

Carbocyclic and Heterocyclic Compounds: Baylis-Hillman Reaction

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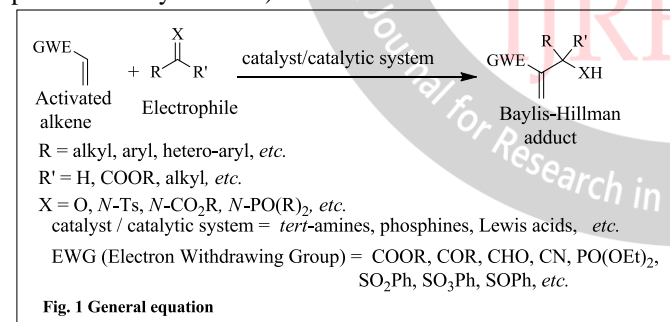
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Abstract— The Baylis–Hillman reaction is a novel carbon-carbon bond forming reaction between at α -position of activated alkene and carbon electrophile under catalytic influence of a tertiary amine to produce the multifunctional molecules. This review highlights how the multifunctional Baylis-Hillman adduct has been used to synthesis of carbocyclic and heterocyclic molecules

Keywords— Carbon-carbon bond formation, tertiary amine, carbocyclic compounds, 1,4-Diazabicyclo (2.2.2) octane.

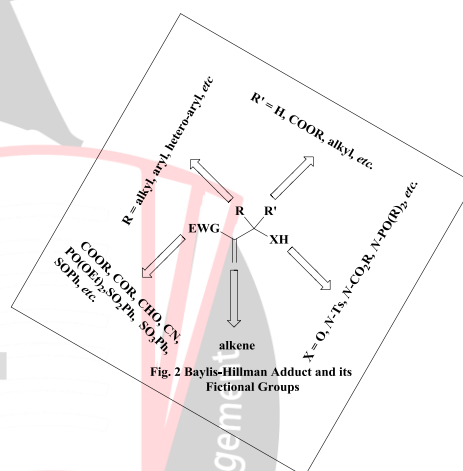
INTRODUCTION

Carbon-carbon bond forming reactions and functional group transformation are very important in organic chemistry. Synthetic chemists have been working in this way for the last several years. The Baylis–Hillman reaction is a novel carbon-carbon bond forming reaction and it is essentially a three-component atom economic reaction between at α -position of activated alkene and carbon electrophile under catalytic influence of a tertiary amine. 1,4-Diazabicyclo (2.2.2) octane [DABCO] is the most commonly used 3^o amine catalyst for this reaction to producing densely functionalized molecules generally referred to as the Baylis-Hillman (B-H) adducts (Fig. 1). This reaction invented by A. B. Baylis and M. E. D. Hillman (German patent¹ filed in the year 1972 and U.S patent² in the year 1973).



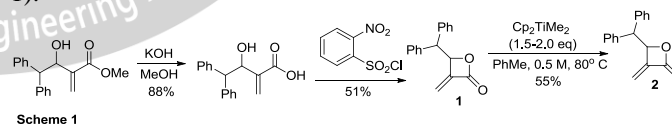
SYNTHESIS OF CARBOCYCLIC AND HETEROCYCLIC COMPOUNDS

Baylis-Hillman adducts (Fig. 2) contains many fictional groups which is easy to transform into important substrates.³⁻⁶ These adducts have also been employed as key synthons in the synthesis of important hetero/carbocycles. Some of the important and developments for the synthesis hetero/carbocycles on the applications of Baylis-Hillman adducts have been presented in this section.

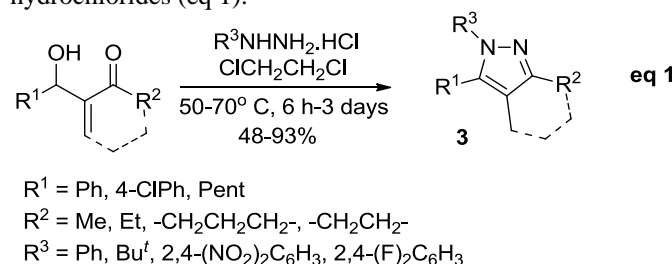


SYNTHETIC TRANSFORMATION OF BAYLIS-HILLMAN ALCOHOLS

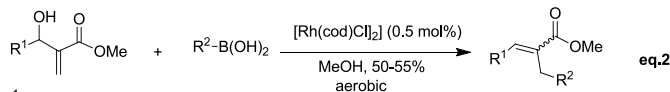
Howell et al.⁷ have described an interesting synthesis of 3-alkylidene-2-methylenexetanes (**2**) via the treatment of α -alkylidene- β -lactones (**1**) (which were prepared from Baylis-Hillman adducts) with dimethyltitanocene (Scheme 1).



Kim et al. have described an interesting regioselective synthesis of 1,3,4,5-tetrasubstituted pyrazoles (**3**) via the reaction of Baylis-Hillman adducts with hydrazine hydrochlorides (eq 1).⁸



Genet and co-workers⁹ have elegantly reported the synthesis of trisubstituted alkenes using the reaction of Baylis-Hillman adducts with arylboronic acids in the presence of rhodium catalyst [Rh(cod)Cl]₂ (eq. 2).

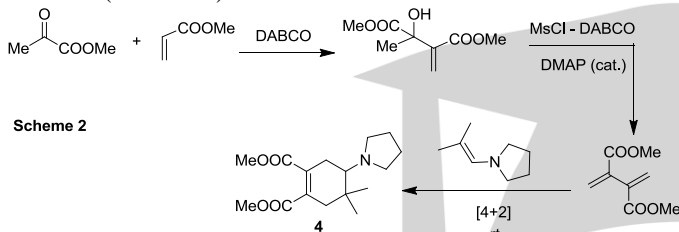


R¹ = Me, *i*-Bu, nonyl, *c*-hex, 4-NO₂Ph, 4-ClPh, naphth-1-yl

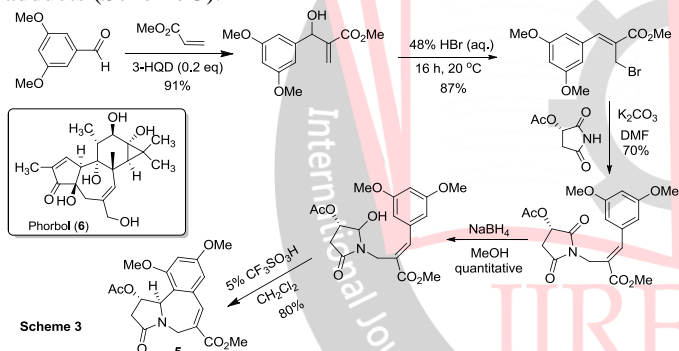
R² = Ph, 4-CF₃Ph, 4-(MeO)Ph, 3-CF₃Ph, 2-MePh, 4-MePh, naphth-1-yl, naphth-2-yl

E / Z : 90-99 / 10-1

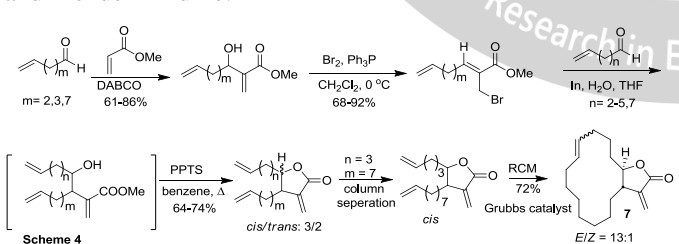
Grundt and Hoffman¹⁰ have reported an interesting synthesis of 2,3-dimethoxy-carbonyl-1,3-butadiene from the Baylis-Hillman adduct derived from methyl acrylate and methyl pyruvate. This diene was subjected to Diels-Alder cycloaddition with pyrrolidinoisobutene to provide adduct **4** (Scheme 2).



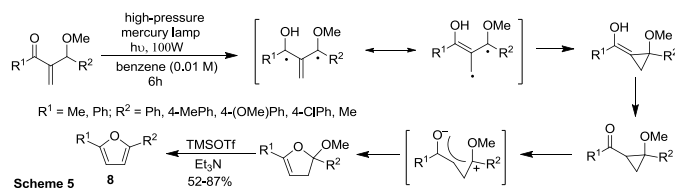
Marson and co-workers¹¹ have stated an interesting synthesis of aza analogues (**6**) of the phorbol (**5**) and related 5-6-7 tricyclic fused frameworks *via* the Baylis-Hillman adducts (Scheme 3).



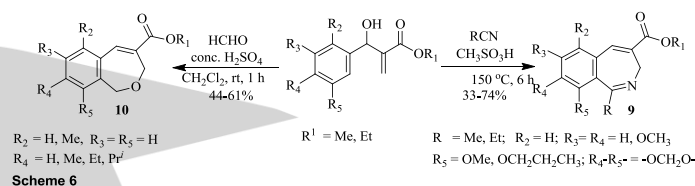
An interesting synthesis of bicyclic lactones (**7**) from the Baylis-Hillman adducts (Scheme 4) reported by Paquette and Mendez-Andino.¹²



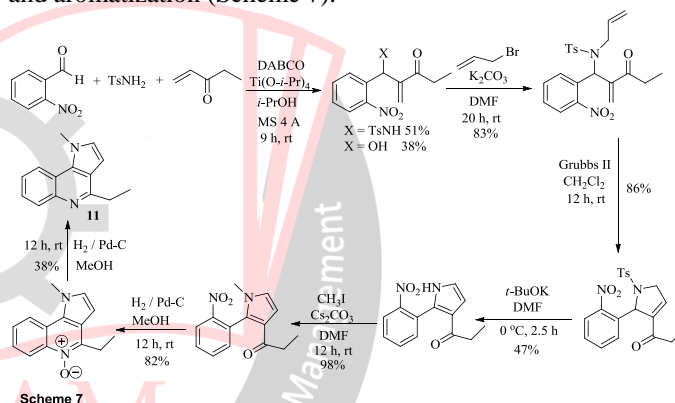
Mikami et al.¹³ have reported an interesting synthesis of substituted furan rings (**8**) *via* the photo chemical reaction of methyl ethers of Baylis-Hillman adducts followed by *in situ* treatment of the resulting dihydropyran derivatives with TMSOTf/Et₃N (Scheme 5).



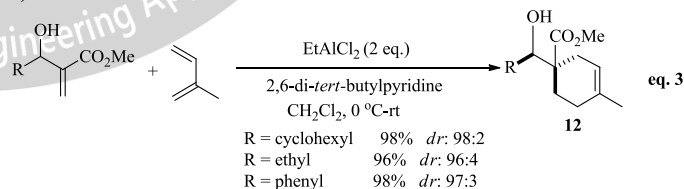
Basavaiah research group reported the Baylis-Hillman alcohols into 2-benzazepines (**9**) *via* the tandem construction of C-N and C-C bonds (*via* Ritter and Houben-Hoesch reactions).¹⁴ Subsequently, they also reported a novel one-pot synthesis of 2-benzoxepines (**10**) *via* the reaction of the Baylis-Hillman alcohols with formaldehyde in the presence of H₂SO₄ involving tandem construction of C-O and C-C bonds¹⁵ (Scheme 6).



Lamaty and coworkers¹⁶ have developed an efficient synthesis of fused pyrrolo pyridines (**11**) through a sequential Baylis-Hillman reaction, ring closing metathesis and aromatization (Scheme 7).



Aggarwal and coworkers¹⁷ have meticulously used the Baylis-Hillman alcohols as excellent dienophiles in Diels-Alder reaction with dienes to provide the corresponding adducts (**12**) with complete diastereocontrol (eq. 3).

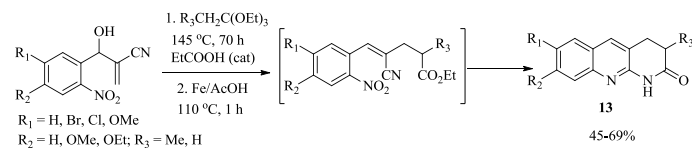


Basavaiah research group¹⁸ has developed one-pot procedure for the synthesis of tri and tetracyclic heterocyclic systems containing [1,8]naphthyridin-2-one framework (**13** & **14**) from the Baylis-Hillman alcohols (Scheme 8 and eq. 4).

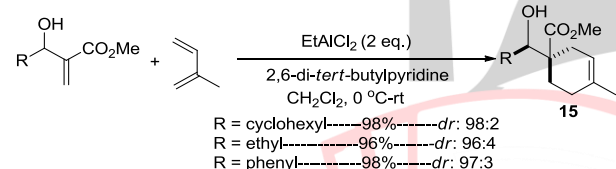
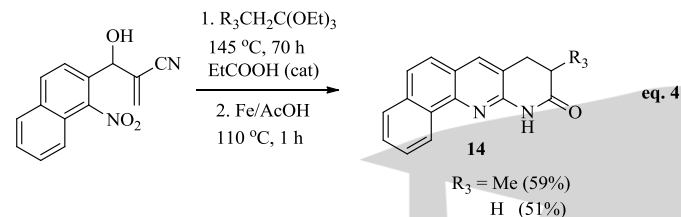
Aggarwal *et al.*¹⁹ successfully used Baylis-Hillman adducts as excellent dienophiles in Diels-Alder reaction with dienes to provide the corresponding adducts (**15**) with complete diastereocontrol (eq. 5).

A simple synthesis of 3-(chloromethyl)coumarin derivatives (**16**) has been developed by Kaye and coworkers²⁰ using the Baylis-Hillman alcohols (Scheme 9).

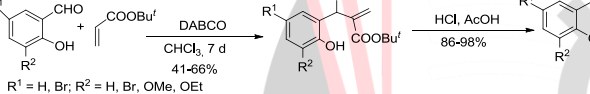
Basavaiah research group²¹ has successfully employed Baylis-Hillman adducts, obtained from chromone derivatives and pyridine-2-carboxaldehyde into tetracyclic indolizine fused chromone systems (**17**) (Scheme 10).



Scheme 8



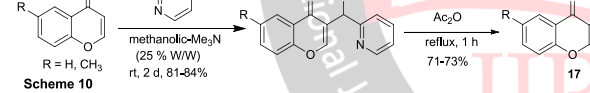
Scheme 9



Scheme 10



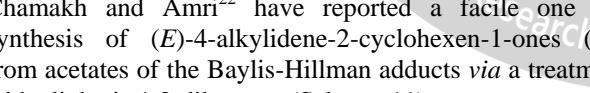
Scheme 11



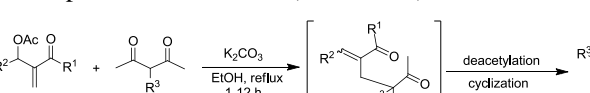
Scheme 12



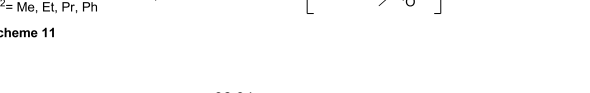
Scheme 13



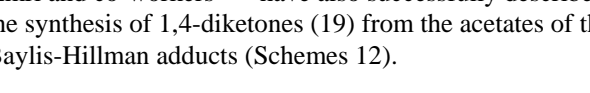
Scheme 14



Scheme 15



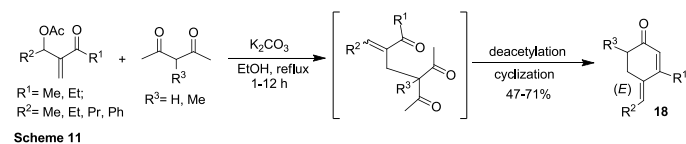
Scheme 16



Scheme 17

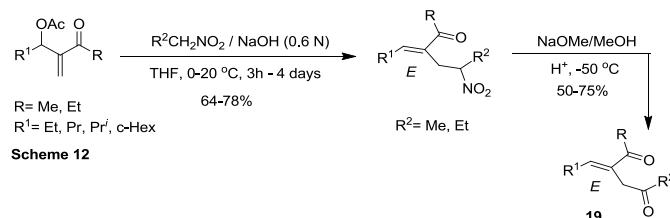
SYNTHETIC TRANSFORMATION OF BAYLIS-HILLMAN ACETATES

Chamakh and Amri²² have reported a facile one pot synthesis of (*E*)-4-alkylidene-2-cyclohexen-1-ones (**18**) from acetates of the Baylis-Hillman adducts *via* a treatment with aliphatic 1,3-diketones (Scheme 11).



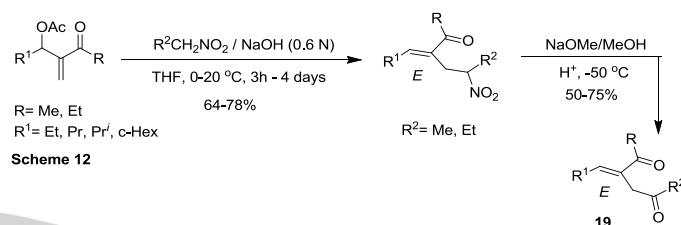
Scheme 11

Amri and co-workers^{23,24} have also successfully described the synthesis of 1,4-diketones (**19**) from the acetates of the Baylis-Hillman adducts (Schemes 12).



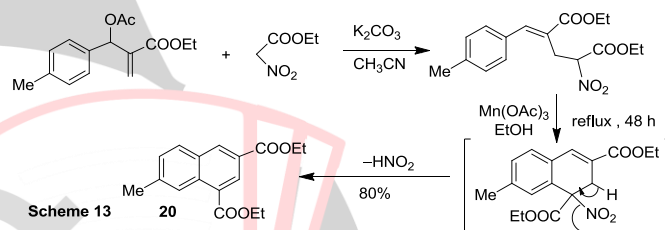
Scheme 12

Amri and co-workers^{23,24} have also successfully described the synthesis of 1,4-diketones (**19**) from the acetates of the Baylis-Hillman adducts (Schemes 12).



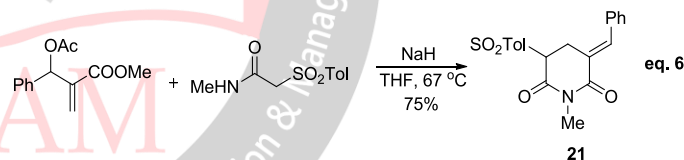
Scheme 12

Kim and co-workers²⁵ have reported an interesting methodology for the synthesis of 1,3-disubstituted naphthalenes (**20**) from the acetates of Baylis-Hillman adducts (Scheme 13)



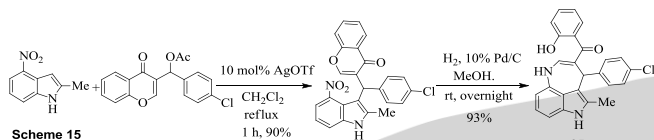
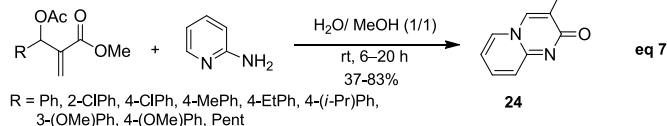
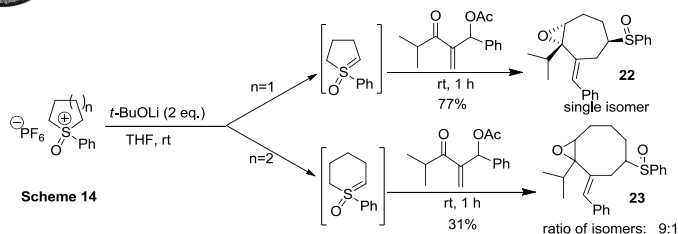
Scheme 13

Chang and co-workers²⁶ have reported a one-pot conversion of Baylis-Hillman adducts into alkyl-3(*E*)-aryl/alkylidene-5-substituted sulfonylpiperidine-2,6-diones (**21**) (eq. 6).

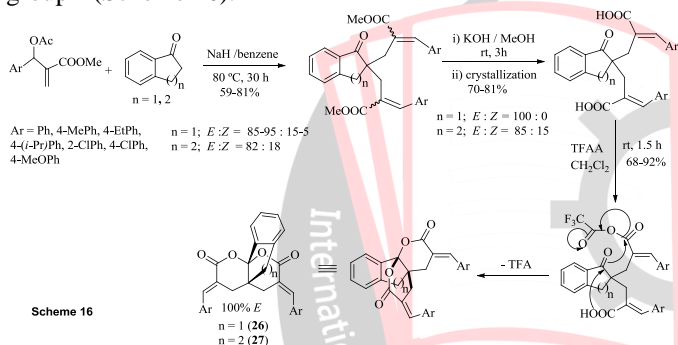


Fujimoto and co-workers a tandem Michael-intramolecular Corey-Chaykovsky reaction of the five membered cyclic oxosulfonium ylide using the Baylis-Hillman acetates leading to the stereoselective synthesis of cycloheptene oxide derivatives (**22**) was reported by Fujimoto and co-workers.^{27,28} A similar reaction with six membered oxosulfonium ylide provided cyclooctene oxide derivatives (**23**) as mixture of stereoisomers in moderate yields (Scheme 14).

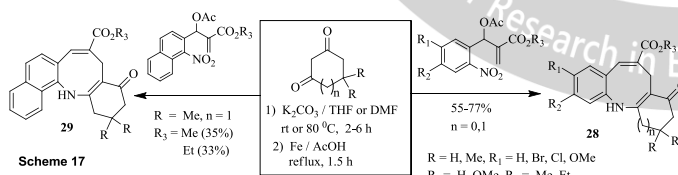
A facile, one-pot synthetic transformation of the acetates of the Baylis-Hillman adducts into fused pyrimidones (**24**) *via* the reaction with 2-aminopyridine in an environment-friendly aqueous media, has been developed by Basavaiah research group (eq 7).²⁹



A simple and convenient three-step synthesis of functionalized [4.4.3] and [4.4.4]propellano-bis lactones (**26** & **27**) via the reaction of Baylis-Hillman acetates with indanone and tetralone developed by Basavaiah research group³¹ (Scheme 16).

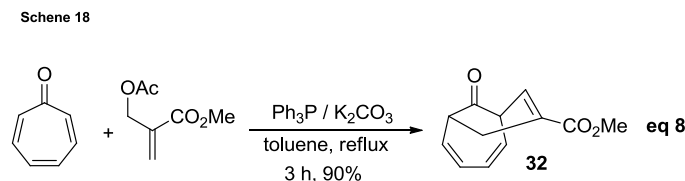
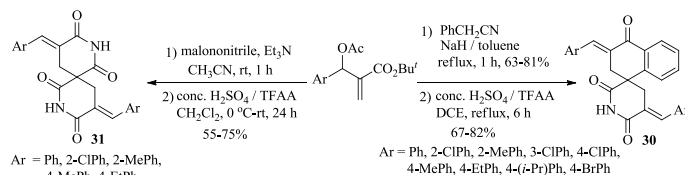


A simple, convenient, and one-pot synthesis of functionalized tri / tetracyclic frameworks (**28** & **29**) containing an important azocine moiety, from the Baylis-Hillman acetates was developed by Basavaiah research group³² (Scheme 17).

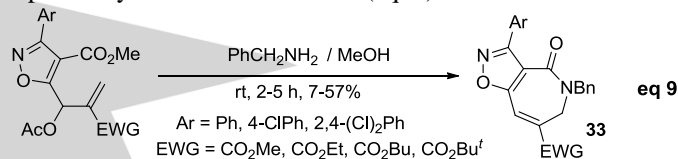


Recently, an interesting synthesis of (*E*)-arylidene-tetralone-spiro-glutarimides (**30**) from the Baylis-Hillman acetates has been reported by Basavaiah research group³³ via biscyclization strategy involving facile C-C and C-N bond formation methodology. Subsequently, the same strategy has been successfully employed to provide di(*E*)-arylidene-spiro-bisglutarimides (**31**) from the Baylis-Hillman acetates (Scheme 18).

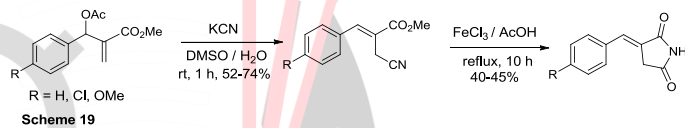
A simple and convenient method for synthesis of bridged nine-membered carbocycles (**32**) in excellent yields via the phosphine-catalyzed reaction of Baylis-Hillman acetate (bromide / chloride / *tert*-butyl carbonate) with tropone involving [3+6] annulation strategy was developed by Lu and coworkers (eq. 8).³⁴



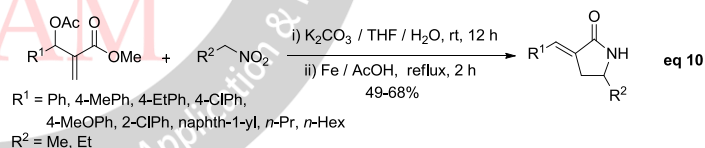
A simple synthesis of azipine derivatives (**33**) from the acetates of Baylis-Hillman adducts has been recently reported by Batra and coworkers (eq. 9).³⁵



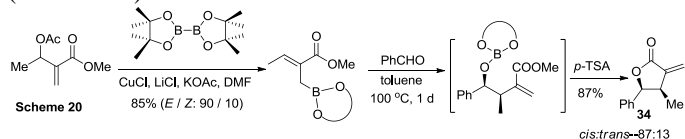
A simple synthesis of arylidinesuccinimide derivatives from the Baylis-Hillman acetates was described by Lee and coworkers according to the (Scheme 19).³⁶



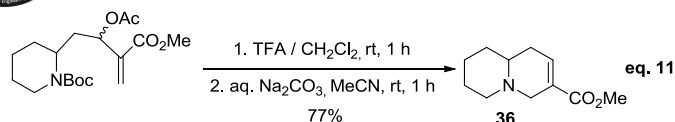
Basavaiah research group³⁷ reported a convenient one-pot synthesis of (*E*)-5-alkyl-3-arylidene pyrrolidin-2-one (γ -lactam) derivatives via the treatment of acetates of Baylis-Hillman adducts with nitroalkanes in the presence of a base, followed by reductive cyclization, using Fe / AcOH (eq. 10).



Ramachandran³⁸ *et. al.* have reported an interesting synthesis of α -substituted β -methylene β -butyrolactone (**34**) via the nucleophilic addition of boronates 125, to the acetates of Baylis-Hillman adducts, followed by the treatment of the resulting allyl boronates with aldehydes (Scheme 20)

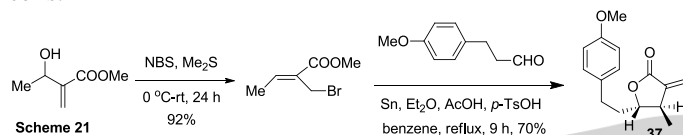


The acetate of the Baylis-Hillman adducts, derived from *N*-protected β -amino aldehydes with methyl acrylate, have been transformed into nitrogen fused heterocycles (**36**) by Clive *et. al.*³⁹ (eq. 11).

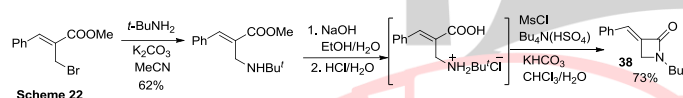


SYNTHETIC TRANSFORMATION OF BAYLIS-HILLMAN BROMIDES

Bermejo and co-workers⁴⁰ have described an interesting synthesis of methylene lactone (**37**), from Baylis-Hillman adduct, methyl 3-hydroxy-2-methylenebutanoate (Scheme 21). This molecule is found to possess extremely interesting properties about its apoptosis inducing ability in HL-60 cells.



Hoffman and Buchholz⁴¹ have reported an interesting synthesis of β -lactam derivatives (**38**) via the nucleophilic addition of aliphatic or aromatic primary amines to allyl bromides derived from Baylis-Hillman adducts (Scheme 22).



REFERENCES

- Baylis, A. B.; Hillman, M. E. D. German patent 2155113, 1972, Chem. Abstr. 1972, 77, 34174q
- Hillman, M. E. D.; Baylis, A. B. U. S. Patent 3743669, 1973
- Singh, V.; Batra, S. Tetrahedron, 2008, 64, 4511
- Basavaiah, D.; Rao, A. J.; Satyanarayana, T. Chem. Rev. 2003, 103, 811
- Ciganek, E. in Organic Reactions: (Ed. L. A. Paquette) Wiley: New York. 1997: Vol. 51. pp 201
- (a) Basavaiah, D.; Devendar, B.; Lenin, D. V.; Satyanarayana, T. Synlett, 2008, 411; (b) Basavaiah, D.; Lenin, D. V. Eur. J. Org. Chem, 2010, 5650; (c) Basavaiah, D.; Reddy, R. J.; Lenin, D. V. Helv. Chimica. Acta, 2010, 1180; (d) Basavaiah, D.; Lenin, D. V. Tetrahedron Lett, 2009, 50, 3538; (e) Basavaiah, D.; Lenin, D. V.; Veeraghavaiah, G. Curr. Science, 2011, 101 (7), 888; (f) Lenin, D. V. I. J. C. R. T, 2018, 6, 2320; (g) Lenin, D. V. W. J. P. R, 2018, 7(6), 641; (h) Lenin, D. V. I. J. C. S, 2018, 2(2), 86; (i) Lenin, D. V. I. J. C. S, 2018, 2(2), 53; (j) Lenin, D. V. I. J. E. S. M, 2018, 7(5), 70; (k) PhD thesis, University of Hyderabad, Rao, A. J., June 2003.; Aravindu, K., April 2010.; Devendar, B.; August 2008.; Sarada, D. S, 2004.; Raju, J. R, 2007.; Rao, J. S, 2004.; Roy, S, 2010.; Satyanarayana, T, 2005, Lenin, D. V, 2010 (l) Basavaiah, D.; Reddy, B. S.; Singh, B. S. Chem. Rev. 2010, 110, 5447
- Martinez, I.; Andrews, A. E.; Emch, J. D.; Ndakala, A. J.; Wang, J.; Howell, A. R. Org. Lett. 2003, 5, 399.
- Lee, K. Y.; Kim, J. M.; Kim, J. N. Tetrahedron Lett. 2003, 44, 6737.
- Navarre, L.; Darses, S.; Genet, J. P. Chem. Commun. 2004, 1108.
- Grundke, C.; Hoffmann, H. M. R. Chem. Ber. 1987, 120, 1461.
- Marson, C. M.; Pink, J. H.; Hall, D.; Hursthouse, M. B.; Malik, A.; Smith, C. J. Org. Chem. 2003, 68, 792.
- Paquette, L. A.; Mendez-Andino, J. Tetrahedron Lett. 1999, 40, 4301.
- Matsumoto, S.; Mikami, K. Synlett 1998, 469.
- Basavaiah, D.; Satyanarayana, T. Chem. Commun. 2004, 32.
- Basavaiah, D.; Sharada, D. S.; Veerendhar, A. Tetrahedron Lett. 2004, 45, 3081.
- Colacino, E.; Andre, C.; Martinez, J.; Lamaty, F. Tetrahedron Lett. 2008, 49, 4953.
- Aggarwal, V. K.; Patin, A.; Tisserand, S. Org. Lett. 2005, 7, 2555.
- Basavaiah, D.; Reddy, K. R. Tetrahedron 2010, 66, 1215.
- Aggarwal, V. K.; Patin, A.; Tisserand, S. Org. Lett. 2005, 7, 2555.
- Kaye, P. T.; Musa, M. A.; Nocanda, X. W. Synthesis 2005, 531.
- Basavaiah, D.; Jaganmohan Rao, A. Tetrahedron Lett. 2003, 44, 4365
- Chamakh, A.; Amri, H. Tetrahedron Lett. 1998, 39, 375.
- Chamakh, A.; M'hirsi, M.; Villieras, J.; Lebreton, J.; Amri, H. Synthesis 2000, 295.
- Hbaieb, S.; Amri, H. J. Soc. Chim. Tunis. 2000, 4, 671.
- Im, Y. J.; Lee, K. Y.; Kim, T. H.; Kim, J. N. Tetrahedron Lett. 2002, 43, 4675
- Chen, C-Y.; Chang, M-Y.; Hsu, R-T.; Chen, S-T.; Chang, N-C. Tetrahedron Lett. 2003, 44, 8627.
- Akiyama, H.; Fujimoto, T.; Ohshima, K.; Hoshino, K.; Yamamoto, I.; Iriye, R. Org. Lett. 1999, 1, 427.
- Akiyama, H.; Fujimoto, T.; Ohshima, K.; Hoshino, K.; Saito, Y.; Okamoto, A.; Yamamoto, I.; Kakehi, A.; Iriye, R. Eur. J. Org. Chem. 2001, 2265.
- Basavaiah, D.; Satyanarayana, T. Tetrahedron Lett. 2002, 43, 4301.
- Shafiq, Z.; Liu, L.; Liu, Z.; Wang, D.; Chen, Y.-J. Org. Lett. 2007, 9, 2525.
- Basavaiah, D.; Satyanarayana, T. Org. Lett. 2001, 3, 3619.
- Basavaiah, D.; Aravindu, K. Org. Lett. 2007, 9, 2453.
- Basavaiah, D.; Reddy, R. J. Org. Biomol. Chem., 2008, 6, 1034.
- Du, Y.; Feng, J.; Lu, X. Org. Lett. 2005, 7, 1987.
- Batra, S.; Roy, A. K. Synthesis 2004, 2550.
- Hong, W. P.; Lim, H. N.; Park, H. W.; Lee, K.-J. Bull. Korean. Chem. Soc. 2005, 26, 655.
- Basavaiah, D.; Srivardhana Rao, J. Tetrahedron Lett. 2004, 45, 1621.
- Ramachandran, P. V.; Pratihar, D.; Biswas, D.; Srivastava, A.; Reddy, M. V. R. Org. Lett. 2004, 6, 481.
- Clive, D. L. J.; Yu, M.; Li, Z. Chem. Commun. 2005, 906.
- Gonzalez, A. G.; Silva, M. H.; Padron, J. I.; Leon, F.; Reyes, E.; Alvarez-Mon, M.; Pivel, J. P.; Quintana, J.; Estevez, F.; Bermejo, J. J. Med. Chem. 2002, 45, 2358.
44. Buchholz, R.; Hoffmann, H. M. R. Helv. Chim. Acta 1991, 74, 1213.