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PII: S0040-4039(15)01034-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.06.041
Reference: TETL 46433

To appear in: *Tetrahedron Letters*

Received Date: 12 March 2015
Revised Date: 8 June 2015
Accepted Date: 13 June 2015

Please cite this article as: Kolosov, M.A., Kulyk, O.G., Al-Ogaili, M.J.K., Orlov, V.D., An effective Biginelli-type synthesis of 1-methoxy-3,4-dihydropyrimidin-2(1*H*)-ones, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.06.041

Graphical Abstract

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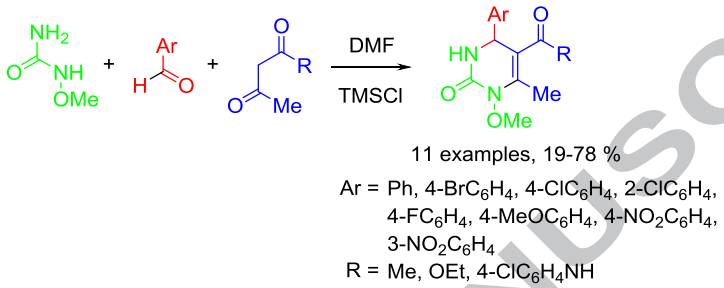

11 examples, 19-78 %

Ar = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$

R = Me, OEt, 4-ClC_6H_4NH

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Biginelli reaction
3,4-dihydropyrimidin-2(1*H*)-ones
N-(methoxy)urea
TMSCl
3,4,7,8-tetrahydroquinazolin-2,5(1*H*,6*H*)-diones

ABSTRACT

The ternary condensation of *N*-methoxyurea, aldehydes and 1,3-dicarbonyl compounds, resulting in novel 1-methoxy-3,4-dihydropyrimidin-2(1*H*)-ones has been examined. Commonly used reaction conditions and catalysts (EtOH/HCl, HOAc, DMF) proved to be unsuitable and we found that the DMF–TMSCl system was the best catalyst. Similarly, the reaction of ureas with 4-chlorobenzaldehyde and 1,3-cyclohexanedione using the DMF/TMSCl system afforded 3,4,7,8-tetrahydroquinazolin-2,5(1*H*,6*H*)-diones, while other catalyst systems resulted in the formation of product mixtures. In addition, we have developed an effective and simple protocol for the synthesis of *N*-(methoxy)urea.

The Biginelli reaction has emerged as an extremely popular tool in synthetic organic chemistry over the last few years.[1] This ternary condensation of urea (thiourea), aldehydes and 1,3-dicarbonyl compounds results in the formation of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs).[2] The latter have been reported to exhibit a wide range of biological activities and are analogs of unsymmetrical dihydropyridines such as amlodipine and nimodipine.[3] Moreover, the Biginelli reaction allows the introduction of up to five different substituents on the DHPM ring in one step, making it an important method for straightforward functionalization.[4]

While certainly a useful method for DHPM synthesis, the Biginelli reaction has attracted the attention of hundreds of scientists all over the world. Unfortunately, much of the attention has focused on the most popular topic of investigation of the effect (e.g. the influence of solvents, conditions or catalysts, microwave irradiation, ultrasonication) on the yields of the Biginelli DHPMs.[1d,5] In most cases, no new compounds have been synthesized, and only new conditions and catalysts have been examined.

Nevertheless, several mechanistic details still remain unclear and several significant steps have been made in the Biginelli DHPM synthesis. For example, *N*-arylureas and 1*N*,3*N*-dialkylureas were recently successfully used in the Biginelli reaction,[6] thus providing entrance to previously unknown *N*-functionalized DHPMs.[1a,7] Additionally, we noted that no attempts to introduce *N*-(alkoxy)ureas in the Biginelli reaction had been made at the present time.

The question to be solved was whether the alpha-effect, steric hindrance and lability of the *N*-alkoxy group would allow the synthesis of the target 1-alkoxyDHPMs. Thus, the main target of the present research was to study the possibility of introducing *N*-(methoxy)urea to the Biginelli reaction using conditions which had previously been successfully used in the syntheses of 1-unsubstituted, 1-alkyl and 1-aryl-DHPMs.[1a,6] Herein, we wish to report the results of our study on the Biginelli DHPM synthesis with *N*-(methoxy)urea.

There are three main approaches to the synthesis of Biginelli DHPMs.[1-5] The first one is classical and consists of the ternary condensation of ureas, aldehydes and 1,3-dicarbonyl compounds under varying conditions using alcohol/strong acid systems,[8] HOAc,[8a,9] DMF,[10] DMF/TMSCl (Scheme 1).[6,11] The second approach, proposed by Atwal, proceeds *via* the $NaHCO_3$–promoted two-component reaction of urea with 2-methylene 1,3-dicarbonyls.[12] The third approach developed by Shutalev is the ternary reaction of aldehydes, urea and sulfinic acids, followed by amidoalkylation of 1,3-dicarbonyl compounds and subsequent ring closure.[13] The last approach does not have general applicability and can only be used in cases where labile/reactive substrates (or products) demand acid-free/mild conditions. Though the first two approaches each have their limitations and drawbacks, we selected them for our studies.

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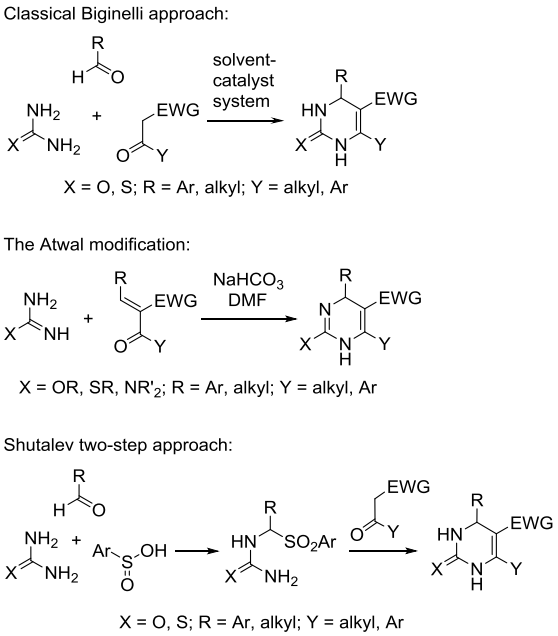
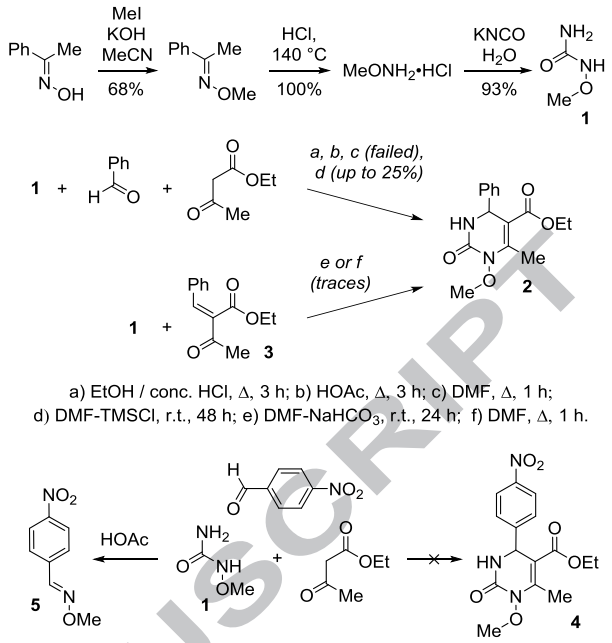


Scheme 1. Common approaches to the synthesis of Biginelli DHPMs.



Scheme 2. Synthesis of *N*-(methoxy)urea and 1-methoxyDHPMs.

Thus, we initially examined whether 1-methoxyDHPMs **2** could be obtained either by the classical Biginelli reaction of *N*-(methoxy)urea **1** with benzaldehyde and ethyl acetoacetate (Scheme 2, routes *a*–*d*), or through the Atwal modification starting from ethyl 2-benzylidene-3-oxobutanoate **3** (Scheme 2, routes *e* and *f*). The starting *N*-(methoxy)urea **1** could easily be obtained in three steps from acetophenone oxime, as depicted in Scheme 2. The method was highly effective and suitable for the synthesis of other *N*-(alkoxy)ureas.

In each case, after reaction completion (TLC), analysis of the residue by ^{1}H NMR, TLC and MS revealed that in the cases *a*, *b* and *c* DHPM **2** had not been formed. Moreover, we failed to obtain 1-MeO-DHPM **4** by the reaction of 4-nitrobenzaldehyde with *N*-(methoxy)urea **1** and ethyl acetoacetate in AcOH. The reaction of 4-nitrobenzaldehyde is usually known to give good results in the Biginelli reaction;[14] however, the only isolated reaction product was 4-nitrobenzaldehyde *O*-methyloxime **5**.[15] Trace amounts of the target DHPM **2** were detected in the cases of *e* and *f*, and route *d* gave the best result with more than 25 % of DHPM **2** being observed in the mixture. The components of this reaction mixture were isolated by column chromatography and identified (Fig. 1).

Despite the low yield of compound **2**, these preliminary results seemed to be important since very little is known about *N*-alkoxypyrimidines and the DMF–TMSCl system was selected as a good starting point for further studies.

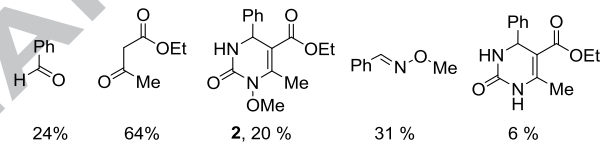
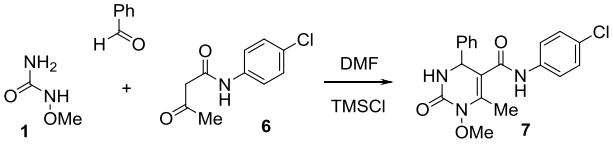


Figure 1. Identified components from the reaction mixture of the TMSCl-DMF-catalyzed synthesis of DHPM **2**.

Inspired by the success of the preliminary studies, we then examined the TMSCl–DMF promoted model reaction of *N*-(methoxy)urea **1** with benzaldehyde and *N*-(4-chlorophenyl)-acetoacetamide **6**.[6] When TMSCl was added in a 6-fold excess, dihydropyridine-5-carboxamide **7** was isolated in 20 % yield (Entry 1). To optimize the reaction conditions, various molar ratios of the reagents, temperatures and reaction times were examined (Table 1). It was found, that an increase in the temperature, reaction time and amount of TMSCl (entries 2, 3, 8) reduced the yield of the target compound. At the same time, utilization of a small excess of benzaldehyde and a 3-fold excess of *N*-methoxyurea (entries 4-7) considerably increased the yield. Clearly the large excess of *N*-methoxyurea required was because of its instability (the formation of *O*-methyloximes see below).

The optimum amounts of TMSCl, reaction time and reagent ratio were determined from the experiments corresponding to entries 1, 3–7, while entries 2 and 8 demonstrated that increased temperature did not facilitate, but suppressed, the formation of DHPM **7**. The best yield (68 %) of DHPM **7** was obtained by carrying out the reaction at room temperature for 48 h using a 3-fold excess of *N*-(methoxy)urea **1** with respect to the β-keto amide **6**, 1.2 eq. of benzaldehyde and a 6-fold excess of TMSCl (Entry 6). It was noteworthy that in most cases the formation of benzaldehyde *O*-methyloxime was detected. Clearly this was formed by decomposition of starting *N*-(methoxy)urea **1** followed by condensation of *O*-methylhydroxylamine with benzaldehyde.[16]

Table 1. Optimization of the reaction conditions[a]



Entry	Molar ratio **1** : PhCHO : **6** : TMSCl	Time (h)	Temperature (°C)	Yield of **7**[b] (%)
1	1 : 1 : 1 : 6	48	r. t.	20
2	1 : 1 : 1 : 6	1	30	traces[c]
		1	80	
		1	100	
		15	r. t.	
3	1 : 1 : 1 : 10	168	r. t.	traces[c]
4	1 : 1.5 : 1 : 6	48	r. t.	12
5	2 : 1 : 1 : 6	48	r. t.	28
6	**3 : 1.2 : 1 : 6**	**48**	**r. t.**	**68**
7	6 : 1.2 : 1 : 6	48	r. t.	43
8	6 : 1.2 : 1 : 6	24	50	29
		24	r. t.	

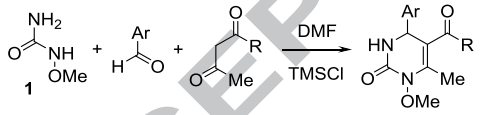
[a] Optimized reaction conditions are in bold.

[b] Yields are for pure compounds recrystallized from EtOAc.

[c] Only traces of DHPM **7** were detected by ^{1}H NMR after evaporation of EtOAc from the reaction mixture.

The obtained results prompted us to study the scope and possible limitations of the reaction. Having an optimized protocol in hand, we examined the reaction of *N*-(methoxy)urea **1** with other aldehydes and 1,3-dicarbonyl compounds[17] and the results are summarized in Table 2.

Table 2. The results of the TMSCl–DMF-catalyzed ternary condensation of various aldehydes and 1,3-dicarbonyls with *N*-(methoxy)urea **1**.

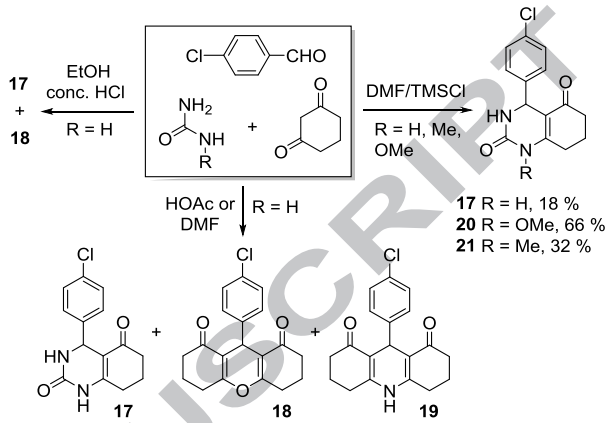


Entry	Product	R	Ar	Yields (%) [a]
1	**2**	OEt	Ph	32
2	**8**	OEt	4-ClC_6H_4	19[b]
3	**9**	Me	4-ClC_6H_4	40
4	**10**	4-ClC_6H_4NH	4-MeOC_6H_4	78
5	**11**	4-ClC_6H_4NH	4-FC_6H_4	54
6	**12**	4-ClC_6H_4NH	4-ClC_6H_4	65
7	**13**	4-ClC_6H_4NH	2-ClC_6H_4	38
8	**14**	4-ClC_6H_4NH	4-BrC_6H_4	68
9	**15**	4-ClC_6H_4NH	4-$NO_2C_6H_4$	61
10	**16**	4-ClC_6H_4NH	3-$NO_2C_6H_4$	75

[a] Yields are for pure compounds recrystallized from EtOAc.

[b] After purification by column chromatography.

Next, we studied the reaction of *N*-(methoxy)urea **1** with 4-chlorobenzaldehyde and 1,3-cyclohexanedione under the same conditions. A survey of the literature on the Biginelli reaction using 1,3-cyclohexanedione as a 1,3-dicarbonyl component showed that the reaction was often complicated by side reactions leading to the formation of mixtures.[18] In fact, the reaction of urea, 4-chlorobenzaldehyde and 1,3-cyclohexanedione in AcOH, DMF or EtOH/conc. HCl afforded mixtures of the target quinazoline **17** along with acridine **19** and/or xanthene **18** (Scheme 3).



Scheme 3. The reaction of ureas with 4-chlorobenzaldehyde and 1,3-cyclohexanedione.

We found that the TMSCl–DMF-promoted reaction of *N*-(methoxy)urea **1** with 4-chlorobenzaldehyde and 1,3-cyclohexanedione proceed smoothly to give 1-methoxy-3,4,7,8-tetrahydroquinazolin-2,5(1*H*,6*H*)-dione **20** in 66% yield. In addition, unsubstituted urea and *N*-methylurea reacted under the same conditions to afford pure quinazolines **17** and **21**, respectively, in low to modest yields.

The mass spectra of DHPM-5-carboxamides **7**, **10**–**16** showed a molecular ion signal of low intensity (except for the spectrum of compound **14** which possessed no M^+ signal) as well as the signals of fragmentation ions ($[M - Ar]^+$, $[M - OMe]^+$, $[M - NHAr]^+$). The mass spectra of DHPM-5-carboxylates **2**, **8** and 5-keto-DHPMs **9**, **17**, **21**, **22** showed molecular ion M^+ signals of high intensity. Finally, the obtained *N*-methoxy compounds were found to be rather stable at room temperature, exhibiting no change in their spectral data after several months.

In conclusion, we have showed the DMF–TMSCl system to be the catalyst of choice for the synthesis of 1-methoxy-DHPMs starting from *N*-(methoxy)urea providing several new DHPMs in moderate yields. The DMF–TMSCl system also proved to be an effective catalyst for the Biginelli-type reaction of 1,3-cyclohexanedione with 4-chlorobenzaldehyde and ureas (including *N*-(methoxy)urea) leading to 3,4,7,8-tetrahydroquinazolin-2,5(1*H*,6*H*)-diones. In addition, a facile and effective protocol for the synthesis of *N*-(methoxy)urea was developed.

Acknowledgments

We thank V. V. Vashchenko, E. V. Vashchenko, V. I. Musatov (STC “Institute for Single Crystals” NAS of Ukraine), L. V. Vasilenko (V. N. Karazin Kharkiv National University), Enamine Ltd. for spectroscopic measurements and V. V. Dotsenko (Kuban State University) for fruitful discussions.

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17. To a solution of *N*-(methoxy)urea **1** (0.32 g, 3.54 mmol), aromatic aldehyde (1.42 mmol) and 1,3-dicarbonyl (1.18 mmol) in dry DMF (minimal amount, approx. 10-20 mL), TMSCl (0.77 g, 7.08 mmol) was added dropwise. The mixture was sonicated at room temperature for 1 h to dissolve the starting materials. The resulting mixture was allowed to stir for 48 h and then poured into water (100 mL). The suspension was extracted with EtOAc (3 × 30 mL), the combined extracts were washed with water (3 × 30 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield the crude products, which were recrystallized from EtOAc to give pure compounds **2, 7, 8, 10–17, 20, 21** (compound **9** was purified by column chromatography).
*Ethyl 1-methoxy-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetra-hydropyrimidine-5-carboxylate (**2**).* White solid, mp: 126–128 °C; IR, ν_{max}, cm^{-1} (KBr): 1629, 1682, 1715 (br), 2990, 3342 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ_H, *J*, Hz): 8.23 (1H, br. d, *J* 3.6, N(3)H), 7.16–7.41 (5H, m, Ph), 5.14 (1H, d, *J* 3.6, C(4)H), 4.03 (2H, q, *J* 7.0, O$CH_2$$CH_3$), 3.70 (3H, s, OCH_3), 2.45 (3H, s, C(6)CH_3), 1.11 (3H, t, *J* 7.0, OCH_2CH_3); ^{13}C NMR (DMSO-d_6, δ_C): 164.97, 150.71, 150.32, 143.00, 128.60, 127.58, 126.10, 100.59, 64.14, 59.90, 52.62, 14.06, 13.27; MS (EI) *m*/*z* (I, %): 290 (M^+, 43), 259 (74), 246 (100), 213 (43), 144 (41). Anal. Calcd. for $C_{15}H_{18}N_2O_4$ (290.31): C, 62.06; H, 6.25; N, 9.65%. Found: C, 62.11; H, 6.32; N, 9.50 %.
*4-(4-Chlorophenyl)-1-methoxy-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (**20**).* Yield 66 %, white solid, mp 176–178 °C; IR, ν_{max}, cm^{-1} (KBr): 1629, 1718, 2939, 3126, 3198 (br), 3251 (br) cm^{-1}; ^{1}H NMR (DMSO-d_6, δ_H, *J*, Hz): 8.28 (1H, br. d, *J* 3.6, N(3)H), 7.37 (2H, d, *J* 8.6, ArH), 7.24 (2H, d, *J* 8.6, ArH), 5.16 (1H, d, *J* 3.4, C(4)H), 3.77 (3H, s, OCH_3), 2.55–2.78 (2H, m, CH_2), 2.16–2.32 (2H, m, CH_2), 1.76–2.07 (2H, m, CH_2); ^{13}C NMR (DMSO-d_6, δ_C): 193.31, 155.62, 150.14, 142.04, 131.97, 128.54, 127.97, 108.10, 64.53, 49.74, 35.60, 22.78, 20.60; *m*/*z* (EI, 70 eV): 306 (M[^{35}Cl]$^+$, 18), 275 (100), 217 (25), 195 (9), 162 (6), 127 (14). Anal. Calcd. for $C_{15}H_{15}ClN_2O_3$ (306.74): C, 58.73; H, 4.93; N, 9.13 %. Found: C, 58.82; H, 5.11; N, 8.99 %.
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Supplementary Material

Supplementary data (synthetic protocols, ^{1}H and ^{13}C NMR, IR and mass-spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.