

SYNTHESIS OF 2,2-DIMETHYL-4-METHOXYCHROMANS¹Albert Lévai^a and Tibor Timár^b^aDepartment of Organic Chemistry, Lajos Kossuth University, H-4010 Debrecen, Hungary^bALKALOIDA Chemical Factory, H-4440 Tiszavasvári, Hungary

Abstract — 2,2-Dimethyl-4-methoxychromans have been synthesized by the reduction of 2,2-dimethyl-4-chromanones with NaBH₄ followed by treatment with hydrochloric acid in methanol solution.

INTRODUCTION

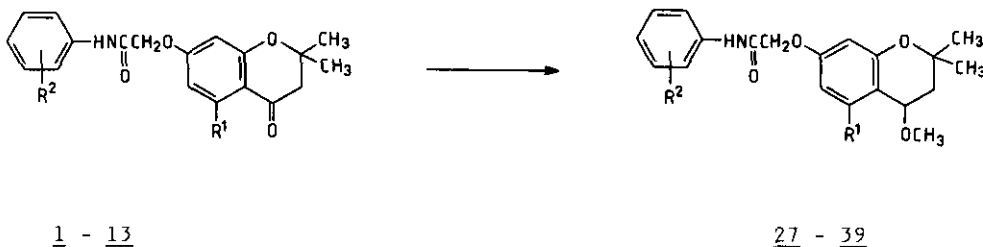
Owing to their bioactivity² 2,2-dimethyl-2H-chromenes became a well-known group of the benzopyran-type heterocycles during the past decade.³ Their especially important representatives are precocene I (2,2-dimethyl-7-methoxy-2H-chromene) and precocene II (2,2-dimethyl-6,7-dimethoxy-2H-chromene) isolated from *Ageratum houstonianum*^{4,5} as well as other plant sources.⁶ Starting from 2,2-dimethyl-4-chromanones, various procedures have been worked out for their synthesis.⁷⁻¹⁷ Very recently, in the course of the preparation of 2,2-dimethyl-2H-chromenes Teixidor et al.¹⁷ isolated 2,2-dimethyl-4,6,7-trimethoxychroman in approx. 10% yield as a by-product on the reduction of 6,7-dimethoxy-2,2-dimethyl-4-chromanone with NaBH₄ in methanol. 2,2-Dimethyl-4-ethoxychroman was synthesized by Merten and Müller starting from salicylaldehyde.¹⁸ To our knowledge, no other examples have hitherto been published for the formation of 2,2-dimethyl-4-alkoxychroman derivatives.

In recent years we have been engaged in the synthesis of precocene analogues as potential plant protecting agents.^{1,14-16,19,20} In our experiments 2,2-dimethyl-4-chromanones were used as starting materials, and some of them were found to give 2,2-dimethyl-4-methoxychromans instead of 2,2-dimethyl-2H-chromenes on reduction with NaBH₄ followed by treatment with hydrochloric acid in methanol.

In the present paper our systematic investigation and the results on the synthesis of 2,2-dimethyl-4-methoxychromans are reported.

RESULTS AND DISCUSSION

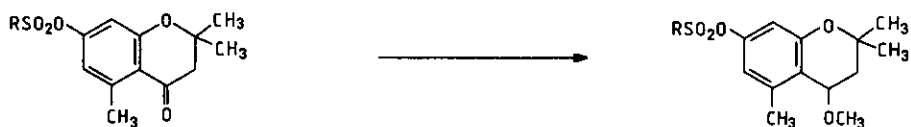
In order to enhance the "original precocene activity" or to consider the appearance of new bioactivities we prepared a series of 2,2-dimethyl-2H-chromenes^{1,14-16,20} with a large variety of substituents in the aromatic ring. If 2,2-dimethyl-4-chromanones possessing a carboxamide moiety at position 7 (1-13) are allowed to react with NaBH₄ and then treated with hydrochloric acid in methanol, 2,2-dimethyl-4-methoxychromans (27-39) precipitate from the solution in good yield.



- | | |
|---|--|
| <u>1</u> , <u>27</u> : R ¹ = R ² = H | <u>8</u> , <u>34</u> : R ¹ = H, R ² = 3-Br |
| <u>2</u> , <u>28</u> : R ¹ = H, R ² = 2-CH ₃ | <u>9</u> , <u>35</u> : R ¹ = H, R ² = 4-Br |
| <u>3</u> , <u>29</u> : R ¹ = H, R ² = 4-CH ₃ | <u>10</u> , <u>36</u> : R ¹ = CH ₃ , R ² = H |
| <u>4</u> , <u>30</u> : R ¹ = H, R ² = 2-Cl | <u>11</u> , <u>37</u> : R ¹ = CH ₃ , R ² = 2-Cl |
| <u>5</u> , <u>31</u> : R ¹ = H, R ² = 3-Cl | <u>12</u> , <u>38</u> : R ¹ = CH ₃ , R ² = 3-Cl |
| <u>6</u> , <u>32</u> : R ¹ = H, R ² = 4-Cl | <u>13</u> , <u>39</u> : R ¹ = CH ₃ , R ² = 4-Cl |
| <u>7</u> , <u>33</u> : R ¹ = H, R ² = 2-Br | |

We also investigated the reduction of alkyl- or arylsulfonyloxy-2,2-dimethyl-4-chromanones (14-17) with NaBH₄ which gave 2,2-dimethyl-4-hydroxychromans.

When the dehydration of these latter substances was conducted, it was found that 4-methoxy-2,2,5-trimethylchroman derivatives (40-43) were formed from those chromanones having a methyl group in position 5.



14 - 17

40 - 43

14, 40: R = CH₃ 16, 42: R = 4-CH₃-C₆H₄

15, 41: R = C₆H₅ 17, 43: R = 4-Br-C₆H₄

Similar results were obtained with compounds possessing either benzyloxy or aminoalkoxy substituents on the aromatic ring, and 2,2-dimethyl-4-methoxychromans 44 - 46 and 47 - 52, respectively, were formed on the acidification of the reduction product in methanol.



18 - 20

44 - 46

18, 44: R¹ = R² = H

19, 45: R¹ = CH₃, R² = H

20, 46: R¹ = H, R² = 4-NO₂-C₆H₄CH₂O



21 - 26

47 - 52

21, 47: R¹ = R² = H, X = CH₂

22, 48: R¹ = R² = H, X = O

23, 49: R¹ = CH₃, R² = H, X = CH₂

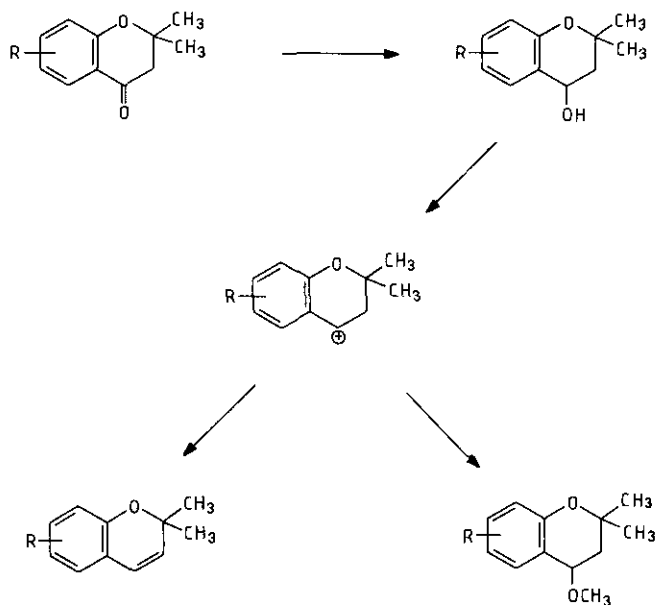
24, 50: R¹ = CH₃, R² = H, X = O

25, 51: R¹ = H, R² = CH₃, X = CH₂

26, 52: R¹ = H, R² = CH₃, X = O

2,2-Dimethyl-4-methoxychromans 27 - 46 are stable white crystalline materials while substances 47 - 52 are oily products which decompose quickly. Structures of all the compounds prepared were elucidated by ^1H -nmr spectroscopy and in the case of 27 - 46 by microanalysis as well. A singlet ^1H signal characteristic for the methoxy group at position 4 is found at about 3.4 ppm. Another characteristic signal in each spectrum is a triplet at approx. 4.5 ppm assigned to the hydrogen at C-4. All other proton signals could be assigned to the appropriate hydrogen atoms of the molecules.

A reasonable explanation for the formation of the 2,2-dimethyl-4-methoxychromans is that elimination and nucleophilic substitution are two concurrent reactions in acidic methanol solution leading either to 2,2-dimethyl-2H-chromenes or to 2,2-dimethyl-4-methoxychromans.



EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^1H -Nmr spectra in CDCl_3 (TMS as int. ref.) were recorded with a Bruker WP 200 SY spectrometer at 200 MHz. Ilc was performed on a Kieselgel 60 F₂₅₄ (Merck) layer using hexane-acetone (7:3 v/v) as eluant.

Table 1. Physical constants and analytical data of compounds 27 - 52

Compound	mp °C	Yield %	Overall formula	Calculated		Found	
				C%	H%	C%	H%
<u>27</u>	124-125	70.5	C ₂₀ H ₂₃ NO ₄	70.36	6.79	70.60	6.74
<u>28</u>	117-118	79.6	C ₂₁ H ₂₅ NO ₄	70.96	7.09	70.93	7.15
<u>29</u>	142-143	84.2	C ₂₁ H ₂₅ NO ₄	70.96	7.09	71.03	7.23
<u>30</u>	144-145	73.6	C ₂₀ H ₂₂ CINO ₄	63.91	5.90	63.89	6.01
<u>31</u>	63-64	58.0	C ₂₀ H ₂₂ CINO ₄	63.91	5.90	63.72	6.07
<u>32</u>	152-153	73.2	C ₂₀ H ₂₂ CINO ₄	63.91	5.90	63.93	5.83
<u>33</u>	132-133	53.1	C ₂₀ H ₂₂ BrNO ₄	57.15	5.27	57.20	5.35
<u>34</u>	77-78	63.8	C ₂₀ H ₂₂ BrNO ₄	57.15	5.27	57.17	5.26
<u>35</u>	154-155	72.4	C ₂₀ H ₂₂ BrNO ₄	57.15	5.27	57.24	5.39
<u>36</u>	134-135	76.4	C ₂₁ H ₂₅ NO ₄	70.96	7.09	70.91	7.13
<u>37</u>	159-160	75.7	C ₂₁ H ₂₄ CINO ₄	64.69	6.20	64.75	6.31
<u>38</u>	109-110	60.6	C ₂₁ H ₂₄ CINO ₄	64.69	6.20	64.23	6.09
<u>39</u>	119-120	55.5	C ₂₁ H ₂₄ CINO ₄	64.69	6.20	64.14	6.08
<u>40</u>	84-85	62.8	C ₁₄ H ₂₀ O ₅ S	56.04	6.72	56.07	6.74
<u>41</u>	102-103	52.4	C ₁₉ H ₂₂ O ₅ S	63.14	5.85	63.09	5.88
<u>42</u>	93-94	76.5	C ₂₀ H ₂₄ O ₅ S	63.98	6.17	64.01	6.29
<u>43</u>	94-95	78.4	C ₁₉ H ₂₁ BrO ₅ S	51.71	4.79	52.21	4.77
<u>44</u>	98-99	53.8	C ₁₉ H ₂₁ NO ₅	66.47	6.12	66.53	6.03
<u>45</u>	113-114	65.4	C ₂₀ H ₂₃ NO ₅	67.39	6.22	67.36	6.27
<u>46</u>	181-182	75.5	C ₂₆ H ₂₂ N ₂ O ₈	63.27	5.10	63.37	5.25
<u>47</u>	oil	87.5	C ₁₉ H ₂₉ NO ₃	-	-	-	-
<u>48</u>	oil	91.0	C ₁₈ H ₂₇ NO ₄	-	-	-	-
<u>49</u>	oil	77.7	C ₂₀ H ₃₁ NO ₃	-	-	-	-
<u>50</u>	oil	86.9	C ₁₉ H ₂₉ NO ₄	-	-	-	-
<u>51</u>	oil	87.6	C ₂₀ H ₃₁ NO ₃	-	-	-	-
<u>52</u>	oil	96.7	C ₁₉ H ₂₁ NO ₄	-	-	-	-

Table 2. $^1\text{H-Nmr}$ spectral properties of compounds 27-52

Compound	δ (ppm)
<u>27</u>	1.42 (s, 3H), 1.52 (s, 3H), 2.08 (m, 2H), 3.52 (s, 3H), 4.48 (t, 1H, J=6.58 Hz), 4.66 (s, 2H), 6.50-7.68 (m, 8 aromatic protons), 8.32 (s, 1H)
<u>28</u>	1.40 (s, 3H), 1.48 (s, 3H), 2.06 (m, 2H), 2.28 (s, 3H), 3.48 (s, 3H), 4.45 (t, 1H, J=6.57 Hz), 4.65 (s, 2H), 6.46-8.02 (m, 7 aromatic protons), 8.22 (s, 1H)
<u>29</u>	1.40 (s, 3H), 1.48 (s, 3H), 2.04 (m, 2H), 2.35 (s, 3H), 3.48 (s, 3H), 4.43 (t, 1H, J=6.58 Hz), 4.58 (s, 2H), 6.42-7.52 (m, 7 aromatic protons), 8.18 (s, 1H)
<u>30</u>	1.40 (s, 3H), 1.46 (s, 3H), 2.02 (m, 2H), 3.36 (s, 3H), 4.44 (t, 1H, J=6.48 Hz), 4.60 (s, 2H), 6.42-8.42 (m, 7 aromatic protons), 9.02 (s, 1H)
<u>31</u>	1.34 (s, 3H), 1.44 (s, 3H), 2.02 (m, 2H), 3.44 (s, 3H), 4.40 (t, 1H, J=6.52 Hz), 4.52 (s, 2H), 6.38-7.66 (m, 7 aromatic protons), 8.26 (s, 1H)
<u>32</u>	1.35 (s, 3H), 1.46 (s, 3H), 2.02 (m, 2H), 3.44 (s, 3H), 4.38 (t, 1H, J=6.58 Hz), 4.54 (s, 2H), 6.40-7.52 (m, 7 aromatic protons), 8.22 (s, 1H)
<u>33</u>	1.36 (s, 3H), 1.46 (s, 3H), 2.04 (m, 2H), 3.42 (s, 3H), 4.42 (t, 1H, J=6.54 Hz), 4.60 (s, 2H), 6.44-8.46 (m, 7 aromatic protons), 9.06 (s, 1H)
<u>34</u>	1.35 (s, 3H), 1.43 (s, 3H), 2.02 (m, 2H), 3.44 (s, 3H), 4.38 (t, 1H, J=6.56 Hz), 4.57 (s, 2H), 6.42-7.83 (m, 7 aromatic protons), 8.22 (s, 1H)
<u>35</u>	1.36 (s, 3H), 1.44 (s, 3H), 2.03 (m, 2H), 3.46 (s, 3H), 4.38 (t, 1H, J=6.58 Hz), 4.54 (s, 2H), 6.40-7.48 (m, 7 aromatic protons), 8.22 (s, 1H)
<u>36</u>	1.42 (s, 6H), 1.83 (dd, 1H, J=14.4, 5.12 Hz), 2.26 (dd, 1H, J=14.4, 2.92 Hz), 2.30 (s, 3H), 3.42 (s, 3H), 4.27 (dd, 1H, J=4.75, 2.56 Hz), 4.54 (s, 2H), 6.32-7.58 (m, 7 aromatic protons), 8.24 (s, 1H)
<u>37</u>	1.42 (s, 6H), 1.82 (dd, 1H, J=14.2, 4.75 Hz), 2.28 (dd, 1H, J=14.2, 2.56 Hz), 2.32 (s, 3H), 3.42 (s, 3H), 4.25 (dd, 1H, J=4.75, 2.56 Hz), 4.60 (s, 2H), 6.35-8.42 (m, 6 aromatic protons), 9.04 (s, 1H)
<u>38</u>	1.43 (s, 6H), 1.84 (dd, 1H, J=14.0, 4.84 Hz), 2.25 (dd, 1H, J=14.0, 2.58 Hz), 2.33 (s, 3H), 3.40 (s, 3H), 4.26 (dd, 1H, J=4.76, 2.52 Hz), 4.54 (s, 2H), 6.28-7.72 (m, 6 aromatic protons), 8.22 (s, 1H)
<u>39</u>	1.42 (s, 6H), 1.82 (dd, 1H, J=14.6, 4.78 Hz), 2.24 (dd, 1H, J=14.6, 2.59 Hz), 2.32 (s, 3H), 3.42 (s, 3H), 4.24 (dd, 1H, J=4.78, 2.57 Hz), 4.56 (s, 2H), 6.28-7.54 (m, 6 aromatic protons), 8.24 (s, 1H)
<u>40</u>	1.38 (s, 3H), 1.40 (s, 3H), 1.80 (dd, 1H, J=13.8, 4.75 Hz), 2.20 (dd, 1H, J=13.8, 2.56 Hz), 2.32 (s, 3H), 3.06 (s, 3H), 3.38 (s, 3H), 4.25 (dd, 1H, J=4.75, 2.56 Hz), 6.56 (d, 1H, J=2.48 Hz), 6.68 (d, 1H, J=2.48 Hz)
<u>41</u>	1.36 (s, 3H), 1.39 (s, 3H), 1.80 (dd, 1H, J=14.0, 4.78 Hz), 2.20 (dd, 1H, J=14.0, 2.56 Hz), 2.24 (s, 3H), 3.32 (s, 3H), 4.21 (dd, 1H, J=4.78, 2.59 Hz), 6.28-7.88 (m, 7 aromatic protons)
<u>42</u>	1.32 (s, 3H), 1.38 (s, 3H), 1.78 (dd, 1H, J=14.4, 2.56 Hz), 2.20 (dd, 1H, J=14.4, 2.56 Hz), 2.24 (s, 3H), 2.42 (s, 3H), 3.38 (s, 3H), 4.22 (dd, 1H, J=4.76, 2.54 Hz), 6.28-7.78 (m, 6 aromatic protons)

Table 2 continued

Compound	(ppm)
<u>43</u>	1.38 (s, 3H), 1.40 (s, 3H), 1.80 (dd, 1H, J=14.2, 4.75 Hz), 2.04 (dd, 1H, J=14.2, 2.56 Hz), 2.06 (s, 3H), 3.42 (s, 3H), 4.24 (dd, 1H, J=4.75, 2.56 Hz), 6.26-7.70 (m, 6 aromatic protons)
<u>44</u>	1.36 (s, 3H), 1.44 (s, 3H), 2.04 (m, 2H), 3.46 (s, 3H), 4.40 (t, 1H, J=6.58 Hz), 5.14 (s, 2H), 6.42-8.26 (m, 7 aromatic protons)
<u>45</u>	1.40 (s, 6H), 1.82 (dd, 1H, J=14.0, 4.75 Hz), 2.24 (dd, 1H, J=14.0, 2.56 Hz), 2.30 (s, 3H), 3.42 (s, 3H), 4.23 (t, 1H, J=6.56 Hz), 5.12 (s, 2H), 6.23-8.20 (m, 6 aromatic protons)
<u>46</u>	1.32 (s, 3H), 1.43 (s, 3H), 2.01 (m, 2H), 3.42 (s, 3H), 4.36 (t, 1H, J=6.54 Hz), 5.16 (s, 4H), 6.42-8.26 (m, 10 aromatic protons)
<u>47</u>	1.34 (m, 2H), 1.46 (s, 6H), 1.58 (m, 4H), 2.01 (m, 2H), 2.46 (m, 4H), 2.76 (t, 2H, J=7.10 Hz), 5.45 (s, 3H), 4.06 (t, 2H, J=7.10 Hz), 4.38 (t, 1H, J=6.56 Hz), 6.34-7.30 (m, 3 aromatic protons)
<u>48</u>	1.36 (s, 3H), 1.42 (s, 3H), 2.02 (m, 2H), 2.56 (m, 4H), 2.80 (t, 2H, J=6.84 Hz), 3.44 (s, 3H), 3.72 (m, 4H), 4.06 (t, 2H, J=6.84 Hz), 4.38 (t, 1H, J=6.59 Hz), 6.38-7.28 (m, 3 aromatic protons)
<u>49</u>	1.40 (s, 6H), 1.60 (m, 3H), 1.60 (m, 5H), 1.78 (dd, 1H, J=13.9, 2.58 Hz), 2.24 (dd, 1H, J=13.9, 2.59 Hz), 2.28 (s, 3H), 2.52 (m, 5H), 2.76 (t, 2H, J=6.26 Hz), 3.38 (s, 3H), 4.06 (t, 2H, J=6.26 Hz), 4.24 (dd, 1H, J=4.80, 2.54 Hz), 6.24 (d, 1H, J=2.42 Hz), 6.38 (d, 1H, J=2.42 Hz)
<u>50</u>	1.40 (s, 6H), 1.80 (dd, 1H, J=14.2, 2.56 Hz), 2.20 (dd, 1H, J=14.2, 2.58 Hz), 2.24 (s, 3H), 2.04 (m, 4H), 2.26 (t, 2H, J=6.42 Hz), 3.40 (s, 3H), 3.70 (m, 4H), 4.06 (t, 2H, J=6.42 Hz), 4.26 (dd, 1H, J=4.76, 2.52 Hz), 6.22 (d, 1H, J=2.48 Hz), 6.38 (d, 1H, J=2.48 Hz)
<u>51</u>	1.30 (s, 3H), 1.40 (m, 2H), 1.41 (s, 3H), 1.56 (m, 4H), 1.92 (m, 2H), 2.02 (s, 3H), 2.48 (m, 4H), 2.73 (t, 2H, J=6.26 Hz), 3.40 (s, 3H), 4.04 (t, 2H, J=6.26 Hz), 4.36 (t, 1H, J=6.18 Hz), 6.42 (d, 1H, J=5.48 Hz), 7.10 (d, 1H, J=5.48 Hz)
<u>52</u>	1.35 (s, 3H), 1.44 (s, 3H), 2.00 (m, 2H), 2.10 (s, 3H), 2.60 (m, 4H), 2.80 (t, 2H, J=6.16 Hz), 3.46 (s, 3H), 3.72 (m, 4H), 4.12 (t, 2H, J=6.16 Hz), 4.42 (t, 1H, J=6.48 Hz), 6.48 (d, 1H, J=5.76 Hz), 7.18 (d, 1H, J=5.76 Hz)

General procedure for the preparation of the 2,2-dimethyl-4-methoxychromans

2,2-Dimethyl-4-chromanone (1 - 26; 10 mmol) was stirred and refluxed in methanol (200 ml), and NaBH₄ (50 mmol) was added in small portions. Stirring and reflux was continued until the disappearance of the starting material (approx. 2 h) according to tlc. The solution was cooled down, its pH adjusted to 2-4 with 4 N HCl and then left to stand at room temperature for 1-3 days. The mixture was diluted with water, the precipitated material filtered off, washed free of acid, and crystallized from methanol to give compounds 27 - 52 (Tables 1 and 2).

ACKNOWLEDGEMENTS

The present studies were sponsored by the ALKALOIDA Chemical Factory (Tiszavasvári, Hungary) for which our gratitude is expressed. Our thanks are due to Mrs. E. Hajnal for her help in the experimental work, to the staff of our Nmr laboratory for the ¹H-Nmr spectra, and to Mrs. K. Tréfás for the microanalyses.

REFERENCES

1. Part 11 in the series on Synthesis of Benzopyran Derivatives. Part 10: A. Lévai and T. Timár, Pharmazie, accepted for publication.
2. W.S. Bowers, "Comprehensive Insect Physiology. Biochemistry and Pharmacology" eds. L.J. Gilbert and G.A. Kerkut, Pergamon Press, 1985, 8, p. 551.
3. F. Camps, "Bioregulators for Pest Control" ed. P.A. Hedin, ACS Symp. Ser. No. 276, 1985, p. 237.
4. A.R. Alertsén, Acta Chem. Scand., 1955, 9, 1725.
5. W.S. Bowers, T. Ohta, J.S. Cleere, and P.A. Marsella, Science, 1976, 193, 542.
6. T.R. Kasturi and T. Manithomas, Tetrahedron Lett. 1967, 2573.
7. H.J. Kabbe and A. Widdig, Angew. Chem., 1982, 94, 254.
8. T. Ohta and W.S. Bowers, Chem. Pharm. Bull., 1977, 25, 2788.
9. A. Banerji and N.C. Goomer, Indian J. Chem., 1981, 208, 144.
10. P. Anastasis and P.E. Brown, J. Chem. Soc., Perkin Trans. I, 1982, 2013.
11. J.W. ApSimon, L.W. Herman, and C. Huber, Can. J. Chem., 1985, 63, 2589.
12. J. Nickl, Chem. Ber., 1959, 92, 1989.
13. F.N. Lahey and R.V. Stick, Aust. J. Chem., 1973, 26, 2307.
14. T. Timár, S. Hosztafi, J.Cs. Jászberényi, K.E. Kövér, and Gy. Batta, Acta Chim. Hung., 1988, 125, 303.

15. T. Timár, J.Cs. Jászberényi, and S. Hosztafi, Acta Chim. Hung., 1988, 125, 457.
16. T. Timár, S. Hosztafi, and J.Cs. Jászberényi, Acta Chim. Hung., 1988, 125, 617.
17. P. Teixidor, F. Camps, and A. Messeguer, Heterocycles, 1988, 27, 2459.
18. R. Merten and C. Müller, Chem. Ber., 1964, 97, 682.
19. I. Kiss, A. Fodor, T. Timár, S. Hosztafi, P. Sebők, T. Török, E. Virágh, and M. Berényi, Experientia, 1988, 44, 790.
20. P. Sebők, T. Timár, J.Cs. Jászberényi, and Gy. Batta, Heterocycles, 1988, 27, 2595.

Received, 10th July, 1989