JOC The Journal of Organic Chemistry

Note

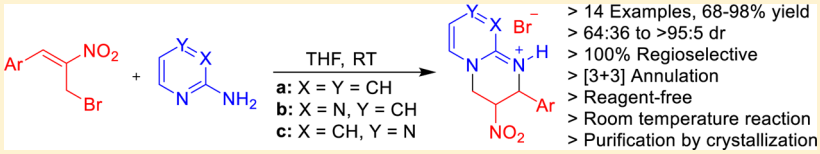
pubs.acs.org/joc

Regio- and Diastereoselective Synthesis of Dihydropyridopyrimidines via Cascade Reactions of 2-Aminopyridines with Morita–Baylis–Hillman Bromides of Nitroalkenes

Lakshminarayana Satham and Irishi N. N. Namboothiri*

Department of Chemistry, Indian Institute of Technology Bombay, Mumbai 400 076, India

Supporting Information



ABSTRACT: The Morita–Baylis–Hillman (MBH) bromides of nitroalkenes have been employed as bielectrophiles for the first time. The 1,3-bielectrophilic reactivity of the MBH bromides has been demonstrated in the synthesis of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines. The reaction of MBH bromides with 2-aminopyridines takes place in the absence of any reagent in a cascade S_N2'-6-endo-trig fashion and is completely regioselective and highly stereoselective. The products, in their hydrobromide salt form, could be conveniently isolated and purified by crystallization. The high stereoselectivity has been rationalized in terms of the greater stability of the transition state in which the Ar and NO_2 groups are anti to each other.

Nitrogenous heterocycles play a pivotal role in the bioactivity of natural products and pharmaceuticals.[1] Heterocyclic ammonium salts,[2] in particular, exhibit CFTR activation,[3] DNA-intercalating antiproliferative activity[4] as well as antimalarial and antileishmanial activities,[5] to name a few. Saturated and partially saturated pyrido[1,2-*a*]pyrimidines belong to the broad class of bioactive bicyclic 6–6 fused systems bearing one nitrogen at the ring junction and another nitrogen elsewhere in the ring.[6]

Numerous small bioactive molecules have evolved from the pyrido[1,2-*a*]pyrimidine skeleton which now emerged as a privileged scaffold in medicinal chemistry.[7] Various pyrido[1,2-*a*]pyrimidines employed in human therapy include neuroleptic risperidone,[8] tranquilizer pirenperone,[9] antiallergic ramastine,[10] antidepressant lusaperidone,[11] and non-narcotic analgesic rimazolium (Figure 1).[12] Pyrido[1,2-*a*]pyrimidines are also potent inhibitors of nitric oxide synthases (NOS).[13]

The diverse bioactivities displayed by pyridopyrimidines motivated synthetic organic and medicinal chemists to develop novel and convenient methods for their synthesis.[14] These include reactions involving aminopyridines in formal aza-Diels–Alder reaction,[15] intramolecular cyclization,[16] cyclization with 1,3-bielectrophiles,[13,17] multicomponent reactions,[18] cyclocondensation,[19] and metal mediated sequence.[20] Synthetic approaches not involving aminopyridines are also known in the literature.[21] However, the synthesis of pyridopyrimidines from readily available starting materials in a regio- and stereoselective manner is still an attractive objective.

From another perspective, the Morita–Baylis–Hillman (MBH) reaction is an elegant methodology for the synthesis of multifunctional molecules that serve as valuable substrates in the synthesis of complex molecules including natural products.[22−24] Its vinylogous version, the Rauhut–Currier (RC) reaction, though limited in substrate scope, also made considerable impact due to its simplicity and applicability in synthesis.[25] The MBH and RC reactions of nitroalkenes have delivered a diverse array of molecules in recent years for applications as synthetic intermediates and biological agents.[26] In particular, the electrophilic reactivity, including the 1,2- and 1,3-bielectrophilic reactivities, of MBH acetates **2**[26−28] and **5**[26,29] has been extensively exploited for the synthesis of various heterocycles and even carbocycles. In 2012, we reported the synthesis of imidazopyridines **3** from MBH acetates **2** and 2-aminopyridines **1** through an S_N2'-5-exo-trig cyclization by exploiting the 1,2-bielectrophilic nature of acetates **2** (Scheme 1a).[28] The imidazopyridines **3** could be easily transformed to anxiolytic drug Alpidem **4a** and hypnotic drug Zolpidem **4b** in a minimum number of steps. However, our initial attempts to synthesize pyridopyrimidines, the 6–6-fused systems, **7** or **8** from MBH acetates **5** and aminopyridine **1a** did not yield positive results (Scheme 1b). At this juncture, we felt that a better leaving group (LG = Br) would enable us to successfully carry out the desired S_N2'-6-endo-trig-cyclization and construct pyridopyrimidine **7**. In the case of such primary allylic bromides **6**,[30] an alternative S_N2–6-endo-trig cyclization to afford the regioisomeric pyridopyrimidine **8** also appeared possible. To our knowledge, such 1,3-bielectrophilic reactivity of nitroallylic bromide **6** is not documented in the literature. Therefore, we

Received: April 20, 2017
Published: May 24, 2017

DOI: 10.1021/acs.joc.7b00947
J. Org. Chem. 2017, 82, 6482–6488

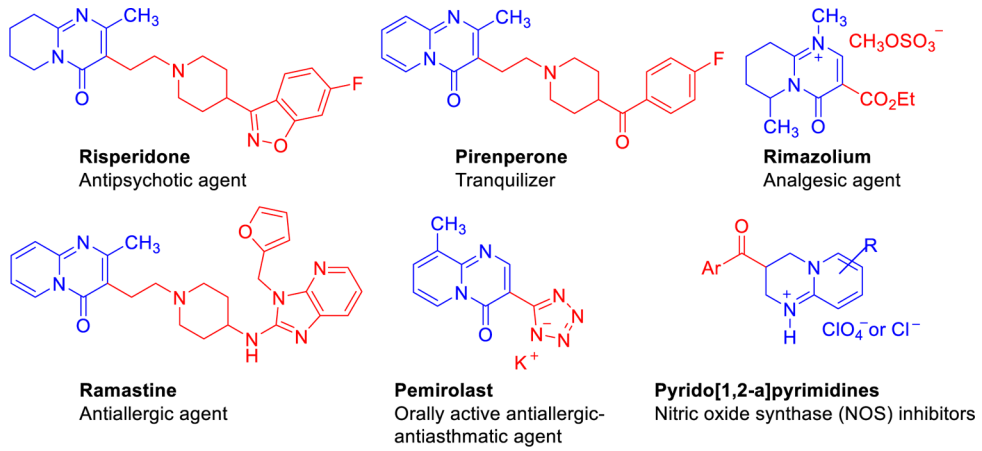
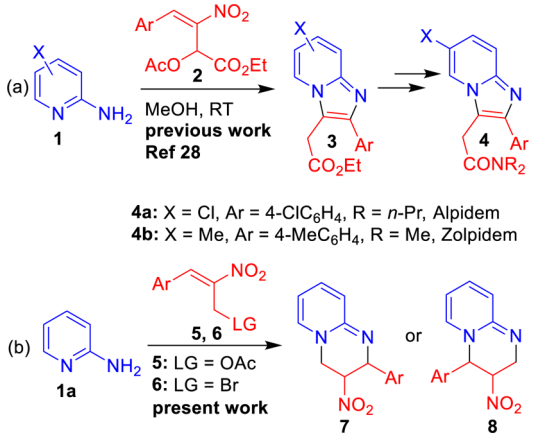


Figure 1. Biologically active pyridopyrimidines.

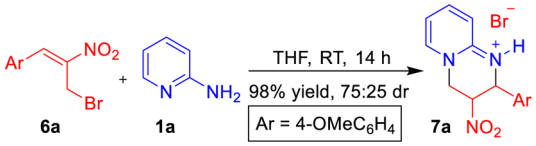
Scheme 1. Reactivity of MBH Adducts of Nitroalkenes with 2-Aminopyridines



report herein the synthesis of pyrido[1,2-*a*]pyrimidines **7** from MBH bromide **6** and 2-aminopyridine **1** via a cascade S_N2'-6-endo-trig cyclization, the second step of which is also an intramolecular *aza*-Michael addition.

The reaction conditions were optimized using MBH bromide **6a** and aminopyridine **1a** as the model substrates (Scheme 2).

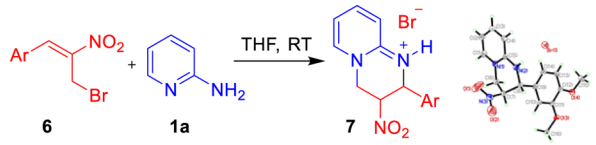
Scheme 2. Optimized Reaction Conditions



At the outset, these two reactants were stirred at room temperature in a polar protic solvent such as MeOH in the absence of any base. To our delight, the pyridopyrimidinium bromide **7a** began precipitating out as a yellow solid in 15 min, and the reaction was complete in 14 h. More importantly, a single regioisomer **7a** was formed, though with moderate diastereoselectivity (67:33) in nearly quantitative yield. At this juncture, solvents representing other categories such as halogenated (CH_2Cl_2), polar aprotic (THF, CH_3CN), and nonpolar (toluene) were screened. While the yields remained nearly quantitative in CH_2Cl_2 and THF (98%), THF was superior both in terms of reaction time and diastereoselectivity (14 h, 75:25 vs 24 h, 69:31). A marginal drop in the reaction rate, product yield, and diastereoselectivity (24–36 h, 84–85% yield, 71:79 to 75:25) was observed in the case of CH_3CN and toluene. Overall, THF turned out to be the best solvent for our reaction. The reactions performed in THF at lower temperatures, 0 °C and −50 °C, required a longer time for completion with a marginal drop in the yield and diastereoselectivity (30–36 h, 90–93% yield, 66:34 to 72:28). Attempts to accelerate the reaction by heating (50 °C) or by using a catalyst such as DABCO led to decomposition of the product.

The above reaction conditions, viz THF, room temperature, were employed to investigate the scope of MBH bromides **6** and aminopyridines **1** (Tables 1 and 2). As for the scope of

Table 1. Scope of MBH Bromides 6



ORTEP of **7b**

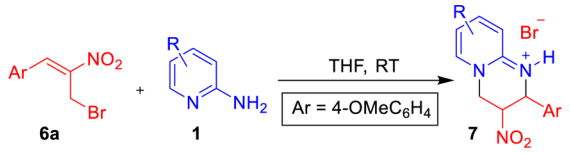
entry	6	Ar	time (h)	7	% yield[a]	dr[b]
1	**6a**	4-$MeOC_6H_4$	14	**7a**	98	75:25
2	**6b**	3,4-$(MeO)_2C_6H_3$	14	**7b**	98	93:07
3	**6c**	3,4-$(OCH_2O)_2C_6H_3$	14	**7c**	97	>95:05
4	**6d**	4-MeC_6H_4	20	**7d**	92	75:25
5	**6e**	1-Naphthyl	18	**7e**	91	90:10
6	**6f**	4-ClC_6H_4	24	**7f**	80	64:36
7	**6g**	3-BrC_6H_4	27	**7g**	94	94:06

[a]After isolation by crystallization. [b]Determined by the ^1H NMR of the crude product.

MBH bromides **6**, *β*-aryl derivatives possessing diverse electron demands, such as those bearing strongly electron donating groups **6a–c**, weakly electron donating group **6d**, electroneutral but sterically demanding **6e**, and weakly electron withdrawing **6f–g** were evaluated for their reactivity with aminopyridine **1a**. The product yields and reaction times were very impressive for those bearing electron rich aryl groups **7a–c** (97–98%, 14 h, entries 1–3). Unlike in the case of **7a** (dr 75:25, entry 1), the diastereoselectivity of **7b–c** were excellent (93:7 to >95:5, entries 2–3). Marginally longer reaction times (18–20 h) were observed in the case of **6d–e** giving the corresponding products **7d–e** in marginally lower yields (91–92%), but the

DOI: 10.1021/acs.joc.7b00947
J. Org. Chem. 2017, 82, 6482–6488

Table 2. Scope of 2-Aminopyridines 1



entry	1	R	time (h)	7	% yield[a]	dr[b]
1	**1b**	4-Cl	48	**7h**	97	88:12
2	**1c**	5-Cl	48	**7i**	92	74:26
3	**1d**	5-Br	24	**7j**	90	82:18
4	**1e**	5-NO_2	72	**7k**	68	86:14
5	**1f**	5-Br, 4-Me	54	**7l**	78	80:20

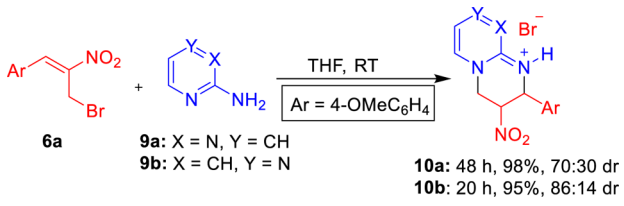
[a]After isolation by crystallization. [b]Determined by ^{1}H NMR of the crude product.

diastereoselectivities were superior in the case of **7e** (90:10, entries 4–5). Although the reaction times were comparable for **6f** and **6g** (24–27 h), the corresponding products **7f** and **7g** were formed with a considerable difference in yield and diastereoselectivities (entries 6–7).

Subsequently, aminopyridines **1** bearing substituents at 4 and/or 5 positions were treated with a representative MBH bromide **6a** under the optimized conditions (Table 2). Although the reaction times were much longer for these substituted aminopyridines **1b–f** compared to those for unsubstituted **1a** (Table 1), the yields remained excellent (90–97%, entries 1–3), except for the ones with strongly deactivating substituent and multiple substituents **1e** and **1f**, respectively (entries 4–5). The diastereoselectivity remained in the range of 74:26 to 88:12.

Other 2-aminoazaheterocycles such as 2-aminopyrimidine **9a** and 2-aminopyrazine **9b** which did not react with secondary MBH acetate **2** during our previous work[28] also reacted with a representative MBH bromide **6a** and afforded fused heterocycles **10a** and **10b**, respectively, in excellent yield (95–98%) and moderate to good diastereoselectivity (70:30 to 86:14, Scheme 3).

Scheme 3



Interestingly, all of the products described above were isolated in their hydrobromide salt form by crystallization from a $CHCl_3$/diethyl ether (1:1) solvent system after sonication. The relative stereochemistry of Ar and NO_2 groups in the major isomer of compounds **7** and **10** was found to be trans by single crystal X-ray analysis of a representative compound **7b** (see the Supporting Information).

Having established the structure and stereochemistry of compounds **7** and **10** by spectroscopic analysis and X-ray crystallography, a plausible mechanism for their formation is proposed taking pyridopyrimidines **7** as the representative products (Scheme 4). It involves the intermolecular aza-Michael addition of aminopyridine **1** through the primary amino group as the nucleophilic center to MBH bromide **6** followed by elimination of bromide (overall S_N2' reaction) generating intermediate **I**. A second aza-Michael addition, this time in an intramolecular 6-endo-trig fashion, leads to the formation of product **7**.

The intramolecular aza-Michael addition of intermediate **I** to form products **7** takes place through two diastereomeric transition states **II-gauche** or **II-anti**. Since there is a possibility of intramolecular H-bonding between N–H and NO_2 in both transitions states, the key factor that controls the stereoselectivity appeared to be the relative stabilities of **II-gauche** and **II-anti**, i.e., in terms of the orientation of the Ar group with respect to the nitro group. It is evident from the X-ray crystal structure of **7b** that the six-membered ring has half-chair conformation and the dihedral angle between Ar and NO_2 is ~165°. This suggests that the more stable transition state is **II-anti**, which leads to the trans isomer as the major product.

In summary, we have developed a regio- and diastereoselective synthesis of dihydropyrido[1,2-*a*]pyrimidines involving a cascade S_N2'-intramolecular aza-Michael addition involving nitroallylic bromide, derived from a Morita–Baylis–Hillman adduct of nitroalkene, as the 1,3-bielectrophile and aminopyridine as the 1,3-binucleophile. The reaction proceeds at room temperature in THF in the absence of any base and has broad substrate compatibility. The regio- and stereochemistry of the products was unambiguously established by single crystal X-ray analysis of a representative compound and explained by a suitable TS model. Formation of the trans-diastereomer as the major product was attributed to greater stability of the corresponding transition state in which the Ar and NO_2 groups are anti to each other.

GENERAL EXPERIMENTAL DETAILS

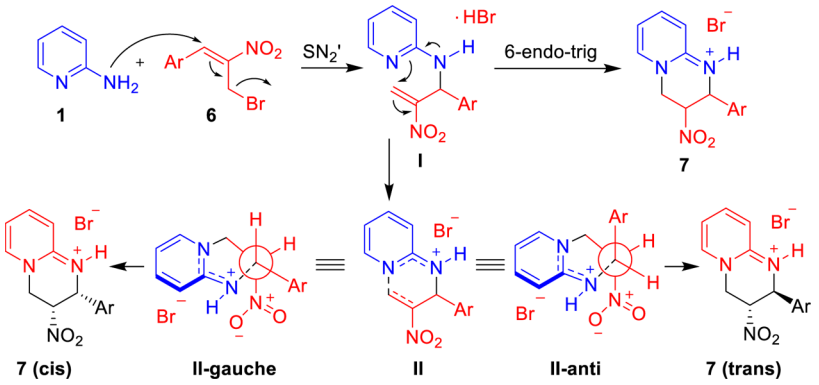
The melting points recorded are uncorrected. NMR spectra (^{1}H, ^{1}H decoupled ^{13}C, and ^{1}H–^{1}H COSY) were recorded with TMS as the internal standard. The coupling constants (*J* values) are given in Hz. High resolution mass spectra were recorded under ESI Q-TOF conditions. X-ray data were collected on a diffractometer equipped with graphite monochromated Mo Kα radiation. The structure was solved by direct methods Shelxs97 and refined by full-matrix least-squares against F^2 using Shelxl97 software.

General Procedure for the Synthesis of Dihydro-pyrido, Pyrimidino, and Pyrazinopyrimidines 7 and 10. To a stirred solution of MBH bromide **6** (0.3 mmol, 1.0 equiv) in THF (2 mL) was added 2-amino aza-heterocycle **1** or **9** (0.3 mmol, 1.0 equiv). The reaction mixture was stirred at rt, and the progress of the reaction was monitored by TLC (disappearance of starting materials and appearance of a fluorescent product spot on the baseline). After completion of the reaction, the solvent was evaporated in vacuo, the crude residue was taken up in $CHCl_3$/diethyl ether (1:1, 10 mL) and was sonicated several times. The suspension was filtered to afford pure product **7** or **10** as a solid inseparable mixture of diastereomers.

*2-(4-Methoxyphenyl)-3-nitro-3,4-dihydro-2H-pyrido[1,2-a]-pyrimidin-1-ium Bromide (**7a**).* White solid; yield 110 mg, 98% (dr 75:25, inseparable); mp 232–234 °C; IR (KBr, cm^{-1}) 3432 (br w), 3157 (w), 3089 (w), 3008 (m), 2936 (s), 2895 (vs), 2839 (s), 1657 (vs), 1597 (s), 1575 (s), 1551 (s), 1513 (s), 1300 (m), 1250 (s), 1179 (m), 1160 (m), 1033 (m), 779 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, major + minor) δ 3.77 (s, 3H), 4.51 (d, J = 14.4 Hz, 1H), 5.07 (d, J = 14.4 Hz, 1H), 5.51–5.55 (unresolved, 1H), 5.78–5.82 (unresolved, 1H), 7.00–7.04 (unresolved, 3H), 7.29–7.33 (unresolved, 1H), 7.41 (d, J = 7.3 Hz, 2H), 7.95–7.99 (unresolved, 1H), 8.16–8.20 (unresolved, 1H), 10.34 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 4.99 (d, J = 14.8 Hz, 1H), 5.15 (d, J = 14.8 Hz, 1H), 10.06 (br s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, major) δ 47.7, 53.3, 55.3, 78.7, 113.4, 114.3, 114.4, 128.0, 128.3, 139.4, 142.6, 150.6, 159.6; ^{13}C{1H} NMR (DMSO-d_6,

DOI: 10.1021/acs.joc.7b00947
J. Org. Chem. 2017, 82, 6482–6488

Scheme 4. Plausible Mechanism



125 MHz, minor) δ 50.2, 52.6, 55.2, 78.1, 113.5, 114.2, 114.6, 125.8, 128.9, 139.0, 141.9, 151.5, 159.8; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{15}H_{16}N_3O_3$ ([M-Br]$^+$) 286.1186; found, 286.1187.

*2-(3,4-Dimethoxyphenyl)-3-nitro-3,4-dihydro-2H-pyrido[1,2-a]-pyrimidin-1-ium Bromide (**7b**).* White solid; yield 117 mg, 98% (dr 93:07, inseparable); mp 233−235 °C; IR (KBr, cm^{-1}) 3438 (br m), 3094 (m), 3057 (m), 3008 (s), 2940 (vs), 2905 (vs), 2835 (s), 1658 (vs), 1599 (vs), 1574 (vs), 1556 (s), 1518 (vs), 1257 (vs), 1241 (s), 1162 (s), 1146 (s), 1125 (m), 1022 (s), 858 (m), 764 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, major + minor) δ 3.76 (s, 3H), 3.79 (s, 3H), 4.48 (d, J = 13.7 Hz, 1H), 5.07 (d, J = 13.7 Hz, 1H), 5.49−5.53 (unresolved, 1H), 5.86−5.90 (unresolved, 1H), 6.92 (unresolved d, 1H), 7.01 (unresolved d, 1H), 7.02 (unresolved t, 1H), 7.16 (s, 1H), 7.34 (d, J = 5.6 Hz, 1H), 7.97 (unresolved t, 1H), 8.16 (unresolved d, 1H), 10.51 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 4.96 (d, J = 13.7 Hz, 1H), 5.16 (d, J = 13.7 Hz, 1H), 7.45 (d, J = 7.1 Hz, 1H), 10.19 (br s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, major) δ 48.3, 54.0, 56.1, 56.2, 79.2, 110.9, 112.2, 113.8, 114.9, 119.5, 129.8, 139.8, 143.0, 149.5, 149.7, 151.1; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{16}H_{18}N_3O_4$ ([M-Br]$^+$) 316.1292; found, 316.1293. Selected X-ray data: C_{16} H_{18} BrN_3 O_4, M 396.24, monoclinic, space group $P21/c$, a = 10.7705(7) Å, b = 10.1713(6) Å, c = 15.4078(9) Å, α = 90°, β = 97.569(6)°, γ = 90°, V = 1673.21(17) Å^3, D_c = 1.573 mg/m^3, Z = 4, F(000) = 808, λ = 0.71073 Å, μ = 2.482 mm^{-1}, total/unique reflections = 7073/2944 [R(int) = 0.0430], T = 293(2) K, θ range = 2.41 to 25.00°. final $R[I > 2\sigma(I)]$: $R1$ = 0.0497, $wR2$ = 0.1412. R (all data): $R1$ = 0.0606, $wR2$ = 0.1499.

*2-(Benzo[d][1,3]dioxol-5-yl)-3-nitro-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-1-ium Bromide (**7c**).* White solid; yield 112 mg, 97% (dr >95:05, inseparable); mp 201−203 °C; IR (KBr, cm^{-1}) 3435 (br m), 2930 (m), 2899 (m), 1655 (s), 1591 (s), 1574 (s), 1556 (s), 1506 (m), 1491 (m), 1258 (s), 1038 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, major) δ 4.51 (d, J = 14.6 Hz, 1H), 5.06 (d, J = 14.6 Hz, 1H), 5.48−5.52 (unresolved, 1H), 5.75−5.79 (unresolved, 1H), 6.07 (s, 2H), 6.93, 6.98 (ABq, J = 7.6 Hz, 2H), 7.02 (t, J = 7.2 Hz, 1H), 7.14 (s, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.96 (t, J = 7.2 Hz, 1H), 8.14 (d, J = 7.2 Hz, 1H), 10.39 (br s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, major) δ 47.7, 53.4, 78.6, 101.5, 107.3, 108.4, 113.3, 114.4, 120.7, 130.9, 139.3, 142.5, 147.7, 147.8, 150.5; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{15}H_{14}N_3O_4$ ([M-Br]$^+$) 300.0979; found, 300.0978.

*3-Nitro-2-(p-tolyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-1-ium Bromide (**7d**).* White solid; yield 96 mg, 92% (dr 75:25, inseparable); mp 214−216 °C; IR (KBr, cm^{-1}) 3465 (br m), 3082 (m), 3016 (m), 2917 (s), 2896 (s), 2851 (m), 1653 (s), 1595 (s), 1568 (s), 1550 (s), 1157 (m), 862 (m), 781 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, major + minor) δ 2.32 (s, 3H), 4.46 (dd, J = 15.4, 2.5 Hz, 1H), 5.06 (dd, J = 15.4, 2.5 Hz, 1H), 5.54−5.58 (unresolved, 1H), 5.77−5.80 (m, 1H), 7.03 (t, J = 6.5 Hz, 1H), 7.24 (d, J = 6.5 Hz, 1H), 7.28 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.97 (t, J = 6.5 Hz, 1H), 8.13 (d, J = 6.5 Hz, 1H), 10.19 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 4.95 (dd, J = 14.9, 3.6 Hz, 1H), 5.12 (d, J = 14.9 Hz, 1H), 8.10 (d, J = 6.6 Hz, 1H), 10.00 (br s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, major) δ 20.7, 47.7, 53.6, 78.7, 113.5, 114.4, 126.8, 129.7, 134.2, 138.5, 139.5, 142.8, 150.6; ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, minor) δ 20.8, 50.3, 52.9, 78.1, 113.6, 114.7, 126.7, 129.5, 131.1, 138.8, 139.1, 142.1, 151.5; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{15}H_{16}N_3O_2$ ([M-Br]$^+$) 270.1237; found, 270.1235.

*2-(Naphthalen-1-yl)-3-nitro-3,4-dihydro-2H-pyrido[1,2-a]-pyrimidin-1-ium Bromide (**7e**).* White solid; yield 107 mg, 91% (dr 90:10, inseparable); mp 240−242 °C; IR (KBr, cm^{-1}) 3459 (br s), 2923 (m), 2885 (s), 2849 (s), 2825 (s), 1654 (s), 1597 (s), 1575 (s), 1551 (s), 1166 (m), 803 (m), 778 (m), 760 (m); ^{1}H NMR (DMSO-d_6, 500 MHz, major + minor) δ 4.40 (d, J = 14.6 Hz, 1H), 5.09 (d, J = 14.6 Hz, 1H), 5.93−5.97 (unresolved, 1H), 6.46−6.50 (unresolved, 1H), 7.05−7.15 (unresolved, 1H), 7.35−7.45 (unresolved, 1H), 7.52−7.62 (m, 2H), 7.65−7.75 (unresolved, 1H), 7.75−7.83 (unresolved, 1H), 8.02−8.15 (m, 3H), 8.22−8.34 (m, 2H), 10.29 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 5.28−5.30 (unresolved, 1H), 10.13 (br s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, major) δ 46.9, 51.5, 77.4, 113.6, 114.4, 121.9, 125.3, 125.5, 126.5, 127.6, 128.8, 129.3, 129.7, 132.5, 133.5, 139.4, 142.7, 150.7; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{18}H_{17}N_3O_2$ ([M-Br]$^+$) 307.1315; found, 307.1312.

*2-(4-Chlorophenyl)-3-nitro-3,4-dihydro-2H-pyrido[1,2-a]-pyrimidin-1-ium Bromide (**7f**).* White solid; yield 88 mg, 80% (dr 64:36, inseparable); mp 231−233 °C; IR (KBr, cm^{-1}) 3451 (br s), 2890 (m), 1654 (vs), 1596 (s), 1569 (s), 1549 (m), 1492 (w), 1160 (w), 861 (w), 776 (m); ^{1}H NMR (DMSO-d_6, 500 MHz, major + minor) δ 4.48 (d, J = 14.7 Hz, 1H), 5.10 (d, J = 14.7 Hz, 1H), 5.64−5.70 (unresolved, 1H), 5.84−5.88 (unresolved, 1H), 7.02−7.08 (unresolved, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.44−7.48 (unresolved, 1H), 7.51−7.58 (unresolved, 3H), 7.96−8.03 (unresolved, 1H), 8.15−8.22 (unresolved, 1H), 10.30 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 5.03 (d, J = 14.8 Hz, 1H), 5.19 (d, J = 14.8 Hz, 1H), 5.87−5.91 (unresolved, 1H), 7.40 (d, J = 8.2 Hz, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, major) δ 47.6, 52.9, 78.3, 113.5, 114.3, 128.9, 129.0, 133.6, 136.2, 139.4, 142.7, 150.6; ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, minor) δ 50.2, 52.4, 78.0, 113.6, 114.6, 128.7, 128.8, 133.1, 133.8, 139.1, 142.1, 151.4; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{14}H_{13}ClN_3O_2$ ([M-Br]$^+$) 290.0691; found, 290.0701.

*2-(3-Bromophenyl)-3-nitro-3,4-dihydro-2H-pyrido[1,2-a]-pyrimidin-1-ium Bromide (**7g**).* White solid; yield 117 mg, 94% (dr 94:06, inseparable); mp 205−207 °C; IR (KBr, cm^{-1}) 3445 (br s), 3094 (m), 3002 (m), 2975 (m), 2924 (m), 2896 (s), 2848 (s), 2774 (m), 1657 (s), 1597 (s), 1577 (s), 1556 (s), 1387 (m), 1320 (s), 1301 (m), 1165 (s), 798 (m), 761 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, major + minor) δ 4.48 (dd, J = 14.3, 2.2 Hz, 1H), 5.09 (d, J = 14.3 Hz, 1H), 5.67 (unresolved, 1H), 5.88 (unresolved, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.41−7.44 (m, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.80 (s, 1H), 7.99 (t, J = 7.5 Hz, 1H), 8.17 (d, J = 7.5 Hz, 1H), 10.33 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 4.97 (d, J = 15.3 Hz, 1H), 5.18 (d, 15.3 Hz, 1H), 5.62 (unresolved, 1H), 10.12 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, tautomer) δ 3.55 (dd, J = 15.8, 3.3 Hz, 1H), 4.12 (d, J = 15.8 Hz, 1H), 5.92 (unresolved, 1H), 6.69 (s, 1H),

DOI: 10.1021/acs.joc.7b00947
J. Org. Chem. 2017, 82, 6482−6488

7.10 (d, J = 7.7 Hz, 1H), 7.70 (s, 1H), 10.22 (br s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, major) δ 48.2, 53.4, 78.8, 114.0, 114.9, 122.7, 126.7, 130.4, 131.6, 132.3, 139.9, 140.4, 143.2, 151.1; ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, minor) δ 50.7, 52.9, 78.5, 114.2, 115.2, 122.4, 126.4, 129.9, 131.4, 132.6, 137.3, 139.6, 142.6, 151.9; ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, tautomer) δ 37.9, 62.1, 77.9, 114.7, 115.7, 123.0, 125.6, 130.1, 132.0, 132.8, 138.4, 139.2, 142.9, 151.4; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{14}H_{13}BrN_3O_2$ ([M-Br]$^+$) 334.0186; found, 334.0186.

*8-Chloro-2-(4-methoxyphenyl)-3-nitro-3,4-dihydro-2H-pyrido-[1,2-a]pyrimidin-1-ium Bromide (**7h**).* White solid; yield 117 mg, 97% (dr 88:12, inseparable); mp 208−210 °C; IR (KBr, cm^{-1}) 3455 (br s), 2916 (m), 2873 (m), 2850 (m), 2819 (m), 2784 (m), 1653 (vs), 1593 (s), 1579 (s), 1551 (m), 1513 (m), 1252 (s), 1023 (m); ^{1}H NMR (DMSO-d_6, 400 MHz, major + minor) δ 3.77 (s, 3H), 4.48 (d, J = 14.5 Hz, 1H), 5.10 (d, J = 14.5 Hz, 1H), 5.54−5.58 (unresolved, 1H), 5.76−5.80 (unresolved, 1H), 7.01 (d, J = 7.1 Hz, 2H), 7.21 (d, J = 5.5 Hz, 1H), 7.33 (d, J = 7.1 Hz, 2H), 7.45 (s, 1H), 8.27 (d, J = 5.5 Hz, 1H), 10.55 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 4.96 (d, J = 15.5 Hz, 1H), 5.19 (d, J = 15.5 Hz, 1H), 5.81−5.85 (unresolved, 1H), 10.31 (br s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 100 MHz, major) δ 47.6, 53.3, 55.3, 78.5, 112.9, 114.1, 114.4, 128.5, 128.6, 141.0, 147.9, 150.7, 159.7; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{15}H_{15}ClN_3O_3$ ([M-Br]$^+$) 320.0796; found, 320.0797.

*7-Chloro-2-(4-methoxyphenyl)-3-nitro-3,4-dihydro-2H-pyrido-[1,2-a]pyrimidin-1-ium Bromide (**7i**).* White solid; yield 110 mg, 92% (dr 74:26, inseparable); mp 205−206 °C; IR (KBr, cm^{-1}) 3445 (br w), 3036 (m), 2978 (s), 2949 (s), 2900 (s), 2868 (s), 2817 (s), 1656 (m), 1567 (vs), 1514 (m), 1366 (m), 1252 (s), 1028 (m), 842 (m), 828 (m); ^{1}H NMR (DMSO-d_6, 500 MHz, major + minor) δ 3.77 (s, 3H), 4.46 (dd, J = 15.3, 2.8 Hz, 1H), 5.05 (d, J = 15.3 Hz, 1H), 5.54−5.58 (unresolved, 1H), 5.74−5.78 (unresolved, 1H), 7.01 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 8.6 Hz, 2H), 8.07 (d, J = 7.6 Hz, 1H), 8.55 (s, 1H), 10.81 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 4.95 (d, J = 15.6 Hz, 1H), 5.11 (d, J = 15.6 Hz, 1H), 5.51−5.55 (unresolved, 1H), 5.79−5.83 (unresolved, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 8.07−8.11 (unresolved, 1H), 8.53 (s, 1H), 10.48 (br s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, major) δ 47.8, 53.3, 55.3, 78.4, 114.4, 115.8, 118.4, 128.1, 128.4, 137.1, 142.6, 149.6, 159.7; ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, minor) δ 50.5, 52.8, 55.2, 77.7, 114.2, 116.0, 118.5, 125.5, 128.8, 136.8, 142.1, 150.6, 159.9; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{15}H_{15}ClN_3O_3$ ([M-Br]$^+$) 320.0796; found, 320.0798.

*7-Bromo-2-(4-methoxyphenyl)-3-nitro-3,4-dihydro-2H-pyrido-[1,2-a]pyrimidin-1-ium Bromide (**7j**).* White solid; yield 120 mg, 90% (dr 82:18, inseparable); mp 222−224 °C; IR (KBr, cm^{-1}) 3432 (br m), 3077 (m), 3037 (m), 2969 (s), 2818 (m), 1652 (s), 1611 (m), 1593 (s), 1558 (s), 1513 (s), 1365 (s), 1254 (s), 1178 (m), 1166 (m), 1030 (m), 841 (m), 830 (m), 747 (m); ^{1}H NMR (DMSO-d_6, 500 MHz, major + minor) δ 3.77 (s, 3H), 4.47 (d, J = 14.8 Hz, 1H), 5.06 (d, J = 14.8 Hz, 1H), 5.53−5.57 (unresolved, 1H), 5.76−5.80 (unresolved, 1H), 7.00 (d, J = 7.8 Hz, 2H), 7.30 (d, J = 9.1 Hz, 1H), 7.42 (d, J = 7.8 Hz, 2H), 8.13 (d, J = 9.1 Hz, 1H), 8.60 (s, 1H), 10.67 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 4.98 (d, J = 15.7 Hz, 1H), 5.12 (d, J = 15.7 Hz, 1H), 5.80−5.84 (unresolved, 1H), 10.38 (br s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, major) δ 47.7, 53.3, 55.3, 78.4, 105.0, 114.4, 115.8, 128.1, 128.4, 139.1, 144.8, 149.7, 159.7; ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, minor) δ 50.4, 52.8, 55.3, 77.7, 104.9, 114.2, 116.0, 125.5, 128.7, 138.8, 144.2, 150.7, 159.9; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{15}H_{15}BrN_3O_3$ ([M-Br]$^+$) 364.0291; found, 364.0290.

*2-(4-Methoxyphenyl)-3,7-dinitro-3,4-dihydro-2H-pyrido[1,2-a]-pyrimidin-1-ium Bromide (**7k**).* Light yellow solid; yield 84 mg, 68% (dr 86:14, inseparable); mp 230−232 °C; IR (KBr, cm^{-1}) 3432 (br m), 2874 (m), 2814 (m), 2785 (m), 1671 (vs), 1610 (s), 1585 (m), 1561 (s), 1535 (w), 1512 (m), 1348 (s), 1337 (s), 1284 (w), 1251 (m), 1182 (m), 1109 (w), 1027 (w), 839 (m); ^{1}H NMR (DMSO-d_6, 500 MHz, major + minor) δ 3.78 (s, 3H), 4.59 (d, J = 15.0 Hz, 1H), 5.28 (d, J = 15.0 Hz, 1H), 5.67−5.72 (unresolved, 1H), 5.77−5.81 (unresolved, 1H), 7.03 (d, J = 7.4 Hz, 2H), 7.36 (d, J = 9.5 Hz, 1H), 7.45 (d, J = 7.4 Hz, 2H), 8.58 (d, J = 9.5 Hz, 1H), 9.50 (s, 1H), 11.35 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 5.02 (d, J = 14.5 Hz, 1H), 5.62−5.66 (unresolved, 1H), 5.77−5.81 (unresolved, 1H), 7.31 (d, J = 7.7 Hz, 1H), 9.44 (s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, major) δ 48.5, 53.7, 55.4, 78.1, 114.4, 114.7, 128.0, 128.7, 135.3, 135.5, 140.4, 152.1, 159.8; MS (ES$^+$) m/z HRMS calcd for $C_{15}H_{15}N_4O_5$ ([M-Br]$^+$) 331.1037; found, 331.1038.

*7-Bromo-2-(4-methoxyphenyl)-8-methyl-3-nitro-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-1-ium Bromide (**7l**).* White solid; yield 108 mg, 78% (dr 80:20, inseparable); mp 177−179 °C; IR (KBr, cm^{-1}) 3437 (br vs), 2960 (m), 2917 (m), 1656 (s), 1592 (s), 1582 (s), 1556 (s), 1513 (m), 1363 (m), 1254 (s), 1180 (m), 1024 (s), 803 (m); ^{1}H NMR (DMSO-d_6, 500 MHz, major + minor) δ 2.40 (s, 3H), 3.76 (s, 3H), 4.42 (d, J = 14.1 Hz, 1H), 5.07 (d, J = 14.1 Hz, 1H), 5.52−5.56 (unresolved, 1H), 5.77−5.81 (unresolved, 1H), 6.98−7.02 (unresolved, 2H), 7.27 (s, 1H), 7.38−7.42 (unresolved, 2H), 8.62 (s, 1H), 10.43 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 4.48−5.02 (unresolved, 1H), 7.31 (d, J = 8.8 Hz, 2H), 8.40 (s, 1H), 10.15 (br s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, major) δ 22.4, 47.1, 53.0, 55.3, 78.5, 109.1, 113.7, 114.4, 128.1, 128.3, 139.0, 149.3, 153.8, 159.6; ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, minor) δ 22.4, 49.9, 52.6, 55.3, 77.9, 79.4, 114.0, 114.2, 125.7, 128.9, 138.7, 150.3, 153.1, 159.8; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{16}H_{17}BrN_3O_3$ ([M-Br]$^+$) 378.0448; found, 378.0439.

*2-(4-Methoxyphenyl)-3-nitro-3,4-dihydro-2H-pyrimido[1,2-a]-pyrimidin-1-ium Bromide (**10a**).* Yellow solid; yield 108 mg, 98% (dr 70:30, inseparable); mp 212−214 °C; IR (KBr, cm^{-1}) 3590 (br w), 3422 (br m), 3265 (w), 3093 (s), 2922 (m), 1651 (vs), 1595 (vs), 1573 (vs), 1512 (s), 1310 (s), 1268 (vs), 1182 (s); ^{1}H NMR (DMSO-d_6, 500 MHz, major + minor) δ 3.77 (s, 3H), 4.49 (dd, J = 15.3, 3.0 Hz, 1H), 5.12 (d, J = 15.3 Hz, 1H), 5.58−5.62 (unresolved m, 1H), 5.73−5.77 (unresolved m, 1H), 7.01 (d, J = 8.6 Hz, 2H), 7.23−7.26 (m, 1H), 7.46 (d, J = 8.6 Hz, 2H), 8.67−8.69 (m, 1H), 8.97−8.99 (m, 1H), 10.85 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 5.00 (dd, J = 15.3, 3.0 Hz, 1H), 5.19 (d, J = 15.3 Hz, 1H), 5.81−5.85 (unresolved, 1H), 10.85 (br s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, major) δ 48.1, 54.0, 55.4, 78.4, 111.1, 114.4, 128.1, 128.5, 149.5, 152.2, 159.7, 166.8; ^{13}C{1H} NMR (DMSO-d_6, 125 MHz, minor) δ 50.4, 53.6, 55.3, 77.9, 110.0, 114.2, 125.4, 128.9, 149.2, 153.1, 159.9, 166.1; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{14}H_{15}N_4O_3$ ([M-Br]$^+$) 287.1139; found, 286.1136.

*2-(4-Methoxyphenyl)-3-nitro-3,4-dihydro-2H-pyrazino[1,2-a]-pyrimidin-1-ium Bromide (**10b**).* Brown solid; yield 104 mg, 95% (dr 86:14, inseparable); mp 183−185 °C; IR (KBr, cm^{-1}) 3435 (br m), 3064 (m), 2983 (s), 2927 (s), 2753 (vs), 1637 (s), 1608 (vs), 1558 (s), 1511 (m), 1373 (m), 1247 (s), 1178 (m), 1142 (m), 1032 (m), 859 (m), 838 (m); ^{1}H NMR (DMSO-d_6, 500 MHz, major + minor) δ 3.79 (s, 3H), 4.50 (d, J = 14.4 Hz, 1H), 5.09 (d, J = 14.4 Hz, 1H), 5.61−5.65 (unresolved, 1H), 5.74−5.78 (unresolved, 1H), 6.95−7.05 (unresolved, 2H), 7.45−7.55 (unresolved, 2H), 8.05−8.10 (unresolved, 1H), 8.18−8.22 (unresolved, 1H), 8.82−8.87 (unresolved, 1H), 11.49 (br s, 1H); ^{1}H NMR (DMSO-d_6, 500 MHz, minor, peaks appearing separately) δ 4.96 (d, J = 13.5 Hz, 1H), 5.18 (d, J = 13.5 Hz, 1H), 5.83−5.87 (unresolved, 1H), 7.33−7.37 (unresolved, 2H), 8.98−9.00 (unresolved, 1H), 11.24 (br s, 1H); ^{13}C{1H} NMR (DMSO-d_6, 125 MHz) δ 47.4, 53.5, 55.4, 78.0, 114.4, 128.3, 128.7, 129.6, 130.2, 141.7, 145.0, 159.8; MS (ES$^+$, Ar) m/z HRMS calcd for $C_{14}H_{15}N_4O_3$ ([M-Br]$^+$) 287.1139; found, 287.1136.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00947.

X-ray file for compound **7b** (CIF)

DOI: 10.1021/acs.joc.7b00947
J. Org. Chem. 2017, 82, 6482−6488

Copies of NMR spectra for all of the new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: irishi@iitb.ac.in.

ORCID

Irishi N. N. Namboothiri: 0000-0002-8945-3932

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

I.N.N.N. thanks SERB, DST India for financial assistance. L.S. thanks CSIR India for a senior research fellowship. We thank Ms. Deepa Nair, Department of Chemistry, IIT Bombay for help with X-ray data.

REFERENCES

(1) Brown, E. G. *Ring Nitrogen and Key Biomolecules: The Biochemistry of N-Heterocycles*; Kluwer Academic: Dordrecht, The Netherlands, 1998.

(2) Review: Brana, M. F.; Cacho, M.; Gradillas, A.; De Pascual-Teresa, B.; Ramos, A. *Curr. Pharm. Des.* **2001**, *7*, 1745.

(3) Galietta, L. J. V.; Springsteel, M. F.; Eda, M.; Niedzinski, E. J.; By, K.; Haddadin, M. J.; Kurth, M. J.; Nantz, M. H.; Verkman, A. S. *J. Biol. Chem.* **2001**, *276*, 19723.

(4) Martinez, V.; Burgos, C.; Alvarez-Builla, J.; Fernandez, G.; Domingo, A.; Garcia-Nieto, R.; Gago, F.; Manzanares, I.; Cuevas, C.; Vaquero, J. J. *J. Med. Chem.* **2004**, *47*, 1136.

(5) (a) Howarth, J.; Hanlon, K. *Tetrahedron Lett.* **2001**, *42*, 751. (b) Howarth, J.; Hanlon, K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2017.

(6) Reviews: (a) Hermecz, I.; Vasvari-Debreczy, L.; Matyus, P. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. V. F., Eds.; Pergamon: London, 1996; Ch. 8.23, p 563. (b) Routaboul, C.; Norez, C.; Melin, P.; Molina, M.-C.; Boucherle, B.; Bossard, F.; Noel, S.; Robert, R.; Gauthier, C.; Becq, F.; Decout, J.-L. *J. Pharmacol. Exp. Ther.* **2007**, *322*, 1023.

(7) Reviews: (a) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473. (b) Hermecz, I.; Vasvári-Debreczy, L. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, U.K., 2008; p 77. (c) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3.

(8) Fenton, C.; Scott, L. J. *CNS Drugs* **2005**, *19*, 429.

(9) Smith, R. L.; Barrett, R. J.; Sanders-Bush, E. *J. Pharmacol. Exp. Ther.* **1995**, *275*, 1050.

(10) Awouters, F.; Vermeire, J.; Smeyers, F.; Vermote, P.; Van Beek, R.; Niemegeers, C. J. E. *Drug Dev. Res.* **1986**, *8*, 95.

(11) Kennis, L. E. J.; Bischoff, F. P.; Mertens, C. J.; Love, C. J.; Van den Keybus, F. A. F.; Pieters, S.; Braeken, M.; Megens, A. A. H. P.; Leysen, J. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 71.

(12) Fürst, S.; Gyires, K.; Knoll, J. *Arzneim.-Forsch.* **1988**, *38*, 552.

(13) Bluhm, U.; Boucher, J.-L.; Buss, U.; Clement, B.; Friedrich, F.; Girreser, U.; Heber, D.; Lam, T.; Lepoivre, M.; Rostaie-Gerylow, M.; Wolschendorf, U. *Eur. J. Med. Chem.* **2009**, *44*, 2877.

(14) Reviews: (a) Hermecz, I. *Adv. Heterocycl. Chem.* **1995**, *63*, 103. (b) Hermecz, I. *Adv. Heterocycl. Chem.* **2003**, *85*, 173.

(15) (a) Mellor, J. M.; Merriman, G. D.; Rataj, H.; Reid, G. *Tetrahedron Lett.* **1996**, *37*, 2615. (b) Mellor, J. M.; Rataj, H. *Tetrahedron Lett.* **1996**, *37*, 2619. (c) Namitharan, K.; Pitchumani, K. *Adv. Synth. Catal.* **2013**, *355*, 93.

(16) (a) Huang, K. S.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2002**, *67*, 2382. (b) Font, D.; Linden, A.; Heras, M.; Villalgordo, J. M. *Tetrahedron* **2006**, *62*, 1433. (c) Cheng, D.; Croft, L.; Abdi, M.; Lightfoot, A.; Gallagher, T. *Org. Lett.* **2007**, *9*, 5175. (d) Toche, R. B.; Ghotekar, B. K.; Kazi, M. A.; Patil, S. P.; Jachak, M. N. *Scholarly Res. Exch.* **2008**, *2008*, 1. (e) Maity, A.; Mondal, S.; Paira, R.; Hazra, A.; Naskar, S.; Sahu, K. B.; Saha, P.; Banerjee, S.; Mondal, N. B. *Tetrahedron Lett.* **2011**, *52*, 3033.

(17) (a) Wu, Y.-J.; He, H.; Hu, S.; Huang, Y.; Scola, P. M.; Grant-Young, K.; Bertekap, R. L.; Wu, D.; Gao, Q.; Li, Y.; Klakouski, C.; Westphal, R. S. *J. Med. Chem.* **2003**, *46*, 4834. (b) Katritzky, A. R.; Rogers, J. W.; Witek, R. M.; Nair, S. K. *ARKIVOC* **2004**, 52. (c) Paira, R.; Maity, A.; Mondal, S.; Naskar, S.; Sahu, K. B.; Saha, P.; Hazra, A.; Padmanaban, E.; Banerjee, S.; Mondal, N. B. *Tetrahedron Lett.* **2011**, *52*, 1653. (d) Rapolu, S.; Alla, M.; Ganji, R. J.; Saddanapu, V.; Kishor, C.; Bommena, V. R.; Addlagatta, A. *MedChemComm* **2013**, *4*, 817. (e) Vartale, S. P.; Halikar, N. K.; Sirsat, S. B.; Pawar, Y. D. *J. Heterocycl. Chem.* **2013**, *50*, 351.

(18) (a) Adib, M.; Sayahi, M. H.; Nosrati, M.; Zhu, L.-G. *Tetrahedron Lett.* **2007**, *48*, 4195. (b) Yang, K.; Xiang, J.; Bao, G.; Dang, Q.; Bai, X. *ACS Comb. Sci.* **2013**, *15*, 519. (c) Ref 15c..

(19) Gupta, P.; Gupta, S.; Sachar, A.; Sharma, R. L. *J. Heterocycl. Chem.* **2010**, *47*, 1188.

(20) Yang, Y.; Shu, W.-M.; Yu, S.-B.; Ni, F.; Gao, M.; Wu, A.-X. *Chem. Commun.* **2013**, *49*, 1729.

(21) Pathak, R.; Batra, S. *Tetrahedron* **2007**, *63*, 9448.

(22) (a) Morita, K.; Suzuki, H.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. (b) Baylis, A. B.; Hillman, M. E. D. *Ger. Offen.* **1972**, 2155113; *Chem. Abstr.* **1972**, *77*, 34174q. (c) Hillman, M. E. D.; Baylis, A. B. U. S. Patent US 3743669, 1973.

(23) Selected books/reviews: (a) Zhao, M.-X.; Wei, Y.; Shi, M. *The Chemistry of the Morita-Baylis-Hillman Reaction, RSC Catal. Ser.*; Shi, M., Wang, F.-J., Zhao, M.-X., Wei, Y., Eds.; Royal Society of Chemistry: Cambridge, U.K., 2011; Vol. *8*, p 1. (b) Ciganek, E. *Org. React.* **1997**, *51*, 201. (c) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1. (d) Basavaiah, D.; Reddy, G. C. *ARKIVOC* **2016**, *ii*, 172. and the references therein. (e) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614.

(24) (a) Le Bras, J.; Muzart, J. *Synthesis* **2011**, *2011*, 3581. (b) Gowrisankar, S.; Lee, H. S.; Kim, S. H.; Lee, K. Y.; Kim, J. N. *Tetrahedron* **2009**, *65*, 8769. (c) Xie, P.; Huang, Y. *Org. Biomol. Chem.* **2015**, *13*, 8578. (d) Zhong, W.; Liu, Y.; Wang, G.; Hong, L.; Chen, Y.; Chen, X.; Zheng, Y.; Zhang, W.; Ma, W.; Shen, Y. *Org. Prep. Proced. Int.* **2011**, *43*, 1. (e) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511. (f) Lima-Junior, C. G.; Vasconcellos, M. L. A. A. *Bioorg. Med. Chem.* **2012**, *20*, 3954.

(25) (a) Rauhut, M. M.; Currier, H. U. S. Patent 3074999, 1963; *Chem. Abstr.* **1963**, *58*, 11224a. Reviews: (b) Xie, P.; Huang, Y. *Eur. J. Org. Chem.* **2013**, *2013*, 6213. (c) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069. (d) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.

(26) Reviews: (a) Kaur, K.; Namboothiri, I. N. N. *Chimia* **2012**, *66*, 913. (b) Nair, D. K.; Kumar, T.; Namboothiri, I. N. N. *Synlett* **2016**, *27*, 2425. (c) Huang, W.-Y.; Anwar, S.; Chen, K. *Chem. Record* **2017**, *17*, 363.

(27) Representative articles: (a) Reddy, R. J.; Chen, K. *Org. Lett.* **2011**, *13*, 1458. (b) Huang, W.-Y.; Chen, Y.-C.; Chen, K. *Chem. - Asian J.* **2012**, *7*, 688. (c) Nair, D. K.; Mobin, S. M.; Namboothiri, I. N. N. *Tetrahedron Lett.* **2012**, *53*, 3349. (d) Magar, D. R.; Ke, Y.-J.; Chen, K. *Asian J. Org. Chem.* **2013**, *2*, 330. (e) Zhu, H.; Shao, N.; Chen, T.; Zou, H. *Chem. Commun.* **2013**, *49*, 7738. (f) Zhang, J.-Q.; Liu, J.-J.; Gu, C.-L.; Wang, D.; Liu, L. *Eur. J. Org. Chem.* **2014**, *2014*, 5885. (g) Majee, D.; Biswas, S.; Mobin, S. M.; Samanta, S. *J. Org. Chem.* **2016**, *81*, 4378. (h) Gopi, E.; Namboothiri, I. N. N. *J. Org. Chem.* **2014**, *79*, 7468.

(28) Nair, D. K.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2012**, *14*, 4580.

(29) (a) Yaqub, M.; Yu, C.-Y; Jia, Y. M.; Huang, Z. T. *Synlett* **2008**, *2008*, 1357. (b) Chen, R.; Fan, X.; Gong, J.; He, Z. *Asian J. Org. Chem.* **2014**, *3*, 877. (c) Cao, C. L.; Zhou, Y. Y.; Zhou, J.; Sun, X. L.; Tang, Y.; Li, Y. X.; Li, G. Y.; Sun, J. *Chem. - Eur. J.* **2009**, *15*, 11384. (d) Nair, D. K.; Menna-Barreto, R. F. S.; da Silva Júnior, E. N.; Mobin, S. M.; Namboothiri, I. N. N. *Chem. Commun.* **2014**, *50*, 6973. (e) Osorio-

DOI: 10.1021/acs.joc.7b00947
J. Org. Chem. 2017, 82, 6482−6488

Planes, L.; Rodríguez-Escrich, C.; Pericàs, M. A. *Catal. Sci. Technol.* **2016**, *6*, 4686. (f) Xiao, W.; Yin, X.; Zhou, Z.; Du, W.; Chen, Y.-C. *Org. Lett.* **2016**, *18*, 116. (g) Shu, T.; Ni, Q.; Song, X.; Zhao, K.; Wu, T.; Puttreddy, R.; Rissanen, K.; Enders, D. *Chem. Commun.* **2016**, *52*, 2609. (h) An, J.; Lu, L.-Q.; Yang, Q.-Q.; Wang, T.; Xiao, W.-J. *Org. Lett.* **2013**, *15*, 542.

(30) For the preparation and S_N2 reaction of MBH bromide **6**: Bakthadoss, M.; Sivakumar, N.; Anthonisamy, D. *Synthesis* **2011**, *2011*, 611.

DOI: 10.1021/acs.joc.7b00947
J. Org. Chem. 2017, 82, 6482−6488