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A regioselective synthesis of 2,4-dialkyl resorcinols

Scott S. Ceglia,* Michael H. Kress, Todd D. Nelson and James M. McNamara†

Merck Research Laboratories, Department of Process Research, 466 Devon Park Drive, Wayne, PA 19087, USA

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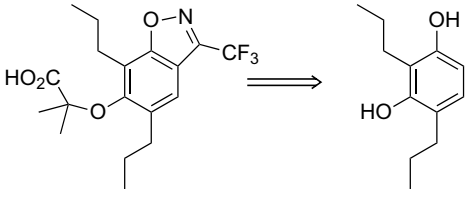
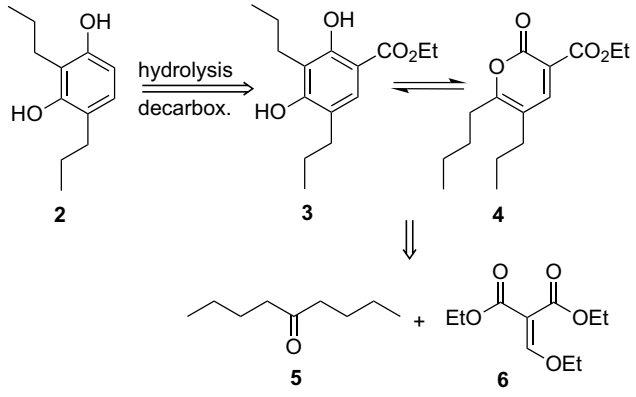
Abstract—A general regioselective synthesis of 2,4-dialkyl resorcinols from ethoxymethylenemalonate ethyl ester and dialkyl ketones is reported.

As part of an ongoing effort to identify agents that are agonists of PPAR, we required an efficient synthesis of substrate **1**.[1] The core of this molecule can be perceived as 2,4-dipropyl resorcinol **2**. The syntheses of complex molecules containing substituted phenols and/or resorcinols often times start with aromatic precursors that require protecting group manipulation and/or additional synthetic steps to establish regiochemical control.[2] Our initial approaches toward **2** followed some of these traditional methodologies and suffered similar drawbacks.[3–5] We desired a more efficient synthesis of resorcinol **2**. As a result, this communication discloses a concise synthesis of 2,4-dipropyl resorcinol **2**, and a general approach to other 2,4-dialkyl resorcinols that is regioselective, convergent, and practical.



1 **2**

The keystone of our approach had its origins in limited references to the isomerization of α-pyrones to aromatic compounds[6] (i.e., **4** to **3**). We envisioned that a rearrangement of the appropriately substituted α-pyrone **4** would afford the framework of our target dialkylated resorcinol. Subsequent saponification and decarboxylation would give 2,4-dipropyl resorcinol **2** (Scheme 1). Intermediate **4** was envisioned to be accessible based on an extension of a literature precedent, by condensation of 5-nonanone **5** with 2-ethoxymethylenemalonate ethyl ester (EMME) **6**.[7]



Scheme 1.

Our initial attempts at this approach toward **4** utilized ethoxide as the base and generated pyrone **4** in a modest HPLC assay yield (33%). The yield of pyrone **4** improved slightly (42%) using KO*t*Bu as the base. Interestingly, with KO*t*Bu as the base, a near equimolar amount of arene **3** was observed. Because alkoxide bases have been shown to induce the isomerization of α-pyrones, we initially speculated that the observed product distribution was under thermodynamic control. As such, we

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* Corresponding author. Tel.: +1 215 652 3361; fax: +1 215 993 3409; e-mail: scott_ceglia@merck.com
† Merck Research Laboratories, Department of Process Research, 126 East Lincoln Ave., Rahway, NJ 07065, USA

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Table 1. Isomerization attempt of pyrone **4**

Base/solvent	Time	Temperature	% Pyrone **4** (recovery)[a]
LHMDS/THF	No age	5 °C	27
W/1 equiv EtOH	1 h	25 °C	38
	1 h	40 °C	90
	16 h	40 °C	93

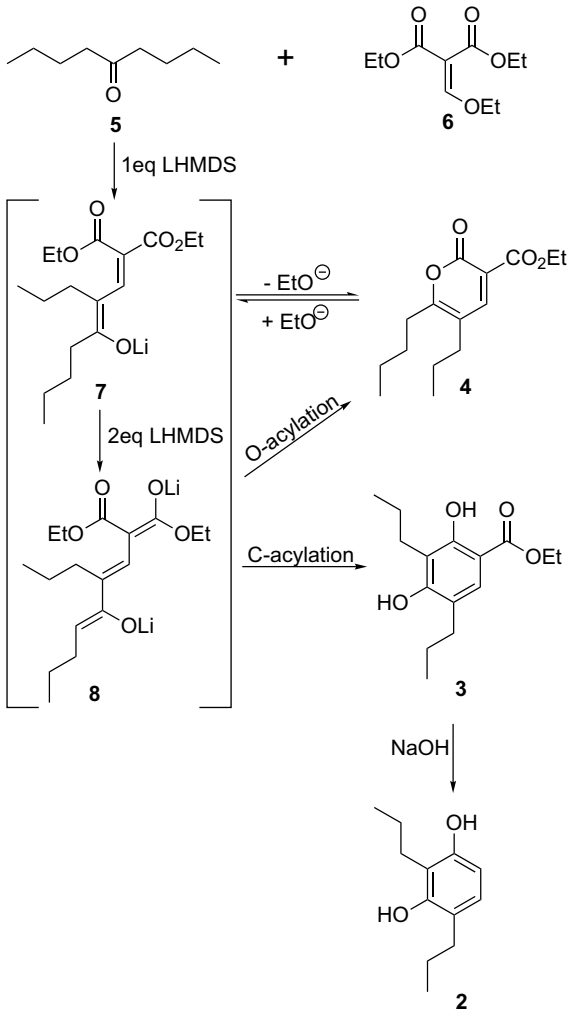
[a] Determined by HPLC assay yield wt % analysis versus standard.

were surprised when we observed no further change in product distribution upon prolonged age (>5 days) at elevated temperature. Subsequent attempts to isomerize isolated pyrone **4** to arene **3** using various bases (KOH/EtOH, NaOEt/EtOH, LHMDS/THF), temperatures, and reaction times were also unsuccessful and led mainly to degradation of **4**[‡]. Intriguingly, attempted isomerization of pyrone **4** with LHMDS and 1 equiv of EtOH, (Table 1) resulted in the immediate disappearance of pyrone **4**; however; conversion back to pyrone **4** was nearly quantitative after a more prolonged age time.

These results indicate that pyrone **4** was not efficiently undergoing isomerization to arene **3**, but that arene **3** was being generated directly.[8] We rationalized the direct formation of arene **3** was occurring via an open chain, dianion manifold (Scheme 2).[9] This pathway would require a minimum of 3 equivalents of base. The first equivalent of base would generate the enolate of 5-nonanone **5** that would add via Michael-addition into EMME **6**. The second equivalent would deprotonate the ethanol liberated from the 1:1 5-nonanone/EMME adduct **7**. Finally, the last equivalent would generate dianion **8**. Intramolecular C-acylation of this dianion intermediate results in arene **3**. Formation of dianion **8** does not however insure the formation of arene **3**. If intramolecular O-acylation of dianion **8** occurs, pyrone **4** would result. Thus, the task at hand was to increase the rate of C-acylation relative to the rate of O-acylation.

We began our investigations into the direct formation of arene **3** by screening a variety of base (>3 equiv) and solvent systems. Due to incompatibilities of EMME **6** with base, we established a reagent addition protocol in which one equivalent of base was added to a solution of ketone **5** in THF. EMME was then added to the resulting enolate solution. Analysis of the reaction profile via HPLC and ^{1}H NMR spectroscopy at this point showed a complex mixture of open-chained tautomers/rotomers of intermediate **7**.

The remaining 2.3 equiv of LHMDS were then charged to the reaction mixture. After 30 min at ambient temperature, the reaction profile had coalesced to predominantly one peak in the HPLC chromatogram, but contained only 50% of arene **3**. The remainder of the

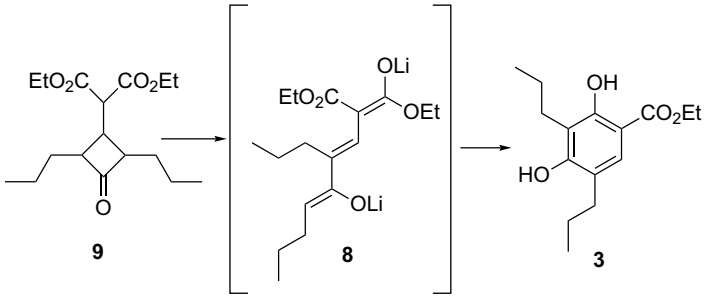


Scheme 2.

material consisted of minor amounts of pyrone **4**, open-chain isomers of **7**, and a cyclobutanone intermediate **9** (determined via ^{1}H NMR spectroscopy), that presumably could form via the double-Michael addition of one molecule of ketone **5** to EMME. Interconversion of cyclobutanone adduct **9** to arene **3** under the reaction conditions can be envisioned to occur via retro-Michael to dianion **8**, followed by ring closure to the more stable tetrasubstituted arene **3** (Scheme 3). In fact, incorporating an extended age (>4 h) at 40 °C, led to the disappearance of cyclobutanone adduct **9**, and a higher yield of arene **3**.

Following this protocol our screening studies yielded the following conclusions. The use of a strong base such as LHMDS or NaHMDS (Table 2, entries 1, 2, and 3) resulted in a high assay yield of arene **3**, with only minor amounts of pyrone **4** being formed. The nature of the counter ion also played a role in the reaction. The use of NaHMDS resulted in a lower yield of arene **3** (Table 2, entry 3 vs 1), and a significantly larger amount of pyrone **4**. In addition, solvent choice was shown to affect the course of the reaction. Use of a nonpolar solvent such as hexane (entry 2) resulted in increased levels of undesired pyrone **4**, while a more polar solvent such as

[‡] We also monitored the formation of resorcinol **2**, which could potentially be formed under the basic reaction conditions by saponification and decarboxylation of arene **3**, but none was detected by HPLC analysis.



Scheme 3.

THF (entry 1) provided a better product distribution. We hypothesized that the nonpolar solvent de-stabilizes dianion **8** and causes rapid O-acylation (Table 2).

Concomitantly, in order to test our original hypothesis, we were exploring the effect that the number of equivalents of base had on the formation of arene **3**, since the reaction could still progress through the mono or dianion pathways under the screening protocol. (Scheme 2). A base equivalency study (Table 3), showed that the presence of excess base minimizes the formation of pyrone **4**, resulting in an even higher yield of arene **3**.

On the basis of these equivalency studies, we switched to an inverse addition protocol (**B**) to finish the base screening study. The results of these experiments indicated that the use of a strong coordinating base (LHMDS) in a polar solvent using an inverse addition protocol was optimal for maximizing the formation of arene **3** and minimizing the formation of pyrone **4**. This optimized procedure for the formation of ester **3** resulted in an 85% isolated yield starting from 5-nonanone **5**.

With an optimized procedure in hand for the formation of **3**, we then turned our attention toward the hydrolysis/decarboxylation of ester **3** to 2,4-dipropyl resorcinol **2**. This transformation was believed to be a relatively facile conversion based on work done on similar resorcinillic esters.[10] Formation of **2** was accomplished by heating ester **3** at reflux in 5 N NaOH for an extended age (>10 h), followed by acidic work up. Our streamlined procedure for the synthesis of resorcinol **2** resulted in an overall 74% isolated yield starting from 5-nonanone **5**.

Table 2. Reaction condition screening experiments

Entry	Base (3.3 equiv)	Solvent	Method	(**3**) %[a]	**3**:**4**[b]
1	LHMDS	THF	A	83	42:1
2	LHMDS	Hexanes	A	65	9:1
3	NaHMDS	THF	A	60	7:1
4	LHMDS	THF	B	85	>80:1
5	LDA	Hexanes/ ethylbenzene	B	76	13:1
6	KO*t*Bu	THF	B	42	1:1
7	NaOEt	Ethanol	B	4	0.1:1
8	BuLi	THF	B	16	2:1

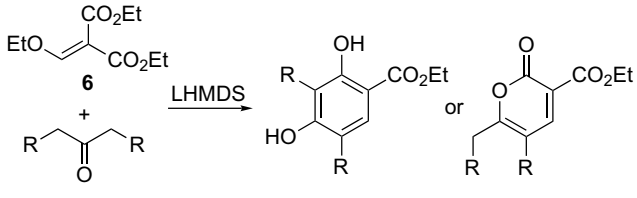
(a) Dropwise addition of remaining 2.3 equiv of LHMDS to a precooled solution of **7**.
(b) Dropwise addition of a solution of **7** to remaining 2.3 equiv of LHMDS.
[a] HPLC assay yield.
[b] Ratio determined using HPLC assay yields calculated from LC weight % standards of **3** and **4**.

Table 3. LHMDS Base equivalent study

Entry	LHMDS charge	% Yield (**3**)	% Yield (**4**)
1	LHMDS (1 equiv)	2	61
2	LHMDS (2 equiv)	37	25
3	LHMDS (3 equiv)	75	3
4	LHMDS (3.3 equiv)	85	<1
5	LHMDS (4 equiv)	88	<1

Substituted resorcinols represent a ubiquitous structural motif present in many natural products and pharmaceutical agents.[11] Resorcinols have also found utility as building blocks for the development of a wide range of macrocycles and molecules that exhibit interesting recognition properties.[12] As such, we were quite interested in whether this new approach to 2,4-dipropylresorcinol **2** could be extended to other enolizable ketones.

To this end, other symmetric ketones were condensed with EMME under our optimized conditions (Scheme 4). The straight-chained alkyl ketones (**5a**, **5b**, and **5c**) performed well, resulting in excellent yields of the 2,4-dialkyl-5-carboethoxy resorcinols (**10a**, **10b**, and **10c**). Reaction of EMME with more sterically demanding symmetric ketones, such as R = isopropyl (**5d**) led to a lower yield (47%) of 2,4-dialkyl-5-carboethoxy resorcinol. When utilizing diphenyl acetone (**5e**), selective formation (73%) of pyrone was observed. This lower yield



5a-e, R= **a**, Me; **b**, Et; **c**, *n*-Pr; **d**, *i*-Pr; **e**, Ph

10a, 88%; **10b**, 97%; **10c**, 88%; **10d**, 47%; **10e**, ---

11a, ---; **11b**, ---; **11c**, ---; **11d**, ---; **11e**, 72%

Scheme 4.

for the isopropyl and selectivity to form the pyrone for the phenyl derivative is presumably due to the greater steric demand imparted on the more rigid arene framework versus that of the pyrone, as well as the potential anion stabilization that can occur in the conjugated phenyl derivative.

In summary, a novel and convenient procedure was developed for the synthesis of 2,4-dipropyl resorcinol **2** via condensation of 5-nonanone **5** with EMME **6** followed by hydrolysis/decarboxylation. This methodology was extended to other symmetrical ketones, which resulted in the high yielding regioselective synthesis of 2,4-dialkyl resorcinols. Evaluation of the scope and selectivity of this reaction with other unsymmetrical and functionalized enolizable ketones will be part of future studies.

Acknowledgements

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References and notes

1. (a) Adams, A. D.; Hu, Z.; von Langen, D.; Dadiz, A.; Elbrecht, A.; MacNaul, K. L.; Berger, J. P.; Zhou, G.; Doebber, T. W.; Meurer, R.; Forrest, M. J.; Moller, D. E.; Jones, A. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3185; (b) Kun Liu, et al. *J. Med. Chem.*, in press.
2. Jones, R. J.; Van De Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettis, T. R. R. *J. Org. Chem.* **2001**, *66*, 3435.
3. Modest to poor regioselectivity of the Claisen rearrangement of *meta* substituted allyl phenyl ethers has recently been demonstrated to be sensitive to the electronic nature of the substituents (a) Gozzo, F. C.; Fernandes, S. A.; Rodrigues, D. C.; Eberlin, M. N.; Marsaioli, A. J. *J. Org. Chem.* **2003**, *68*, 5493; (b) Bhide, B. H.; Akolkar, V. D.; Prabhu, V. G. *Indian J. Chem.* **1992**, *31*, 143.
4. The rearrangement of 5-*n*-pentylresorcinol bis-allyl ether, has been recently reported to afford 2,4-bisallyl-5-*n*-pentylresorcinol in 70% yield with no mention of regioselectivity (a) Amorati, R.; Attanasi, O. A.; Ali, B. E.; Filippone, P.; Mele, G.; Spadavecchia, J.; Vasapollo, G. *Synthesis* **2002**, 2749; (b) Graybill, T. L.; Casillas, E. G.; Pal, K.; Townsend, C. A. *J. Am. Chem. Soc.* **1999**, *121*, 7730.
5. (a) Thermal rearrangement of resorcinol bis-allyl ether in *o*-dichlorobenzene resulted in a 2:1 mixture of regioisomers favoring 2,4-diallylresorcinol and resulted in only a 37% isolated yield from resorcinol; (b) Addition of ethylmagnesium bromide to 2,4-dimethoxybenzaldehyde, followed by catalytic hydrogenation under acidic conditions, provided a near quantitative yield of 4-propylresorcinol dimethyl ether. Directed *ortho*-metallation (with *n*-propyl iodide quench) did not completely alkylate; we routinely observed 88–90% yield of the 2,4-dipropyl resorcinol dimethyl ether that still required deprotection to afford **2**.
6. (a) Schmidt, Hans-Georg. EP 0074497, 1983; (b) Schmidt, Hans-Georg. DE 32 35 019 A1, 1983; (c) Money, T.; Comer, F. W.; Webster, G. R. B.; Wright, I. G.; Scott, A. I. *Tetrahedron* **1967**, *23*, 3435; (d) Money, T. *Chem. Rev.* **1970**, *70*, 553.
7. (a) Milata, V. *Aldrichim. Acta* **2001**, *34*, 20; (b) Boger, D. L.; Mullican, M. M. *J. Org. Chem.* **1984**, *49*, 4033.
8. Direct formation of functionalized aromatics has recently been reported via [3+3] cyclization of (3-siloxymethylidene)acetylacetone or 1,1,-diacylcyclopropanes with 1,3-bis-silyl enol ethers in a similar fashion (a) Dede, R.; Langer, P. *Tetrahedron Lett.* **2004**, *45*, 9177; (b) Bose, G.; Nguyen, V. T. H.; Ullah, E.; Lahiri, S.; Gorls, H.; Langer, P. *J. Org. Chem.* **2004**, *69*, 9128.
9. For dianion reviews see: (a) Thompson, C. M.; Green, D. *Tetrahedron* **1991**, *47*, 4223; (b) Petragani, N.; Yonashiro, M. *Synthesis* **1982**, 521; For dianion reviews see: (c) Kaiser, E. M.; Petty, J. D.; Knutson, P. L. *Synthesis* **1977**, 509.
10. (a) Anker, R. M.; Cook, A. H. *J. Chem. Soc.* **1945**, 311; (b) Marmor, R. S. *J. Org. Chem.* **1972**, 2901; (c) Schmidt, H.-W. *Synthesis* **1985**, 778.
11. (a) Nicolau, K. C.; Vassilikogiannakis, G.; Simonsen, K. B.; Baran, P. S.; Zhong, Y.-L.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 3071; (b) Furstner, A.; Seidel, G. *J. Org. Chem.* **1997**, *62*, 2332; (c) Trifonov, L. S.; Bieri, J. H.; Prewo, R.; Dreiding, A. S. *Tetrahedron* **1983**, *39*, 4243.
12. (a) Davis, C. J.; Lewis, P. T.; Billodeaux, D. R.; Fronczek, F. R.; Escobedo, J. O.; Strongin, R. M. *Org. Lett.* **2001**, *3*, 2443; (b) Papefstathiou, G. S.; MacGillivray, L. R. *Org. Lett.* **2001**, *3*, 3835; (c) Saito, S.; Rudkevich, D. M.; Rebek, J., Jr. *Org. Lett.* **1999**, *1*, 1241.