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High degree of chemoselectivities recorded during the Reformatsky reaction on coumarinyl phenyl ketones and formyl coumarins

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Bromo-zinc enolate reagents show excellent chemo-selectivity towards 7-methoxy-8-coumarinyl phenyl ketones (1, 2) and furnish α-alkylidene chromene derivatives (5-10) together with bridged-lactone (11), cinnamate derivative (12) and γ-benzopyran (13). 7-Methoxy-8-formylcoumarins (3, 4) afford β-hydroxy esters (14, 16) and α,β-unsaturated esters (15, 17-21) showing excellent chemoselectivity with E-configuration.

Keywords: Bromo-zinc enolates, Coumarin, Configuration, Stereoselectivity, Chromene

Coumarins bearing various types of side chains at position 8 constitute well defined families having a vast member of phytochemicals and are enlisted with other diversified natural products[1-3]. A very few reports were recorded on Reformatsky reaction on coumarin in literature[4,5]. In our laboratory we extensively studied Grignard Reaction[6-8] and Reformatsky Reaction[9] on various carbonyl substituted Coumarins. Recently we have successfully applied Reformatsky Reaction using various bromozinc enolate reagents on Coumarins containing carbonyl functionalities. We wish to report here some interesting and unexpected observations in this paper.

The Coumarinyl phenyl ketones **1**,**2** selected for the purpose were allowed to react with bromozinc enolates of various α-bromo ester gave α-benzelidine chromene derivatives **5-10**, bridged Coumarin derivative **11**, α,β-unsaturated ester **12** and γ-benzopyran **13**. The reagents attack exclusively on lactone moiety without touching keto carbonyl group. Next 8-formylcoumarins **3**, **4** were allowed to react with bromozinc enolate of ethyl acetate furnished β-hydroxy esters **14**, α,β-unsaturated ester **16** from **3** and β-hydroxy ester **15**, α,β-unsaturated ester **17** from **4**. The bromozinc enolates derived from propionate and isobutyrate react with Coumarins **3** and **4** afforded α,β-unsaturated esters **18**, **19** using propionate enolates and olefinic derivatives **20**, **21** from isobutyrate enolates.

It is interesting to note here that the compounds 2-methoxy-3-acetyl-4-methoxy-8-diene **22** and 2-methoxy-3-acetyl-4-methoxycinnamate (23,24) has been isolated[6] when the Grignards (RMgX,R=Me, Et, iPr),were used to prepare new 4-methyl 5-methoxy-8-substituted Coumarin derivatives **25**, **26**, **27** using bromozinc enolates of ethyl acetate. All the compounds for the coumarin derivatives thus prepared are very close to the structure of the natural product *Murrya exotica*.

Results and Discussions

The products isolated during the Reformatsky Reaction **5-10** were subjected to UV and IR spectral studies. In all the cases the reagents attack exclusively on lactone carbonyl which is confirmed by IR absorption band at around 1680-1682 cm^{-1} and disappearance of IR absorption at 1730 cm^{-1} in starting compounds. Similarly UV absorption at around 370 nm (log€ 4.22), 282 (log€ 4.03) prove the presence of α-benzelidine chromene derivatives (Table 1 and Table 2).

Though the nature of the side chain in compounds (5-10) as α-alkylidene group has been identified also by NMR spectroscopy. Stereo Chemical informations on this side chain could only be assigned after carrying out an extensive COSY (δ^1H- δ^1H) and NOE investigations[10]. Thus, assigning with full certainty the various ^{1}H NMR signals by COSY (^{1}H-^{1}H) experiment. Final proof regarding the configuration (E or Z) of the double bond between C_2 - $C_{1'}$ and the ethoxycarbonyl functionality has been established conclusively from NOE studies exploiting fully the correctly assigned signals. On irradiating 1"-CH_3

Table 1 — Physical characterization data of new compounds

Compd	Mol. Formula	m.p. (°C)	Yield (%)	Elemental analysis in C% &H%
5	$C_{21}H_{18}O_5$	159	40	72, 5.14
6	$C_{22}H_{20}O_5$	190	36	72.5, 5.49
7	$C_{22}H_{20}O_5$	178	54	72.5, 5.5
8	$C_{23}H_{22}O_5$	184	67	73.1, 5.82
9	$C_{23}H_{22}O_5$	167	59	73.1, 5.82
10	$C_{24}H_{24}O_5$	163	62	73.4, 5.82
11	$C_{27}H_{30}O_7$	87	57	70.0, 6.34
12	$C_{29}H_{36}O_8$	178	37	70.0,7.0
13	$C_{30}H_{36}O_8$	175	38	70.86, 7.0
14	$C_{15}H_{16}O_6$	92	35	61.64,5.43
15	$C_{16}H_{18}O_6$	88	25	62.74,5.88
16	$C_{15}H_{14}O_5$	78	58	65.70,5.10
17	$C_{16}H_{16}O_5$	58	42	66.40,5.50
18	$C_{16}H_{16}O_5$	70	60	66.60,5.55
19	$C_{17}H_{18}O_5$	81	42	67.10,5.90
20	$C_{14}H_{14}O_3$	56	29	72.90,6.16
21	$C_{15}H_{16}O_3$	51	25	73.61,6.50
25	$C_{16}H_{16}O_3$	79	46	74.90,6.21
26	$C_{16}H_{16}O_5$	96	42	66.30,5.40
27	$C_{17}H_{18}O_5$	110	51	68.0, 5.90

signal in (8) and methylene signal of 1"-CH_2CH_3 in (9). NOE enhancements were observed for the aromatic pr**o**tons of the ketophenyl group located at C-8 position. This conclusively point out that Me and Et groups in **8**)and **9** respectively are present in close proximity in space with respect to ketophenyl group located at C-8 position. Again the NOE enhancement of 3-H and 4-H signals by irradiating methylene group of 1"-COO CH_2CH_3 conclusively established that 1"-COOEt and 3-H are in close proximity relationship in space between 1"-R (R=Me, Et) and ketophenyl group located at C-8 and also between 3-H and 1"-COOEt unequivocally settled as configuration of the double bond between C-2 and C-1" as E. Again the close proximity between methylene group of 1"-$COOCH_2CH_3$ and 3-H and 4-H in (8) and (9) also confirmed that their preferred conformation as *s-trans* (see Supplementary Information).

The products isolated during the reaction of bromozinc enolates of isobutyrate on **1** and **2** afforded **11** and **12**. The reagent attack exclusively on lactone carbonyl group without touching the ketophenyl

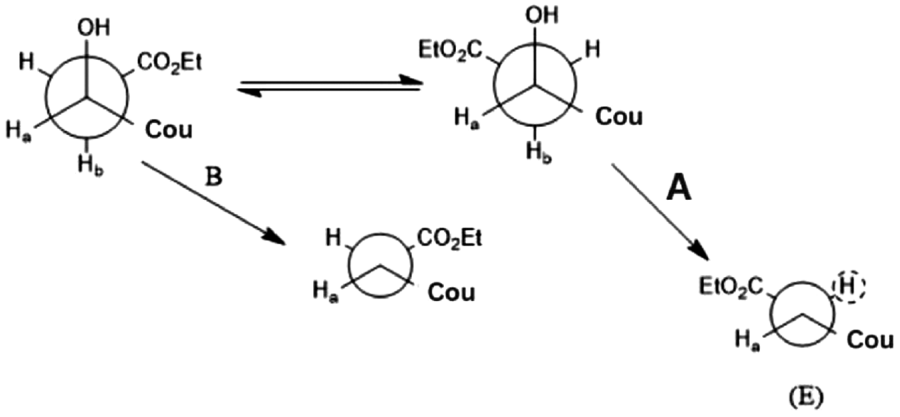
Table 2 — Spectroscopic data of new compounds

Compd	$UV_{max.}$ log€	IR (cm^{-1})	MS: *m/z* (rel.int.)
5	370(4.3)	1680	350(41), 323(2)
		1638	306(39), 278(100)
	282(4.13)	1613	261(19), 201(2)
			170(12), 105(49)
			84(22), 77(95)
6	372(4.13)	1683	384(64), 319(55)
	251(3.90)	1641	292(100), 275(24)
			215(24), 201(26)
			105(31), 77(43)
7	372(4.20)	1685	364(100), 319(55)
	251(4.32)	1640	392(100), 291(63)
		1610	277(20), 247(20)
8	374(4.41)	1674	349(73)
	287(4.2)	1594	333(24), 306(100)
	252(3.8)		305(41), 261(12) 105(23), 77(27)
9	373(4.40)	1682 1632	363(100) 335(15), 319(15)
	289.4(3.98)	1575	305(21), 291(17) 105(52), 77(36)
10	376(4.19)	1682	392(78), 377(100)
	287(3.83)	1630	349(24), 331(17)
	252(4.81)	1601	319(10), 305(10) 275(17), 105(49)
11	250(4.04)	1740	
	212(4.39)	1672 1620	
12	284(3.89)	1743 1712	512(32), 494(51) 435(20), 431(24) 407(100), 397(12)
	213(4.37)	1674	282(32), 292(48)
13	282(3.91)	1742	393(25), 392(82) 319(82), 241(43)
	249(4.37)	1674	177(12), 105(87) 84(100)
14	308(3.89)	3508	292(100), 277(59) 262(7), 229(54)
	263(3.93)	1728 1598	200(90), 199(100)

(*Contd.*)

Table 2 — Spectroscopic data of new compounds — (*Contd*.)

Compd	$UV_{max.}$ log€	IR (cm^{-1})	MS: *m/z* (rel.int.)
15	318(4.15)	3502	306(16), 291(12)
	259(3.89)	1718 1688	288(100), 261(9) 243(30), 229(70) 215(35)
16	320(4.06)	1703	
	254(4.04)	1688 1604	
17	320(4.25)	1720	
	256(4.03)	1686 1604	
18	318(4.20)	1722	288(100), 287(75)
	255(4.00)	1700 1599	260(3), 259(17) 243(28.7), 200(17) 215(35), 199(44.4)
19	318(4.00)	1710	302(75), 271(100)
	258(3.86)	1599	257(57), 243(26) 241(75), 215(45) 189(14), 185(36)
20	321(4.05)	1721	230(70), 215(100)
	282(3.93)	1598	201(31), 199(25)
	255(4.17)	1495	185(37), 168(20.5)
21	320(4.05)	1720	244(100), 229(90)
	280(3.93)	1600	215(32.5), 201(20.5)
	256(4.17)	1497	200(33.3), 199(25)
25	320(4.04)	1720	242(30.9), 227(100) 215(28), 211(12)
	282(3.93)	1702	189(42), 158(40)
	264(4.15)	1636	HRMS: *m/z* 242.1103
26	321(4.01)	1721	
	280(3.98)	1700	
	260(4.02)	1600	
27	321(4.00)	1720	
	280(3.98)	1698	
	262(4.10)	1601	

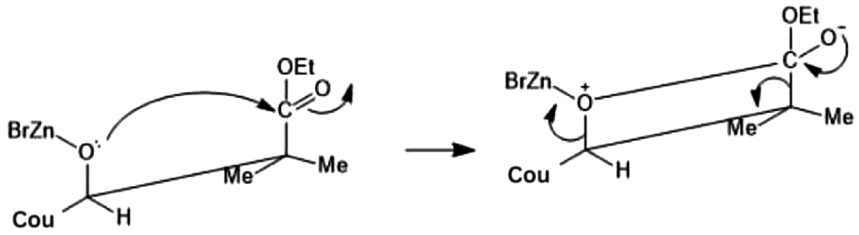


Scheme 1 — Configuration of α,β-unsaturated esters

group. The structure of the compound **11** has been settled as bridged lactone, the compound **13** as γ-pyran derivative and unsaturated phenolic compound **12** have been fully assigned through IR, ^{1}H and ^{13}C NMR.

It should be noted that the reaction of bromozinc enolate of ethyl acetate with the compounds **3**, **4** afforded β-hydroxy esters **14**, **15** and the structures has been confirmed through ^{1}H, ^{13}C NMR. HMQC and HMBC techniques have also been applied to establish the structures of **14** and **15**. The ^{13}C resonance were assigned in specific carbon through gated decoupling experiment[11,12]. The formation of α,β-unsaturated ester **16-19** indicate that the regioselectivity is distinctly in favour of unsaturated ester.

The configuration of α,β-unsaturated esters has been assigned as E is fully in conformity with ^{1}H NMR data and literature data[11,12]. This can be rationalized by the equilibrium shown in Scheme 1



Scheme 2 — Bromozinc complex intermediate with syn-planer conformation

and assuming that the transition state energy level for the E-olefinic derivatives (path A) formation is lower than that of Z- olefinic derivatives (path B) (Curtin Hammett principle[11]).

The configuration of α,β-unsaturated esters **16**, **17** has been assigned E-configuration in ^{1}H NMR spectra as 1'H and 2'H each appears as doublet (J = 16.9 Hz). Finally NOE studies unequivocally confirmed that E configuration of the double bond in **16-19**. In **16**, **17** enhancement in the intensity of 1'-H at δ7.98 - δ8.02 was noticed on irradiation of 2'$CO_2CH_2CH_3$ methylene proton at around δ 4.06 by 20%. Irradiation of 1'H, enhancement of intensity of 7-OCH_3 and 6-H indicate that 7-OCH_3 and 6-H are in close proximity in space with 1'-H and the side chain C-8-C-1' is most likely out of plane and slightly close to 6-H and 7-OMe methylene group of 2'-$CO_2CH_2CH_3$ further suggest that the preferred conformation is *s-trans*[13].

The reaction of **3** and **4** with α-bromo-zinc enolate of ethyl α-bromo-isobutyrate afforded **20** and **21**. Presumably the formation of the products **20** and **21** involve a concomitant elimination[14] of ethoxycarbonyl and hydroxy groups from the respective bromozinc complex formed as an intermediate, *via* syn-planer conformation (Scheme 2). The olefinic side chain at C-8 of compounds **20** and **21** have been assigned as E-configurations.

The products isolated **25**, **26** and **27** have been assigned as 4-methyl 5-methoxy 8-substituted Coumarins from spectral analysis. ^{1}H NMR data showed aromatic proton appear as doublet for C-6 and C-7 and in the side chains of α,β-unsaturated esters. 1'-H and 2'- H appear each as doublet with J value 12 Hz indicate the double bond in **25-29** have been assigned Z-configuration.

Thus the above results indicate that bromo-zinc enolates are fairly good reagent for introducing side chain in coumarins with high degree of chemo, regio and stereoselectivities[15].

Experimental Section

Melting points and boiling points are uncorrected. The UV and IR spectra were recorded on Perkin-Elmer Hitachi 200 and Perkin-Elmer 177 spectrometers respectively. ^{1}H NMR spectra were recorded on Jeol FX-100 machine. Mass spectra were recorded in RMU 6L mass spectrometer. The products gave M^+ ion and fragmentations thereof. ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian XL-400 NMR spectrometer.

General procedure for Reformatsky reaction of **1**, **2**, **3** and **4** with various bromo-zinc enolates derived from ethyl ester of α-bromo acids. To a stirred solution of respective bromo-zinc enolates of ethyl ester of bromo acid (6.0 mmol), zinc wool (400 mg, 6mmol) and dry benzene (50 mL) were prepared and the solution were added to either of Coumarin **1** (5 mmol) or **2** (5 mmol) or **3** (5 mmol) or **4** (5 mmol) in dry benzene (30 mL) drop-wise with constant stirring under nitrogen atmosphere for 0.5 h. The mixture was refluxed for 5 h and work-up conducted by using 100 mL 20% ice cold sulphuric acid and the products extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate and finally with saturated brine. Removal of solvent afforded the crude products from which the pure products **5-19** were isolated by column chromatographic separation (Fig. 1).

Similarly, to a stirred solution of bromo-zinc enolate of ethylbromoacetic acid (6 mmol), zinc wool (6 mmol) and dry benzene thus prepared was added either of the compounds **22** (5 mmol) or **23** (5 mmol) or **24** (5 mmol) in dry benzene (30 mL) drop-wise with constant stirring under nitrogen atmosphere for 0.5 h. The reaction mixture was refluxed for 3 h. Thereafter, usual work-up followed by chromatographic separation produced the Coumarin derivatives **25**, **26** and **27** (Fig. 1).

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

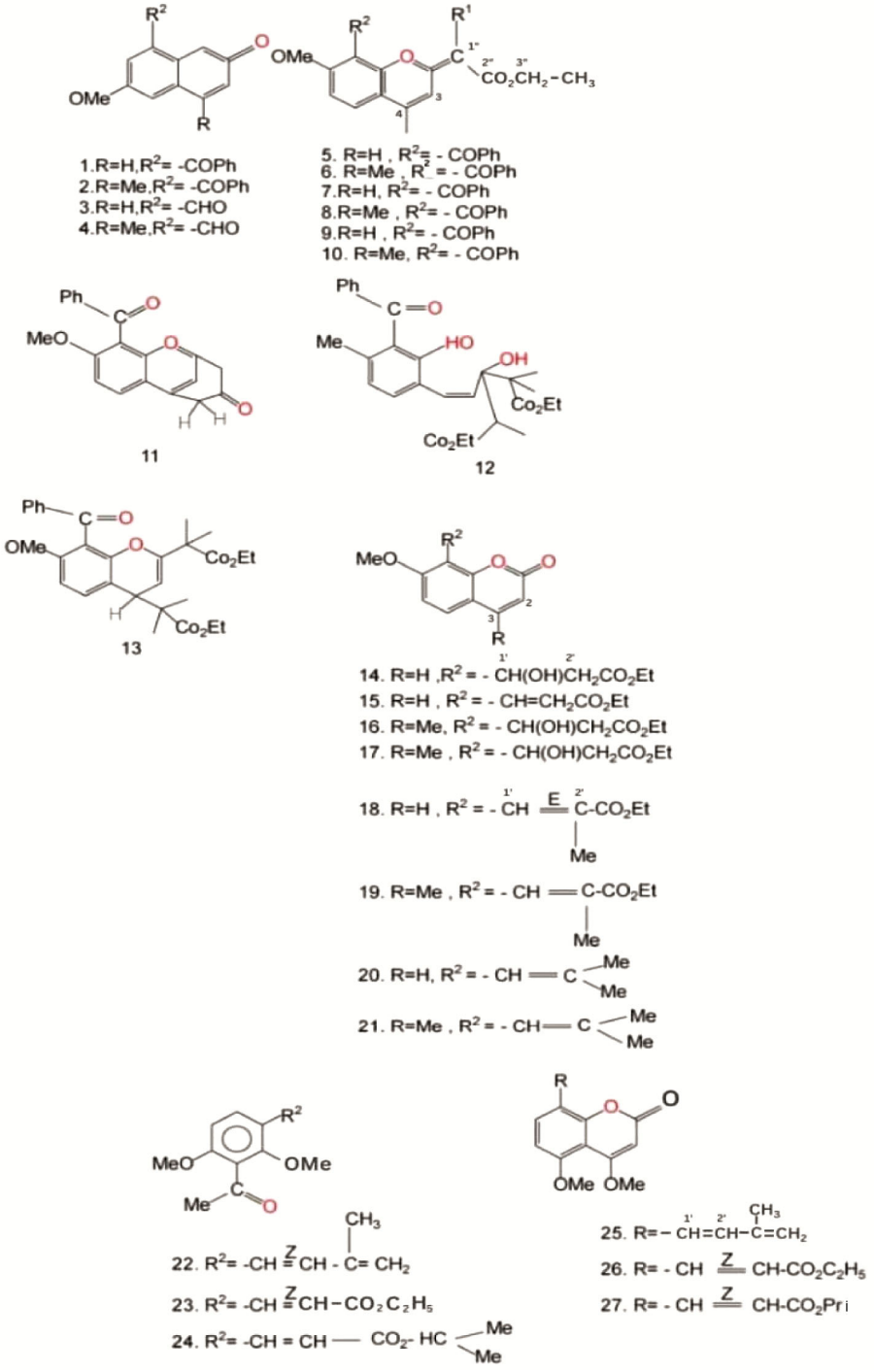


Fig. 1 — Structure of the synthesised compounds

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