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A concise and stereoselective synthesis of (+/−)-*erythro*-methylphenidate

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Abstract—A concise and stereoselective synthesis of racemic *erythro*-methylphenidate (**1**) is described. The coupling reaction between piperidine-2-thione (**3**) and 2-bromo-2-phenylmethylacetate (**4**) afforded the β-enaminocarbonyl compound **2** in 60% yield by a modified Eschenmoser sulfide contraction reaction. In most cases the bicyclic thiazolidinone **5** was produced. Diastereoselective reduction of **2** in the presence of borohydrydes furnished the (+/−)-*erythro*-methylphenidate in good yields with *dr* >95%.

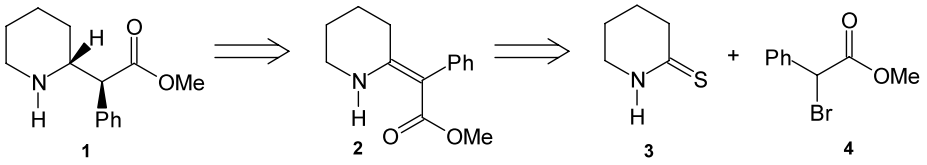
The (+/−)-*threo*-methylphenidate hydrochloride (Ritalin®), is an indirect catecholamine agonist,[1] and is the drug treatment of choice for the attention deficit/hyperactivity disorder (AD/HD),[2] one of the most common behavioral disorders of childhood which affects 5–10% of the general population.[3] The activity of Ritalin® promotes an enhancement of the cognitive performance in both adults and children diagnosed with AD/HD.[4] Although Ritalin® is available in the market as the racemate, the (2*R*,2′*R*)-(+)-*threo*-methylphenidate has been reported to be up to 38 times[5] more active than (2*S*,2′*S*)-(−)-*threo*-methylphenidate and several racemic[6–9] and chiral[10–13] synthesis of *threo*-methylphenidate were reported previously.

Although the *erythro*-methylphenidate exhibits very few therapeutic properties and toxic hypertensive effects,[14] the stereoselective synthesis of the *erythro*-isomer can be helpful due to the possibility of resolution and epimerization of the *erythro*-isomer.[2,15] This approach was used early in the original synthesis of (+/−)-*threo*-methylphenidate. Close to this, an enantioselective synthesis of (2*S*,2′*S*)-*erythro*-methylphenidate was recently published by Prashad and co-workers.[16]

Due to this fact and relating to our interest in the synthesis of β-aminocarbonyl compounds[17,18] we would like to communicate in this paper our approach to the synthesis of (+/−)-*erythro*-methylphenidate **1** applying a new concise stereoselective synthetic strategy.

We envisaged obtaining **1** based on a stereoselective reduction of a β-enaminocarbonyl compound **2** which is readily accessible by the Eschenmoser sulfide contraction reaction[19,20] (Scheme 1).

The needed piperidine-2-thione (**3**) was prepared in 91% yield after reaction of piperidine-2-one with Lawesson reagent.[21] The bromoester **4** was obtained by sterification and subsequent α-bromination[22] of 2-phenylacetic acid in 71% overall yield after purufication by horizontal destilation at reduced pressure. Next, the condensation reaction of compounds **3** and **4** was carried out under the Eschenmoser sulfide contraction reaction



Scheme 1. The retrosynthetic analysis of **1** based on the eschemoser sulfide contraction reaction.

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protocol to provide the key intermediate β-enaminocarbonyl compound **2** (Table 1).

The classical conditions to carry out this reaction generally employ CH_2Cl_2 as the solvent, Et_3N as the base and excess of Ph_3P as the sulfur scavenger. Other tertiary amines and phosphorous thiophiles[23] are reported in the literature as being effective, as well as reaction performed in the absence of a thiophile.[24]

While trisubstituted β-enaminocarbonyl compounds are readily prepared starting from thiolactams and α-bromoesters under the usual protocol, the tetrasubstituted derivatives, such as **2**, require carefully controlled conditions to avoid undesired side reactions.[25,26] The main examples in the literature to prepare the tetrasubstituted β-enaminocarbonyl compounds are limited to the employment of a secondary α-triflates[27,28] or α-bromocarbonyl reagent with a second electron withdrawing group (CN, COR, CO_2R, NO_2) attached to the α-carbonyl carbon.[29–31]

Table 1. Reaction conditions and yields of compounds **2** and **5** via Scheme 2

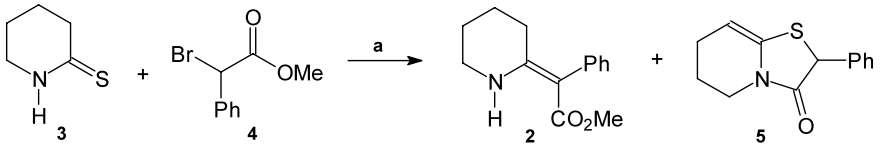
Entry	Base (2.0 equiv.)	Thiophile (no. equiv.)	Yield (%)	
			2	**5**
1	Et_3N	Ph_3P (4.0)	42	20
2	Et_3N	Ph_3P (2.0)	46	21
3	Et_3N	Ph_3P (1.0)	45	20
4	Et_3N	*n*-Bu_3P (2.0)	44	16
5	Et_3N	$(EtO)_3P$ (2.0)	–	–
6	DBU	Ph_3P (2.0)	35	41
7	Et_3N	–	6	25
8	Py	–	13	11
9	DMAP	–	27	4
10	DABCO	–	32	12
11	DIPEA	–	41	12
12	DBN	–	41	13
13	TMEDA	–	46	21
14	DBU	–	60	–
15	KO*t*-Bu	–	20	35

In our first attempt to carry out the condensation of compounds **3** and **4** by the usual Eschenmoser protocol we were able to isolate the β-enaminocarbonyl compound **2** in 42% yield along with 20% yield of a second product which was identified as the bicyclic thiazolidinone **5** (Scheme 2).

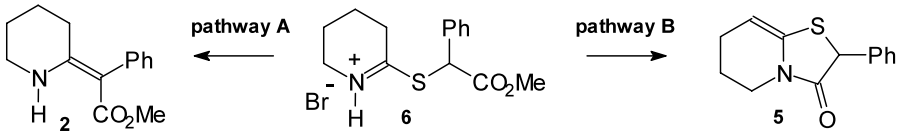
The products **2** and **5** were separated and purified by column chromatography and their ^1H and ^{13}C NMR and IR spectra are in accordance with the proposed structures.[32] The formation of a thiazolidinones was recently reported in the literature by Padwa[33] and Michael[34] for analogous reactions and the factors controlling its formation are not yet clear. The geometry of the double bond in **2** was shown to be *Z* by the analysis of the NOE experiment: irradiation of allylic protons of the piperidine ring at δ 2.10 showed a 5.30% increment in the *ortho*-hydrogens of the phenyl ring. Attempting to achieve the best yields of compound **2** and to avoid the formation of thiazolidinone **5**, we carried out the reaction under various different conditions employing three different thiofiles and a set of bases. The results are summarized in Table 1.

We observed that different amounts of Ph_3P as the thiophile in the reaction using Et_3N as the base did not produce a significative change in the proportion of **2** and **5** and the yields were essentially the same (Table 1, entries 1–3). The use of *n*-Bu_3P caused a small decrease in the yield of thiazolidinone **5** (Table 1, entry 4) and no products were observed employing $(EtO)_3P$ as the thiophile (Table 1, entry 5). Changing from Et_3N to DBU (Table 1, entry 6) caused a decrease in the formation of product **2** and an increase in the yield of **5**. With these initial results, we decided to monitor the reaction course by GC analysis. In the first hour of reaction, it was possible to detect the formation of compounds **2** and **5** and partial consumption of piperidine-2-thione, even in the absence of base and thiophile.

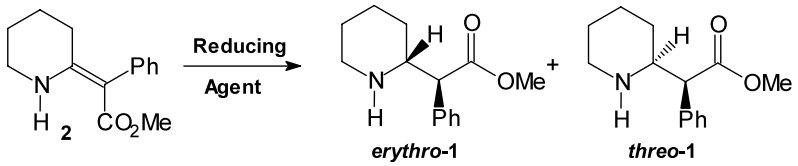
We supposed that a competitive side reaction would form the thiazolidinone **5** from the initially formed thioalkylated salt **6**[20] (pathway B) and the addition of a base could enhance the yield of compound **2** (pathway A) by the current accepted mechanism of the Eschenmoser sulfide contraction reaction[14] (Scheme 3).



Scheme 2. The Eschenmoser sulfide contraction reaction. *Reagents and conditions*: (a) (i) CH_2Cl_2, rt, 24 h; (ii) Et_3N (2.0 equiv.), rt, then; (iii) Ph_3P (2.0 equiv.), rt, 18 h.



Scheme 3. Formation of products **2** and **5** from the intermediate salt **6**.



Scheme 4. Reduction of the β-enaminoester **2**.

Table 2. Reduction reaction of β-enaminoester **2**

Entry	Reducing agent	Conditions	Solvent	*erythro*:*threo* (%)	Yield (%)
1	PtO_2	$HClO_4$, 1 atm H_2, rt	MeOH	80:20	90
2	$NaBH_4$	AcOH, rt	CH_3CN	96:4	91
3	$NaCNBH_3$	HCl, rt	CH_3CN	96:4	90
4	$NaHB(OAc)_3$	AcOH, rt	CH_3CN	96:4	89
5	$NaHB(OAc)_3$	rt	CH_3CN	93:7	72
6	Mg	60°C	MeOH	85:15	40

The addition of 2 equiv. of Et_3N without subsequent addition of a thiophile afforded **2** in only 6% yield and **5** in 25% yield (Table 1, entry 7). In this way, a set of available tertiary amines as bases was investigated. In all cases a variable ratio of compounds **2** and **5** was observed (Table 1, entries 8–14) and the use of KO*t*-Bu furnished the compound 5 as a major product (entry 15). Interestingly, the best yield of compound **2** (60%) was achieved when DBU was employed in the absence of a thiophile (Table 1, entry 14) in which thiazolidinone **5** was not isolated. We believe that these results can be closely related with both the bulkiness and the basicity of employed bases but a rationale for this competition remains unclear.

With product **2** in hand, the next step was the reduction of the double bond to obtain the corresponding β-aminoester derivative **1** (Scheme 4). Attempts to carry out the hydrogenation in the presence of 5% Pd–C[35] (1 atm) and 10% Pd–C (1, 5 and 15 atm) as well as $Pd(OH)_2$ (5 atm) were not effective to reduce the compound **2**.

The utilization of PtO_2 and PtO_2/AcOH (1 atm) also did not afford the reduced product. However, when the reaction was carried out in the presence of PtO_2/$HClO_4$[36] the (+/−)-*erythro*-methylphenidate[37] (**1**) was formed in 90% yield as a 80:20 mixture (Table 2, entry 1).

The relative configuration of the reduced product was inferred by comparing the spectral data of ^1H and ^{13}C NMR reported in the literature.[12] The diastereoisomeric ratio was determined by gas chromatography and ^1H NMR analysis of the crude mixture and showed essentialy the same results. Trying to improve stereoselectivity, we tried to use a general methodology based on reduction by metal-hydrides. Owing to low electrophilicity, enaminocarbonyls show poor reactivity toward hydrides.[38] Sodium borohydride–carboxylic acid is, however, an effective reducing agent for enamines and for the *N*-alkylation of the relative amines.[39] Reduction of **2** with $NaBH_4$/AcOH was ineffective but performing the reaction in presence of CH_3CN as solvent afforded the *erythro*-isomer **1** in *dr* 96:4 in 91% yield after chromatography (Table 2, entry 2). High diastereoselectivity was also observed using $NaCNBH_3$/HCl[40] as the reducing agent (Table 2, entry 3). For the $NaHB(OAc)_3$/AcOH[41] (Table 2, entry 4) the reaction shows *dr* 96:4 to the *erytho*-isomer **1** in a relative good yield, and this reducing agent is effective (Table 2, entry 5) even in the absence of acetic acid (*dr* 93:7 and 72% yield). Metalic magnesium in MeOH[42] was also tested, but reduction of **2** occurred in poor yield of *erythro*-**1** in *dr* 85:15 (Table 2, entry 6).

In conclusion, we have described a novel, concise, and stereoselective strategy for the synthesis of (+/−)-*erythro*-methylfenidate **1** in three steps from piperidine-2-one in 52% overall yield through the modified Eschenmoser sulfide contraction reaction. Interestingly, the thiazolidinone **5** is concurrently formed in variable amounts depending on the reaction conditions and an investigation of the reaction mechanism for its formation is underway.

Acknowledgements

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32. Spectral data of compound **2**: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) = 9.72 (br s, 1H); 7.34–7.1 (m, 5H); 3.55 (s, 3H); 3.51–3.33 (m, 2H); 2.10 (t, J = 6.6 Hz, 2H); 1.79–1.68 (m, 2H); 1.63–1.54 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) = 170.3, 161.3, 152.9, 138.1, 132.3, 127.8, 94.4, 50.4, 41.4, 27.7, 22.3, 19.9; IR (KBr) ν 3344, 3046, 2926, 1581. Spectral data of compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.45–7.31 (m, 5H); 5.06 (s, 1H); 4.92 (t, J = 4.3 Hz, 1H); 3.75–3.67 (m, 2H); 2.42 (dd, J = 15.6, 5.9 Hz, 2H); 1.95–1.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 170.8, 137.5, 129.8, 128.2, 98.1, 51.1, 42.1, 22.5, 20.4; IR (neat) ν 3061, 2928, 2849, 1696, 1645, 1387.
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