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Reaction of methyl bromocycloalkanecarboxylates with zinc and dihydroisoquinoline derivative

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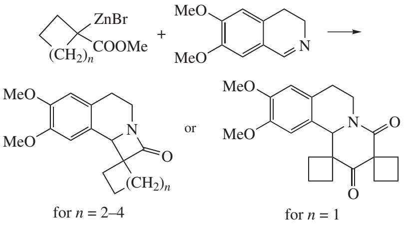
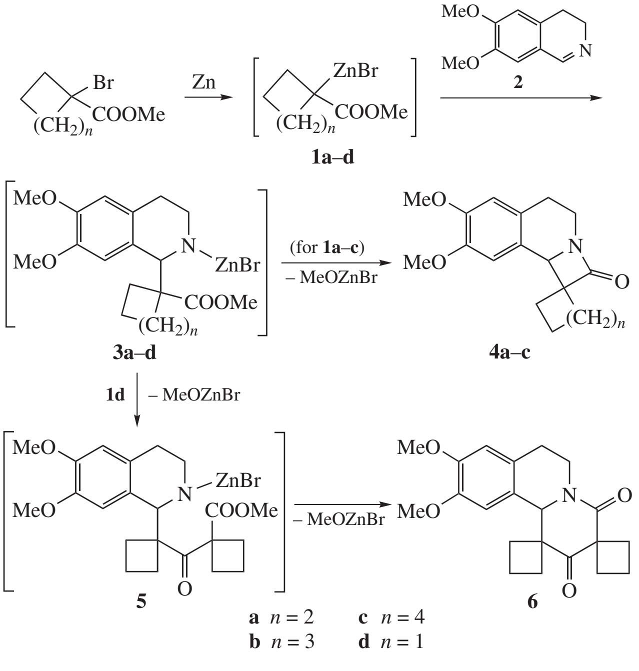
The reaction of 5–7-membered methyl 1-bromocycloalkanecarboxylates with zinc and 6,7-dimethoxy-3,4-dihydroisoquinoline leads to 7,8-dimethoxy-5,9b-dihydro-2*H*,4*H*-spiro{azeto[2,1-*a*]isoquinoline-1,1′-cycloalkan}-2-ones. In the case of 1-bromocyclobutanecarboxylate, 9′,10′-dimethoxy-7′,11b′-dihydro-2′*H*,4′*H*,6′*H*-dispiro{cyclobutane-1,1′-pyrido[2,1-*a*]isoquinoline-3′,1′′-cyclobutane}-2′,4′-dione is formed. The structures of the products were confirmed by X-ray diffraction.



Carbocyclic Reformatsky reagents react with aromatic azomethines to give intermediates that can undergo further cyclization to form spiroazetidinones,[1] some of them being biologically active.[2,3] Herein, we performed reactions of the Reformatsky reagents **1a–d**, derived from methyl 1-bromocycloalkanecarboxylates and zinc, with 6,7-dimethoxy-3,4-dihydroisoquinoline **2** that can be regarded as cyclic azomethine[4] (Scheme 1). In the first step, Reformatsky reagents **1a–d** react with compound **2** *via* addition to the C=N bond to produce intermediates **3a–d**. Five-, six- and seven-membered adducts **3a–c** undergo cyclization caused by the attack of the amide nitrogen atom to the ester carbonyl group and accompanied by elimination of bromozinc methoxide. As a result, 7,8-dimethoxy-5,9b-dihydro-2*H*,4*H*-spiro{azeto[2,1-*a*]isoquinoline-1,1′-cycloalkan}-2-ones **4a–c**[†] were obtained in 57–63% yields.



Scheme 1

The structures of products **4a–c** were confirmed by elemental analysis, IR and ^{1}H and ^{13}C NMR spectroscopy. Structure of product **4b** was ultimately established by X-ray diffraction (XRD).[‡] This compound crystallizes in the centrosymmetric space group (Figure 1).

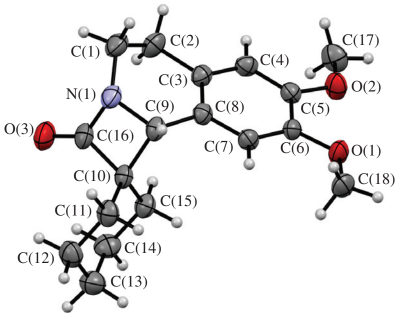


Figure 1 Molecular structure of compound **4b** with thermal ellipsoids drawn at 50% probability level.

[†] *Compounds* **4a–c**, **6** *(general procedure).* A solution of methyl 1-bromocycloalkanecarboxylate **1** (0.022 mol) and 6,7-dimethoxy-3,4-dihydroisoquinoline **2** (0.02 mol) in anhydrous toluene (10 ml) was added dropwise with stirring to a boiling mixture of zinc chips (2 g), a catalytic amount of mercury dichloride, anhydrous toluene (20 ml), and HMPA (2 ml). The mixture was refluxed for 3 h, cooled, decanted, and hydrolyzed with 5% acetic acid. The organic layer was separated, and the aqueous one was twice extracted with toluene. The organic phase was dried with anhydrous sodium sulfate, the solvents were distilled off, and the products were twice recrystallized from ethyl acetate. For characteristics of compounds **4a–c** and **6**, see Online Supplementary Materials.

[‡] The X-ray diffraction analysis of compounds **4b** and **6** was performed on an automatic single crystal Xcalibur S diffractometer by a standard procedure [MoKα radiation, graphite monochromator, ω-scanning with 1° step, 295(2) K]. Absorption corrections were not applied due to its smallness. The solution and refinement of the structure were carried out using the SHELXTL.[10]

Unexpectedly, reaction of four-membered Reformatsky reagent **1d** with azomethine **2** instead of expected lower homologue of type **4** afforded 9′,10′-dimethoxy-7′,11b′-dihydro-2′*H*,4′*H*,6′*H*-dispiro{cyclobutane-1,1′-pyrido[2,1-*a*]isoquinoline-3′,1′-cyclobutane}-2′,4′-dione **6** in 36% yield (see Scheme 1). Raisng the reactant ratio **1d** : **2** to 2.5 : 1 provided the yield of product **6** as high as 68%. Most probably, formation of spiro system consisting of azetidinone and cyclobutane rings is difficult due to strain factors (*cf*. ref. 5 for an unsuccsessful attempt to obtain spiroazetidinones by the Staudinger reaction). Therefore, the resulting intermediate **3d** is attacked by the second molecule of the Reformatsky species **1d** with the formation of intermediate **5** (the possibility of addition of Reformatsky reagents to esters was proposed[6–8]). Finally, intermediate **5** undergoes cyclization with the second elimination of bromozinc methoxide to afford dispiro product **6**. The structure of compound **6** was confirmed by spectroscopy and XRD analysis. According to single crystal XRD results (Figure 2),[‡] compound **6** crystallizes in the centrosymmetric space group as a solvate with methanol (1 : 1). The molecules are linked *via* intermolecular O–H··O hydrogen bonds between the hydroxy group and the carbonyl oxygen atom O(4) (methanol molecule is not shown).

In summary, the reactions studied provided new functional compound with spiro rigid structures being promising for biological investigations.

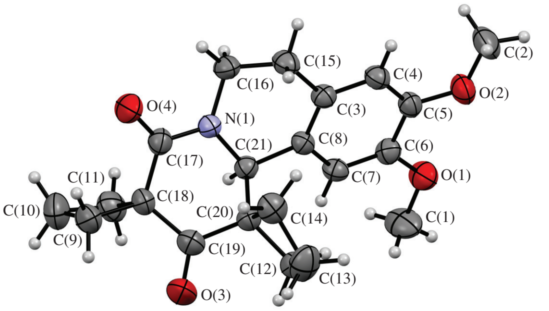


Figure 2 Molecular structure of compound **6** with thermal ellipsoids drawn at 50% probability level, solvate MeOH molecule is omitted.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.07.011.

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Crystal data for **4b**. $C_{18}H_{23}NO_3$, $M = 301.37$, orthorhombic, space group *Pbca*, $a = 11.5729(5)$, $b = 10.0353(7)$ and $c = 26.7160(15)$ Å, $V = 3102.73$ Å^3, $Z = 8$. Total of 15553 reflections were collected, from which 3843 were independent ($R_{\text{int}} = 0.0287$) and 2573 with $I > 2\sigma(I)$. Completeness for $\theta = 28.30°$ was 99.7% ($\mu = 0.087$ mm^{-1}). The final refinement parameters were $R_1 = 0.063$, $wR_2 = 0.0958$ (for all reflections); $R_1 = 0.0363$, $wR_2 = 0.089$ for the reflections with $I > 2\sigma(I)$ by quality factor $S = 1.001$. Maximum and minimum of residual electronic density were 0.183 and –0.175 e Å^{-3}.

Crystal data for **6**. $C_{21}H_{25}NO_4$, CH_4O, $M = 387.46$, monoclinic, space group $P2_1/n$, $a = 9.4099(6)$, $b = 14.7932(11)$ and $c = 14.3620(12)$ Å, $\beta = 94.863(6)°$, $V = 1992.03$ Å^3, $Z = 4$. Total of 8871 reflections were collected, from which 4869 independent ($R_{\text{int}} = 0.0232$) and 2270 with $I > 2\sigma(I)$. Completeness for $\theta = 28.28°$ was 98.5% ($\mu = 0.091$ mm^{-1}). The final refinement parameters were $R_1 = 0.0978$, $wR_2 = 0.0819$ (for all reflections); $R_1 = 0.0394$, $wR_2 = 0.0766$ for the reflections with $I > 2\sigma(I)$ by quality factor S = 1.000. Maximum and minimum of residual electronic density were 0.155 and –0.158 eÅ^{-3}.

CCDC 1920834 and 1920835 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.