibited significant analgesic activity, reliably increasing the latent time of animals being on the hot plate and not inferior in efficiency to the reference drug diclofenac sodium administered at the same dose.

Carrying out the reaction of (–)-isopulegol with benzyl cyanide in the presence of CF_3SO_3H made it possible to increase the yield of the target product **6** from 40 %, achieved in the presence of H_2SO_4, to 60 %.



Structure of 1,3-oxazine **5** was confirmed by X-ray analysis.



1. Zinad, D.S., et al. *Chem. Biol. Drug Des.* **2020**, *95*, 16.
2. Li-Zhulanov N.S., et al. *Chem. Heterocycl. Compd.* **2020**, *56*(7), 936

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