entropy term can be based on the term $R \ln (Z_f/Z_r)$. Most calculations of entropy changes in ion–molecule equilibria have been based on ratios of partition functions expressing the distributions of internal energy in the separated reactant and product species. These partition functions are derived from a model of the system which assumes that interactions, such as those taken into account in calculating Z_f and Z_r, do not exist. The inclusion of a term $R \ln (Z_f/Z_r)$ in the entropy merely reflects the fact that, in the particular case of equilibria involving ions, such interactions do play a role. According to thermodynamics, the calculation of ΔS from statistical mechanics involves two parts, that arising from the ratios of internal partition functions (the "ideal" contribution) and that arising from the effects of the intermolecular forces on the configuration integral. The latter contribution is generally expressed in terms of the fugacity, which is usually derived from the experimentally observed pressure–volume–temperature relationships of a gas or from van der Waals constants. Obviously the fugacities of ions are not experimentally accessible in these ways. However, a calculation[7] of the contribution to $\Delta G°$ by intermolecular interactions is based on a consideration of the same potential functions which are the basis for the calculation of Z. Hence, it is to be expected that a statistical mechanical derivation of ΔS for ion–molecule equilibria would result in expressions which are equivalent to those derived here from kinetic considerations.

Table III lists some values of ΔS which are derived from the results of Meot-Ner and Field,[3d] who determined $\Delta G°$ for charge-transfer equilibria in aromatic systems at 450 and 600 K. Since the changes in $\Delta G°$ over this temperature range are small (±0.3 kcal/mol), these authors concluded that the entropy change for charge-transfer equilibria in these systems is zero. The comparisons shown in Table III demonstrate that, for all the reaction pairs studied by those authors in which there should be no other contributions to the entropy, the sign of the entropy change is always correctly predicted from the collision contribution. (In these measurements the experimental error is of approximately the same magnitude as the entropy change being determined.) Table III also shows the only entropy determinations in the literature[2a] for proton-transfer equilibria in which it is predicted there should be no other contributions to the entropy change. The collision contribution correctly predicts the sign and approximately the magnitude of the measured entropy change.

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References and Notes

(1) J. J. Solomon and F. H. Field, *J. Am. Chem. Soc.*, **97**, 2625 (1975), and references therein.
(2) (a) R. Yamdagni and P. Kebarle, *J. Am. Chem. Soc.*, **98**, 1320 (1976); (b) D. H. Aue, H. M. Webb, and M. T. Bowers, *ibid.*, **98**, 311 (1976), and references therein; (c) D. K. Bohme, P. Fennelly, R. S. Hemsworth, and H. I. Schiff, *J. Am. Chem. Soc.*, **95**, 7512 (1973), and references therein; (d) J. L. Beauchamp in "Interactions Between Ions and Molecules", P. Ausloos, Ed., Plenum Press, New York and London, 1975, p 413.
(3) (a) V. G. Anicich, M. T. Bowers, R. M. O'Malley, and K. R. Jennings, *Int. J. Mass Spectrom. Ion Phys.*, **11**, 99 (1973); (b) V. G. Anicich and M. T. Bowers, *ibid.*, **13**, 351 (1974); (c) S. G. Lias, P. Ausloos, and Z. Horvath, *Int. J. Chem. Kinet.*, in press; (d) M. Meot-Ner and F. H. Field, *Chem. Phys. Lett.*, **44**, 484 (1976); (e) P. Ausloos and S. G. Lias, *Proc. Int. Conf. Mass Spectrom., 7th*, in press.
(4) See, for instance, S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes", McGraw-Hill, New York and London, 1941, p 7, or K. J. Laidler, "Chemical Kinetics", McGraw-Hill, New York and London, 1965, p 66.
(5) (a) J. L. Franklin, Ed., "Ion-Molecule Reactions", Plenum Press, New York, N.Y., 1972; (b) P. Ausloos, Ed., "Interactions Between Ions and Molecules", Plenum Press, New York and London, 1975; (c) S. G. Lias and P. Ausloos, "Ion-Molecule Reactions. Their Role in Radiation Chemistry", American Chemical Society, Washington, D.C., 1975.
(6) The collision rate constants, Z, are usually calculated using the Langevin–Gioumousis–Stevenson formalism (P. Langevin, *Ann. Chim. Phys.*, **5**, 245 (1905); G. Gioumousis and D. P. Stevenson, *J. Chem. Phys.*, **29**, 294 (1958)) for reactions involving nonpolar molecules, $Z = 2\pi e(\alpha/\mu)^{1/2}$, or the Su–Bowers A. D. O. formalism (T. Su and M. T. Bowers, *Int. J. Mass Spectrom. Ion Phys.*, **12**, 347 (1973); T. Su and M. T. Bowers, *J. Am. Chem. Soc.*, **95**, 1370 (1973); M. T. Bowers and T. Su in ref 2d, p 163) for reactions involving molecules having a permanent dipole moment, $Z = 2\pi e/\mu^{1/2}[\alpha^{1/2} + c\mu_D(2/\pi kT)^{1/2}]$, (where α is the polarizability of the molecule, e is the charge on the electron, μ is the reduced mass of the colliding pair, μ_D is the permanent dipole, and c is a parameter having values between 0 and 1 which is a function of $\mu_D/\alpha^{1/2}$) or the alternative approach recently proposed by Barker and Ridge (R. A. Barker and D. P. Ridge, *J. Chem. Phys.*, **64**, 4411 (1976)). All of these models are based on a calculation of the attractive potential existing between the ion and molecule because of interactions between the charge and the induced dipole or permanent dipole of the molecule. Although these calculations do not take into account certain terms in the ion–molecule potential of interaction (such as quadrupole moments, for instance), more complete calculations, as well as comparisons with experimentally determined ion–molecule collision rates, indicate that these equations predict the value of Z correctly, within 15–20%.
(7) See, for instance, R. Fowler and E. A. Guggenheim, "Statistical Thermodynamics", Cambridge University Press, New York, N.Y., 1952, Chapter VII.
(8) A. A. Maryott and F. Buckley, *Natl. Bur. Stand. (U.S.) Circ.*, 537 (1953).
(9) H. M. Rosenstock, K. Draxl, B. Steiner, and J. Herron, *J. Chem. Phys. Ref. Data*, **6**, in press.

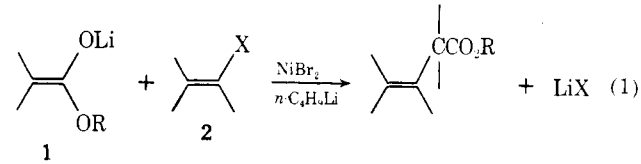
S. G. Lias,* P. Ausloos
Institute for Materials Research
National Bureau of Standards, Washington, D.C. 20234
Received February 21, 1977

A Nickel Catalyst for the Arylation and Vinylation of Lithium Ester Enolates

Sir:

α-Aryl and α-vinyl carbonyl groupings are structural features of a large number of biologically important molecules. A method for the direct arylation or vinylation of enolate anions would greatly simplify the synthesis of such molecules. Progress to this goal has been reported by a number of workers,[1] with perhaps the most promising approach to date being the trapping of photogenerated aryl radicals with ketone enolates (the $S_{RN}1$ reaction).[2]

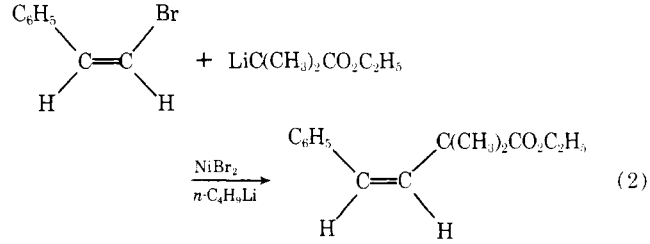
We wish to report that the addition of *n*-butyllithium to suspensions of nickel(II) bromide in tetrahydrofuran (THF) at dry ice temperature forms material which catalyzes an efficient substitution reaction of lithium ester enolates (**1**) with aryl or vinyl halides (**2**) (eq 1). The reaction occurs with clean



1 **2**

retention of stereochemistry at the halogen-bearing carbon, as judged from results obtained with the configurational isomers of β-bromostyrene (eq 2, 3).[3]

The reaction with the lithium enolate of ethyl crotonate (**5**) occurs at the γ carbon to give chain extended vinylation or

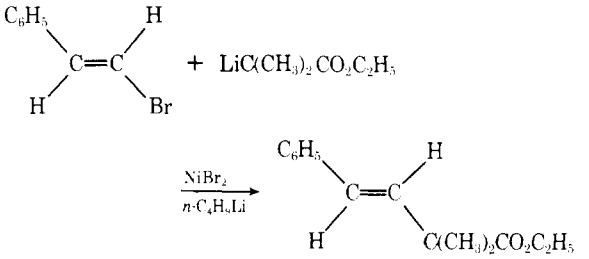


3, 50% (<1% trans isomer, GLC)

Table I. Reaction of Lithium Ester Enolates with Vinyl and Aryl Halides

Enolate	Halide	Product[a]	Yield, %[b]
$LiCH_2CO_2C(CH_3)_3$	C_6H_5I	$C_6H_5CH_2CO_2C(CH_3)_3$	73
	C_6H_5Br		41
	C_6H_5Cl		3
	$CH_3CH{=}CHBr$	$CH_3CH{=}CHCH_2CO_2C(CH_3)_3$	99
	$CH_2{=}CBrCH_3$	$CH_2{=}C(CH_3)CH_2CO_2C(CH_3)_3$	94
	$CH_3CH{=}CHBrCH_3$	$CH_3CH{=}CH(CH_3)CH_2CO_2(CH_3)_3$	60
	$C_6H_5CH{=}CHBr$	$C_6H_5CH{=}CHCH_2CO_2C(CH_3)_3$	83
$Li(CH_3)CHCO_2C(CH_3)_3$	$CH_3CH{=}CHBr$	$CH_3CH{=}CHCH(CH_3)CO_2C(CH_3)_3$	53
$Li(CH_3)_2CCO_2C_2H_5$	$CH_3CH{=}CHBr$	$CH_3CH{=}CHC(CH_3)_2CO_2C_2H_5$	72
$Li(C_6H_5)CHCO_2C_2H_5$	C_6H_5I	$(C_6H_5)_2CHCO_2C_2H_5$	46
$LiCH_2CH{=}CHCO_2C_2H_5$	$CH_3CH{=}CHBr$	$CH_3CH{=}CHCH_2CH{=}CHCO_2C_2H_5$	40

[a] All products exhibited spectral and analytical data in accordance with assigned structures. [b] GLC yields; isolated yields were generally 10–20% lower.



(3)

4, 57% (<1% cis isomer, GLC)

arylation products (eq 4). This is in contrast to the usual reactions of **5** with electrophiles which occur almost exclusively at the α carbon.[4]

$$LiCH_2CH{=}CHCO_2C_2H_5$$
5

$$+ C_6H_5I \xrightarrow[n\text{-}C_4H_9Li]{NiBr_2} PhCH_2CH{=}CHCO_2C_2H_5 \quad (4)$$

60% (<1% α-phenyl isomer)

Attempts to extend the vinylation or arylation procedure to ketone or ketone-derived enolates have so far given only very modest yields.

Results obtained with a variety of halides and ester enolates are shown in Table I.

The following procedure for reaction of lithio *tert*-butyl acetate with iodobenzene is representative. A flask equipped with septum inlet and magnetic stirring is maintained under a positive argon pressure and charged with 10 mmol (2.18 g) of anhydrous nickel(II) bromide and 10 mL of THF. The flask is immersed in a dry ice/acetone bath and 2 mmol (1.37 mL) of a 1.46 M solution of *n*-butyllithium in hexane is injected. The resultant black suspension is stirred for 5 min, then 10 mmol (1.11 mL) of iodobenzene is injected, followed by 10 mmol (10 ml) of a 1 M solution of lithio *tert*-butyl acetate[5] in THF. The solution is allowed to reach room temperature and stirred for 30 min. The cooling bath is then reapplied and the reaction mixture is quenched by addition of 6 mL of 6 N hydrochloric acid. Pentane is added and the mixture is stirred at room temperature until the organic layer is nearly colorless. GLC analysis of the dried (anhydrous K_2CO_3) organic layer established the presence of 7.3 mmol (73% yield) of *tert*-butyl phenylacetate. Vacuum distillation gave 1.27 g (66% yield) of pure product, bp 110 °C (15 mm), $n^{20}D$ 1.4825.

The catalyst suspension gradually loses activity if allowed to reach room temperature prior to addition of halide and enolate. For example, the yield of *tert*-butyl phenylacetate obtained by the above procedure decreased to 51% when catalyst aged for 1 h at 25 °C was used. Attempts to isolate the catalyst either by filtration or evaporation have so far given only inactive material.

Optimal yields for a general procedure were obtained with a full equivalent of nickel(II) bromide; however, the catalytic nature of the reaction is shown by the result shown in eq 5, demonstrating a 350% yield of vinylation product based on either nickel(II) bromide or *n*-butyllithium.

$$CH_3CH{=}CHBr + LiCH_2CO_2C(CH_3)_3 + NiBr_2$$
1.0 mmol 1.0 mmol 0.2 mmol

$$+ n\text{-}C_4H_9Li \rightarrow CH_3CH{=}CHCH_2CO_2C(CH_3)_3 \quad (5)$$
0.2 mmol 0.7 mmol

Other organolithium reagents also react with nickel(II) bromide to generate active catalyst, but the yields are somewhat lower than those obtained with *n*-butylithium (eq 6). No detectable substitution occurs in the absence of either nickel(II) bromide or organolithium.

$$CH_3CH{=}CHBr + LiCH_2CO_2C(CH_3)_3 \xrightarrow[RLi]{NiBr_2} CH_3CH{=}CHCH_2CO_2C(CH_3)_3 \quad (6)$$

99%, R = n-C_4H_9; 76%, R = CH_3; 63%, R = C_6H_5; 51%, R = $C(CH_3)_3$

The following comments concerning the mechanism of the reaction are made. The retention of configuration obtained with the β-bromostyrene isomers probably rules out a radical pathway,[6] at least for these halides. The higher yields obtained with iodides compared to the corresponding bromides or chlorides (Table I) are evidence against a classical nucleophilic aromatic substitution mechanism on a nickel-activated π system.[7] A number of substitution reactions of aryl halides promoted by phosphine or cyclooctadiene complexes of nickel(0) has been reported.[2d,8] Oxidative addition of aryl halide to nickel(0) is considered to be a key step in these reactions.[9] Surprisingly, we find that addition of triphenyl- or tri-*n*-butylphosphine to suspensions of nickel(II) bromide either before or after addition of *n*-butyllithium gives totally inactive material. Furthermore, no substitution product was obtained from the reaction of lithio *tert*-butyl acetate with 1-bromopropene using tetrakis(tri-*n*-butylphosphine)nickel(0)[10] as catalyst. If the present reaction does proceed through a nickel(0) species, it appears that the absence of strongly coordinating ligands plays an essential role in its success.

Acknowledgment. This research was supported in part by a research grant from the National Science Foundation.

References and Notes

(1) For leading references as well as a useful alternative approach to the synthesis of α-aryl ketones and aldehydes see, C. L. Sacks and P. L. Fuchs, *J. Am. Chem. Soc.*, **97**, 7372 (1975).
(2) (a) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 1407 (1973); (b) R. A.

Rossi and J. F. Bunnett, *ibid.*, **38**, 3020 (1973); (c) J. V. Hay, T. Hudlicky, and J. F. Wolfe, *J. Am. Chem. Soc.*, **97**, 374 (1975); (d) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *ibid.*, **97**, 2507 (1975).

(3) The ^{1}H NMR spectra of **3** and **4** are consistent with the assigned stereochemistry: **3** (CCl_4, TMS), δ 7.1 (br s, 5 H), 6.3 (d, J = 12, 1 H), 5.5 (d, J = 12, 1 H), 3.6 (q, J = 6.5, 2 H), 1.3 (s, 6 H), 1.0 (t, J = 6.5, 3 H); **4** (CCl_4, TMS), δ 7.1 (br s, 5 H), 6.2 (s, 2 H), 4.1 (q, J = 6.8, 2 H), 1.3 (s, 6 H), 1.2 (t, J = 1.3, 3 H). Final assignment of stereochemistry is based on FSO_3H-catalyzed isomerization of either **3** or **4** to an equilibrium mixture containing 95% of isomer assigned trans stereochemistry (**4**).

(4) (a) M. W. Rathke and D. F. Sullivan, *Tetrahedron Lett.*, 4249 (1972). (b) Katzenellenbogen has reported increased amounts of γ-alkylation associated with copper enolates of certain α,β-unsaturated esters: J. A. Katzenellenbogen and A. L. Crumrine, *J. Am. Chem. Soc.*, **96**, 5662 (1974).

(5) Ester enolate solutions were prepared by addition of the appropriate ester to THF solutions of lithium diisopropylamide at dry ice temperature. The resultant solutions were maintained at −78 °C and transferred to the catalyst suspension by Teflon tubing and argon pressure.

(6) For a recent review of the stereochemical features of vinylic radical processes, see L. A. Singer in "Selective Organic Transformation", Vol. II, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y. 1970, p 269.

(7) For example, a classical nucleophilic aromatic substitution mechanism[7a] is postulated for substitution reactions of the halogen in π-(halobenzene)chromium tricarbonyl complexes.[7b] The observed dependence of yield and reactivity on leaving group is F > Cl > I.[7c] (a) Cf. J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958). (b) M. F. Semmelhack and H. T. Hall, *J. Am. Chem. Soc.*, **96**, 7092 (1974). (c) M. F. Semmelhack and H. T. Hall, *ibid.*, **96**, 7091 (1974).

(8) (a) M. F. Semmelhack, R. D. Stauffer, and T. D. Rogerson, *Tetrahedron Lett.*, 4519 (1973); (b) K. Tamao, M. Zembayashi, Y. Kiso, and M. Kumada, *J. Organomet. Chem.*, **55**, C91 (1973); (c) L. Cassar, *ibid.*, **54**, C57 (1973); (d) J. P. Corriu and J. P. Masse, *J. Chem. Soc., Chem. Commun.*, 144 (1972).

(9) (a) G. W. Parshall, *J. Am. Chem. Soc.*, **96**, 2360 (1974); (b) D. G. Morrell and J. K. Kochi, *ibid.*, **97**, 7262 (1975).

(10) Tetrakis(tri-*n*-butylphosphine)nickel(0) was prepared essentially as described by M. Aresta, C. F. Nobile, and A. Sacco, *Inorg. Chim. Acta*, **12**, 167 (1975).

(11) Alfred P. Sloan Fellow, 1975–1977.

Alan A. Millard, Michael W. Rathke*[11]

Department of Chemistry, Michigan State University
East Lansing, Michigan 48824

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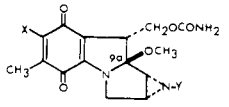
Synthetic Studies toward Mitomycins. 1. Total Synthesis of Deiminomitomycin A

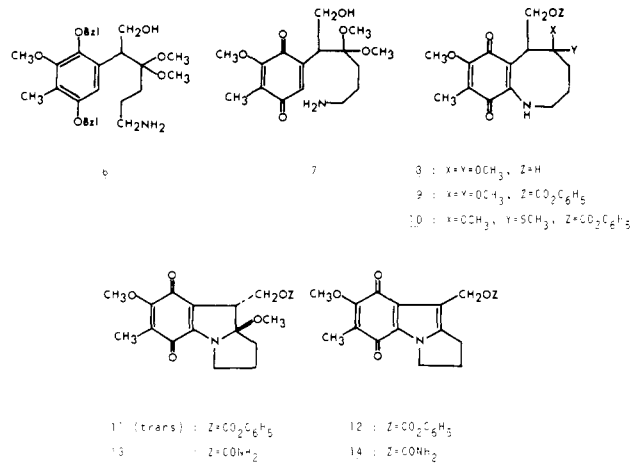
Sir:

The mitomycins (**1a–e**) are a class of antibiotics with activity against gram-positive and gram-negative bacteria and also against several kinds of tumors.[1] Since their structures were first elucidated in 1962,[1] numerous synthetic approaches to the mitomycins have been reported.[2] However, the mitomycins



1a : mitomycin A; X=OCH_3, Y=H
1b : mitomycin B, see reference 4.
1c : mitomycin C; X=NH_2, Y=H
1d : porfiromycin; X=NH_2, Y=CH_3
1e : mitomycin; see reference 5.

themselves have not yet been synthesized. It seemed to us that the most difficult problem in synthesizing the naturally occurring mitomycins is related to introducing the 9a methoxy group since this is known to be the most labile functionality present in the target molecules.[3] In this communication, we wish to report a total synthesis of deiminomitomycin A (**13**). This synthesis involves two key cyclizations: the intramolecular Michael reaction used to construct the eight-membered ring of **8** and the trans-annular cyclization of **10** to **11** under conditions mild enough to introduce and preserve the 9a methoxy group.

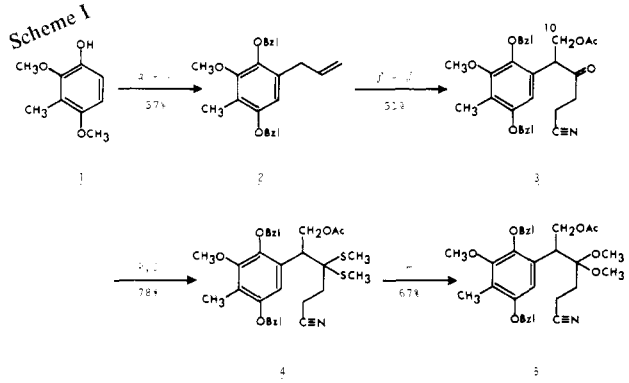


6 7 3 : X=Y=OCH_3, Z=H
9 : X=Y=OCH_3, Z=$CO_2C_6H_5$
10 : X=OCH_3, Y=SCH$_3$, Z=$CO_2C_6H_5$
11 (trans) : Z=$CO_2C_6H_5$ 12 : Z=$CO_2C_6H_5$
13 : Z=$CONH_2$ 14 : Z=$CONH_2$

Scheme I summarizes the 13-step synthesis of nitrile **5** from 2,4-dimethoxy-3-methylphenol (**1**)[6,7] readily available from 2,6-dimethoxytoluene. Although the carbon atom at the 10 position[8] could be introduced directly by Claisen rearrangement (i.e., $ArOCH_2CH{=}CHCH_2OCH_2C_6H_5 \rightarrow Ar'CH(CH_2OCH_2C_6H_5)CH{=}CH_2$), we found the route shown to be more practical. All the steps in Scheme I proceeded straightforwardly except for the ketallization of **3** (or the corresponding primary alcohol) to **5.** Owing to difficulties encountered in avoiding the elimination of acetic acid (or water) under various ketallization conditions, the 3-step transformation of **3** to **5** was used. The product of step *k* was the thioketal thioiminoether which was converted to thioketal nitrile **4** by brief treatment with triethylamine in methanol at room temperature.

Lithium aluminum hydride reduction of **5** in ether gave amine **6**[9] (mp 60–62 °C), which was subjected to hydrogenolysis (1 atm of H_2, Pd on C/CH_3OH, room temperature, 15 min) followed by treatment with oxygen (1 atm of O_2, CH_3OH, room temperature, 20–40 h) to afford the eight-membered quinone **8**[9] (red needles; mp 110–112 °C; UV (CH_3OH) 218 nm (log ϵ 4.36), 304 (4.05), 509 (3.15); ^{1}H NMR ($CDCl_3$) 1.87 (3 H, s), 3.20 (3 H, s), 3.27 (3 H, s), 4.07 ppm (3 H, s)) in 40–50% yield. Clearly, an intermediate in this transformation was benzoquinone **7**, the primary amino group of which cyclized intramolecularly to the quinone moiety in the Michael fashion. Although an eight-membered ring was formed, the Michael reaction was extremely facile and **8** was

Scheme I



1 2 3 4 5

[a] $CH_2{=}CHCH_2Br/K_2CO_3$/acetone, reflux, mp 32–33 °C.[9] [b] $C_6H_5N(CH_3)_2$, reflux, oil.[10] [c] 70% HNO_3/HOAc, room temperature, oil.[10] [d] Zn/HOAc, 0 °C, mp 110–113 °C.[9] [e] $C_6H_5CH_2Br/K_2CO_3$/DME–DMF, reflux, mp 41–42 °C.[9] [f] $H_2O_2/C_6H_5CN/K_2CO_3/CH_3OH$–dioxane, room temperature, mp 56–57 °C.[9] [g] LDA/CH_3CN, −30 °C, oil.[10] [h] CrO_3/H_2SO_4/aqueous acetone, mp 99–101 °C.[9] [i] $NaOCH_3$/$(CH_2O)_3$/CH_3OH–THF, 0 °C, mp 86–87 °C.[9] [j] Ac_2O/Py, 0 °C, oil.[10] [k] $CH_3SH/BF_3{\cdot}2AcOH$, −30 °C, oil.[10] [l] Et_3N/CH_3OH, room temperature, mp 103–104 °C.[9] [m] $HgCl_2/Et_3N/CH_3OH$, mp 88–89 °C.[9]